Rheumatic Disorders

6

THE YEAR IN RHEUMATIC DISORDERS

R. MADHOK
H. A. CAPELL and
H. S. LUTHRA

CLINICAL PUBLISHING

THE YEAR IN RHEUMATIC DISORDERS

VOLUME 6

EDITED BY:

RAJAN MADHOK, HILARY A CAPELL and HARVINDER LUTHRA

CLINICAL PUBLISHING

OXFORD

Clinical Publishing
an imprint of Atlas Medical Publishing Ltd

Oxford Centre for Innovation
Mill Street, Oxford OX2 0JX, UK

Tel: +44 1865 811116
Fax: +44 1865 251550
E mail: info@clinicalpublishing.co.uk
Web: www.clinicalpublishing.co.uk

Distributed in USA and Canada by:
Clinical Publishing
30 Amberwood Parkway
Ashland OH 44805 USA
tel: 800-247-6553 (toll free within U.S. and Canada)
fax: 419-281-6883
email: order@bookmasters.com

Distributed in UK and Rest of World by:
Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN UK
tel: +44 1235 465500
fax: +44 1235 465555
e mail: trade.orders@marston.co.uk

First published 2008

A catalogue record for this book is available from the British Library

ISBN-13 978 1 84692 018 9
Electronic ISBN 978 1 84692 579 5
ISSN 1476-2188

Project manager: Prepress Projects Ltd, Perth, UK
Printed by Marston Book Services Ltd, Abingdon, Oxford, UK

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Editorial board

Contributors

Kimberly K Amrami, MD
Associate Professor of Radiology, Chair, Division of Body Magnetic Resonance Imaging, Department of Radiology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Sandeep Bawa, MBChB MRCP MSc
Rheumatology Department, Nuffield Orthopaedic Centre, Headington, Oxford, UK

Joanne Burke, BSc PhD
Division of Medical Education, Glasgow University Medical School, Glasgow, UK

Meng May Chee, MBChB(Glas) MRCP
Specialist Registrar, Centre for Rheumatic Diseases, Glasgow Royal Infirmary NHS Trust, Glasgow, UK

Ernest Choy, MD FRCP
Senior Lecturer, Consultant Rheumatologist, Sir Alfred Baring Garrod Clinical Trials Unit, Academic Department of Rheumatology, Kings College Hospital, Weston Education Centre, London, UK

Max Field, BSc MD FRCP
Centre for Rheumatic Diseases, University Dept of Medicine, Queen Elizabeth Building, Glasgow Royal Infirmary, Glasgow, UK

Leroy Griffing, MD
Assistant Professor of Medicine, Rheumatology Department, Mayo Clinic, Scottsdale, Arizona, USA

Ariane Herrick, MD FRCP
Senior Lecturer in Rheumatology, Rheumatic Diseases Centre, Hope Hospital, Salford, Manchester, UK

Raashid Luqmani, DM FRCP (Edin)
Consultant Rheumatologist, Rheumatology Department, Nuffield Orthopaedic Centre, Headington, Oxford, UK

Nisha Manek, MD
Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Iain McInnes, FRCP PhD
Professor of Experimental Medicine and Rheumatology, Centre for Rheumatic Diseases, Glasgow Royal Infirmary, Glasgow, UK

Gayle McKellar, MBChB MRCP
Research Registrar, Centre for Rheumatic Diseases, Glasgow Royal Infirmary NHS Trust, Glasgow, UK

Kevin G Moder, MD
Associate Professor of Medicine, Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

Chetan Mukhtyar, MBBS MD MRCP
Rheumatology Department, Nuffield Orthopaedic Centre, Headington, Oxford, UK

Martin E Perry, MRCP
Centre for Rheumatic Diseases, Glasgow Royal Infirmary NHS Trust, Glasgow, UK

Naveed Sattar, MRCPath PhD
Professor of Metabolic Medicine, Division of Cardiovascular and Medical Sciences, Glasgow Royal Infirmary University NHS Trust, Glasgow, UK

Ram Raj Singh, MD FACP FASN FACR
Professor of Medicine and of Pathology and Laboratory Medicine, Department of Medicine, Division of Rheumatology, Los Angeles, California, USA

Jasvinder Singh, MD
Center for Epidemiological and Clinical Research, Minneapolis VA Medical Center, Minneapolis, Minnesota, USA

Gurkirpal Singh, MD
Adjunct Clinical Professor of Medicine, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, California, USA

Steven Ytterberg, MD
Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Part I

Advances in practice

1

Non-steroidal anti-inflammatory drugs and COX-2 inhibition

GAYLE MCKELLAR, GURKIRPAL SINGH

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) remain one of the most commonly used classes of medications worldwide |**1**|. While the gastrointestinal (GI) toxicity of NSAIDs is well recognized |**2–5**|, recent data indicate increasing concerns with the cardiovascular toxicity of these medications. Several recent studies have demonstrated that the increase in cardiovascular risk is perhaps a 'class effect' of all NSAIDs, and is not related to cyclo-oxygenase-2 (COX-2) selectivity |**6–10**|. In this chapter, we summarize some of the recent studies in this area.

Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I study

Singh G, Fort JG, Goldstein JL, *et al. Am J Med* 2006; **119**: 255–66

BACKGROUND. This paper reported the findings of the Successive Celecoxib Efficacy and Safety Study I: a multinational randomized double-blind controlled trial. The primary outcome measure was upper GI safety of celecoxib compared with non-specific NSAIDs in patients with osteoarthritis (OA). A total of 8800 patients received celecoxib (4400 received 100 mg twice daily and 4400 received 200 mg twice daily) and 4394 received a traditional NSAID (905 participants in North America received naproxen and 3489 participants in the rest of the world received diclofenac). Additional efficacy variables were pain and physical function as measured by patient's assessment of arthritis pain – visual analogue scale, patient global assessment of arthritis and the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.

INTERPRETATION. Of the patients randomized to celecoxib, 37.2% had GI side-effects compared with 40.3% in the NSAID group ($P < 0.001$). It followed that the odds ratio (OR) for complicated upper GI side-effects was higher in the NSAID group: OR 6.02, 95% confidence interval (CI) 1.50–34.57 (Fig. 1.1). After the 12-week intervention period, it

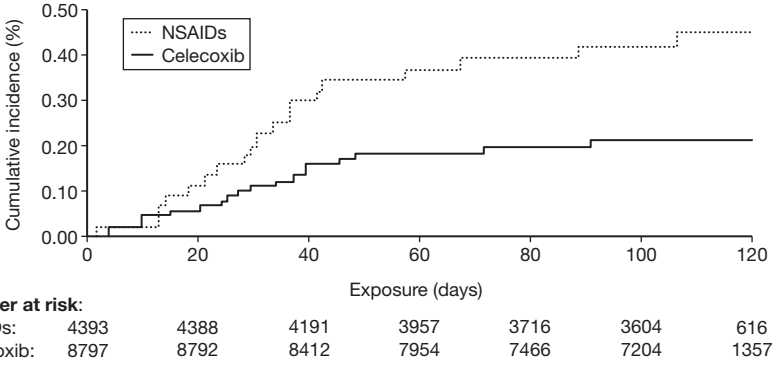

Fig. 1.1 Cumulative risk of confirmed upper GI events in patients treated with celecoxib and NSAIDs (naproxen and diclofenac). Log-rank test for difference, $P = 0.019$. Source: Singh *et al.* (2006).

was found that celecoxib was as effective as traditional NSAIDs in efficacy for treating osteoarthritis symptoms.

Comment

This shows the effectiveness of standard doses of celecoxib in the treatment of OA, with significantly less serious upper GI side-effects recorded. The study failed to show any significant increased number of cardiovascular thromboembolic events – but, importantly, the study was not sufficiently highly powered to look at this.

Cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs and the risk of ischaemic stroke

Andersohn F, Schade R, Suissa S, Garbe E. *Stroke* 2006; **37**: 1725–30

BACKGROUND. Few data exist regarding the risk of ischaemic stroke with COX-2 inhibitors. This large nested case–control study sourced data from the United Kingdom General Practice Research Database (UK GPRD). The first database entry for ischaemic stroke was identified and prescription data interrogated. For each patient receiving a COX-2 inhibitor who experienced an ischaemic stroke, up to four control subjects were randomly selected to assess the risk of treatment.

INTERPRETATION. Current use of rofecoxib and etoricoxib were associated with a significantly increased risk of ischaemic stroke (multivariate OR 1.71 and 2.38 respectively) (Table 1.1). The risk was maintained even if the patient had no prior history of cerebrovascular disease, atrial fibrillation or hypertension. OR was increased with higher daily dose and longer treatment duration of COX-2 therapy.

Table 1.1 Risk of ischaemic stroke associated with COX-2 inhibitors and NSAIDs

	Cases ($n = 3094$)	Control subjects ($n = 11859$)	Adjusted OR (95% CI)*	Multivariate OR (95% CI)†
Non-use‡	643 (20.8%)	2759 (23.3%)	1	1
COX-2-selective NSAIDs§				
Rofecoxib	121 (3.9%)	334 (2.8%)	1.64 (1.30–2.07)	1.71 (1.33–2.18)
Celecoxib	67 (2.2%)	296 (2.5%)	1.02 (0.77–1.36)	1.07 (0.79–1.44)
Etoricoxib	10 (0.3%)	24 (0.2%)	1.84 (0.87–3.86)	2.38 (1.10–5.13)
Non-selective NSAIDs§				
Diclofenac	275 (8.9%)	995 (8.4%)	1.25 (1.06–1.48)	1.32 (1.10–1.57)
Ibuprofen	182 (5.9%)	809 (6.8%)	1.00 (0.82–1.22)	1.12 (0.91–1.37)
Naproxen	39 (1.3%)	173 (1.5%)	1.03 (0.71–1.48)	1.16 (0.80–1.70)
Other NSAIDs	320 (10.3%)	1176 (9.9%)	1.19 (1.02–1.38)	1.20 (1.02–1.40)

*Adjusted for use of the other NSAIDs.
†Adjusted for use of the other NSAIDs and all cerebrovascular risk factors.
‡Non-use of any NSAID during the year before the index date.
§Exclusive categories.
Patients with current use of > 1 NSAID (46 cases, 183 control subjects) are not shown.
Source: Andersohn *et al.* (2006).

Comment

While much has been published on the risk of acute myocardial infarction with COX-2 inhibitors of late, this is one of the first studies to specifically look at risk of stroke. NSAIDs associated with higher rates of hypertension, such as rofecoxib and etoricoxib, also seem to increase the risk of stroke.

Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomized comparison

Cannon CP, Curtis SP, FitzGerald GA, *et al. Lancet* 2006; **368:** 1771–81

Background. This study set out to assess the relative cardiovascular toxicity of diclofenac and etoricoxib in patients with osteoarthritis and rheumatoid arthritis (RA) aged over 50. Patients with cardiovascular and GI risk factors were included in order to assess the widest possible range of patients. A non-inferiority trial design was used. Data were pooled from three separate randomized double-blind clinical trials. In the MEDAL study, the first 4333 patients with OA and all patients with RA were randomized to etoricoxib 90 mg once daily or diclofenac 75 mg once daily; the remaining OA patients were randomized to etoricoxib 60 mg

once daily or diclofenac 75 mg once daily. In the Etoricoxib versus Diclofenac sodium Gastrointestinal tolerability and Effectiveness (EDGE) study: OA patients only, randomized to etoricoxib 90 mg once daily or diclofenac 50 mg three times daily (matching placebo used). In the EDGE II study, which recruited RA patients only, subjects were randomized to etoricoxib 90 mg once daily or diclofenac 75 mg twice daily (matching placebo used). Antihypertensive therapy, aspirin and gastric protection were allowed and encouraged in appropriate cases.

Interpretation. A total of 24 913 patients with OA and 9787 with RA were enrolled. A total of 16 819 patients received etoricoxib and 16 483 received diclofenac. The number of fatal thrombotic, cerebrovascular and peripheral vascular events on etoricoxib was nearly identical to the number observed in patients on diclofenac [hazard ratio (HR) of 0.96, 1.08 and 0.92 respectively]. Rates of upper GI events (perforation, bleeding, obstruction and ulcer) were lower with etoricoxib than with diclofenac (0.67 vs. 0.97 per 100 patient-years) (Fig. 1.2).

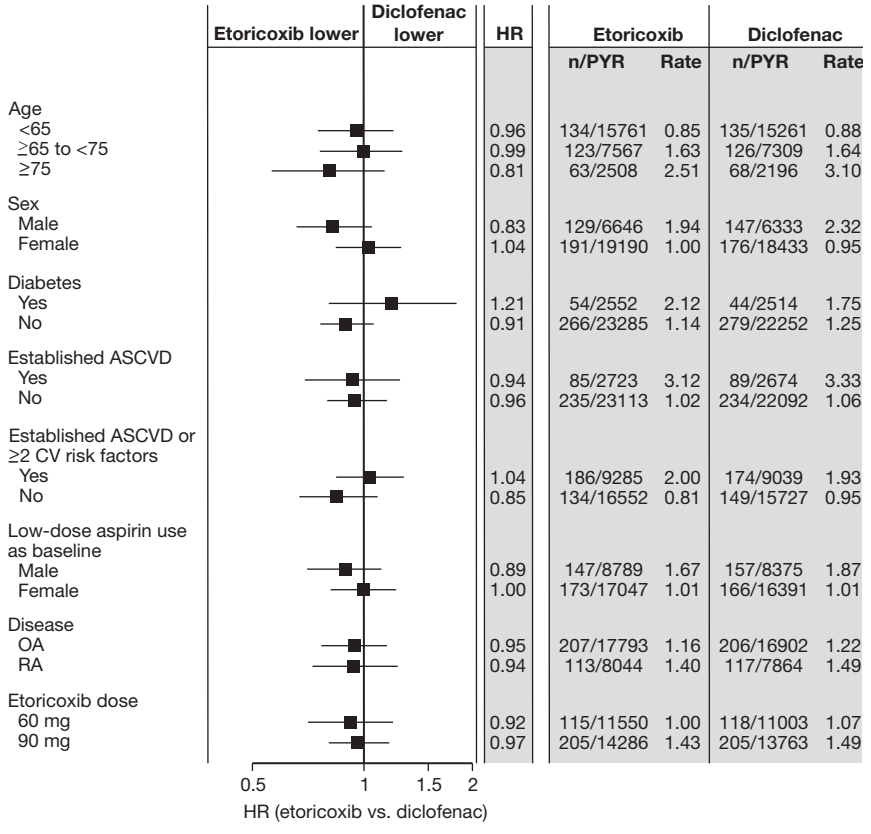

Fig. 1.2 Incidence of thrombotic cardiovascular events in prespecified subgroups, per-protocol population. ASCVD, atherosclerotic cardiovascular disease. Source: Cannon *et al.* (2006).

Comment

Etoricoxib was chosen for its high COX-2 selectivity and few GI side-effects. Diclofenac was chosen as it is the most widely prescribed NSAID and because it does not interfere with the antiplatelet effect of low-dose aspirin. The data show that rates of thrombotic cardiovascular events were similar in both groups. The lack of a placebo group does limit the ability to ascertain the absolute cardiovascular risks of the two drugs.

Cardiovascular risk and inhibition of cyclo-oxygenase

McGettigan P, Henry D. *JAMA* 2006; **296:** 1633–44

BACKGROUND. Controlled observational studies published between 1985 and January 2006 were reviewed systematically in this meta-analysis. Case–control or cohort studies that reported on cardiovascular events with NSAIDs and/or COX-2 inhibitors were eligible.

INTERPRETATION. Of 7086 potentially relevant studies, 23 were reviewed for this article: 17 case–control studies (86 193 cardiovascular events, 528 000 control subjects) and six cohort analyses (75 520 COX-2 users, 375 619 NSAID users, 594 720 unexplained patients). A dose-related increased risk of cardiovascular events was seen with rofecoxib. Naproxen was not associated with a reduced risk. The highest risk of the NSAID group was seen with diclofenac – a drug said to have similar COX-2 properties to celecoxib (Table 1.2).

Comment

A limitation is that the majority of this information comes from databases. In this way, drugs prescribed or dispensed are recorded rather than the drugs actually taken. Non-prescription NSAID or aspirin use cannot be accounted for. However, this study raises concern of the cardiovascular safety of diclofenac, an older drug.

Table 1.2 Risk ratios of cardiovascular events with different NSAIDs and COX-2 inhibitors

Drug	Risk ratio	95% CI
Rofecoxib (≤25 mg/day)	1.33	1.00–1.79
Rofecoxib (≥25 mg/day)	2.19	1.64–2.91
Celecoxib	1.06	0.91–1.23
Diclofenac	1.40	1.16–1.70
Naproxen	0.97	0.87–1.07
Ibuprofen	1.07	0.97–1.18

Table 1.3 Relative risk (RR) of hospitalization for heart failure (HF) associated with NSAID use

Risk factor	Cases ($n = 1396$)	Control subjects ($n = 5000$)	RR*	95% CI
NSAID use				
Non-use	487	2014	1.00	
Current (0–30 days)	196	524	1.32	1.06–1.64
Single use	190	506	1.34	1.08–1.68
Multiple use	2	7	0.37	0.06–2.27
Switch	4	11	1.15	0.33–3.98
Intermediate (31–90 days)	52	188	0.87	0.61–1.25
Recent (91–365 days)	131	470	0.90	0.70–1.16
Past (> 365 days)	530	1804	0.96	0.82–1.13
NSAID duration†				
Non-use	487	2014	1.00	
1–30 days	49	105	1.64	1.11–2.43
31–365 days	54	173	0.98	0.68–1.42
365–730 days	28	62	1.59	0.94–2.69
> 730 days	65	184	1.37	0.98–1.92
NSAID dose†				
Non-use	487	2014	1.00	
Low–medium	101	288	1.27	0.96–1.68
High	89	218	1.44	1.06–1.94
NSAID half-life†				
Non-use	487	2014	1.00	
< 12 h	116	305	1.29	0.99–1.69
≥12 h	39	99	1.44	0.94–2.22
Slow release	35	102	1.44	0.93–2.22

NSAID indication‡				
Non-use	487	2014	1.00	
Rheumatoid arthritis	12	20	1.73	0.79–3.80
Osteoarthritis	144	386	1.33	1.04–1.71
Other pain	104	31	1.13	0.71–1.78
Vascular pain	4	4	2.05	0.48–8.82
Unknown	10	5	1.36	0.39–4.80
NSAID individual use†§				
Non-use	487	2014	1.00	
Indomethacin	13	16	3.39	1.50–7.67
Naproxen	19	38	2.01	1.08–3.74
Diclofenac	60	183	1.08	0.76–1.52
Ibuprofen	60	159	1.43	1.10–2.02
Meloxicam	6	23	0.66	0.24–1.83
Ketoprofen	6	18	1.19	0.43–3.35
Piroxicam	8	25	1.38	0.58–3.28
Other NSAIDs¶	18	44	1.42	0.76–2.68

*Frequency matched on age, sex and calendar year and adjusted for sex, age, calendar year, body mass index, smoking, alcohol, aspirin, steroids, acetaminophen, anticoagulants, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, valvular diseases, rhythm disorders, renal failure, hypertension and hospitalizations in the previous year.
†Among current users vs. non-users of NSAIDs. The effect of daily dose, half-life and individual drugs was analysed among current users of a single NSAID.
‡In 10 control subjects and in five cases the indication was unknown.
§Only if there were five or more exposed cases and control subjects; otherwise categorized as 'other NSAIDs'.
¶Other NSAIDs were aceclofenac, acemetacin, azapropazone, etodolac, fenbufen, fenoprofen, flurbiprofen, mefenamic acid, nabumetone, tenoxicam, tiaprofenic acid and sulindac.
Source: Huerta *et al.* (2006).

Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population

Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA. *Heart* 2006; **92**: 1610–15

Background. A nested case–control study where a cohort from analysing the UK GPRD aged 60–84 years was followed until time of first admission with heart failure. Patients' case records were then interrogated to define NSAID exposure, with a view to evaluating the impact of NSAID use in general, in addition to assessing the effect of individual drugs, doses and durations on the incidence of heart failure (HF) admissions.

Interpretation. A total of 1396 cases of first hospital admission for HF and 5000 matched control subjects were identified and analysed (Table 1.3). Fourteen per cent of patients with HF and 10% of control subjects were NSAID users with an adjusted risk (AR) of 1.5 (95% CI 1.1–1.6) for overall NSAID use. No significant difference was seen with longer duration or higher dose of therapy. The risk of hospitalization varied with different NSAIDs, for example: meloxicam 0.66, diclofenac 1.08, ibuprofen 1.43, naproxen 2.01 and indomethacin 3.39. The incidence of HF increased in the presence of comorbidities (obesity, smoking, previous diagnosis of HF without hospitalization, myocardial infarction, diabetes, hypertension and anaemia) – the adjusted relative risk (RR) of current NSAID use and prior HF = 8.60. The concurrent prescription of antihypertensives with NSAIDs results in a calculated adjusted RR of 3.76.

Comment

The primary indication for NSAID use in 70% of the patients was osteoarthritis. An overall 30% increase in first hospitalization for HF was seen in the NSAID group compared with the general population, with risk said to be slightly higher at the beginning of therapy (although the authors admit that this information is based on only one exposed case). This paper suggests that there should be one extra case of first hospitalization for HF for every 1000 NSAID users aged 60–84 years annually. Concern remains that prescription of NSAIDs in an older age group or in higher-risk patients would cause a further increase in this number and subsequently necessitates caution with their prescription.

Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations

Lanas A, Garcia-Rodriguez LA, Arroyo MT, *et al. Gut* 2006; **55**: 1731–8

Background. The risk of GI bleeding from NSAIDs has been well documented. This study set out to determine the actual risk of upper GI complications with COX-2-selective and traditional NSAIDs alone or in combination in real-life settings.

Interpretation. This hospital-based case–control study reviewed retrospective data collection in addition to prospective case ascertainment. Patients (2777) admitted to hospitals in Spain with haematemesis or melaena and with endoscopic findings of peptic ulcer lesions were identified. Control subjects (5532) were identified, matched by age (± 5 years), hospital and month of admission. Twenty-four per cent of the cases had taken non-aspirin NSAIDs in the week prior to admission compared with 9% of control subjects. For adjusted risks for individual NSAIDS/COX-2s see Table 1.4. Current aspirin use was associated with a RR of 5.3 (4.5–6.3) for upper GI bleeding. This takes into account a RR of 3.8 (2.7–5.2) for a dose of 100 mg daily, to 21.2 (8.7–51.9) for a daily dose of > 1 g. The combination of NSAIDs, aspirin, anticoagulants and clopidogrel was also reviewed (Table 1.5).

Comment

The large sample size reviewed allowed confident identification of the risk of upper GI bleeding with NSAIDs, aspirin and COX-2s – alone and in combination. Of the traditional NSAIDs, diclofenac and ibuprofen had the lowest risk of GI bleed. Of the COX-2s no increased risk was seen with celecoxib but a twofold increase with rofecoxib was identified.

Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems

Lapeyre-Mestre M, Rueda de Castro AM, Bareille M-P, *et al. Fundam Clin Pharmacol* 2006; **20**: 391–5

Background. In the 1980s, a number of NSAIDs were withdrawn because of fatal hepatotoxicity. French and Spanish pharmacovigilance databases regarding adverse drug reports were reviewed over the time period 1982–2001. This was

Table 1.4 Relative risk of upper gastrointestinal bleeding associated with NSAID and COX-2 use

Drug	Adjusted condition RR	95% confidence interval
Celecoxib	1.0	0.4–2.1
Rofecoxib	2.1	1.1–4.0
Diclofenac	3.1	2.3–4.2
Ibuprofen	4.1	3.1–5.3
Naproxen	7.3	4.7–11.4
Piroxicam	12.6	7.8–20.3

Table 1.5 Relative risk of upper gastrointestinal bleeding associated with NSAIDs, COX-2s and anticoagulant use

Combination	Adjusted condition RR	95% confidence interval
NSAID + low-dose aspirin	12.7	7.0–23.0
COX-2 + low-dose aspirin	14.5	3.3–63.9
NSAID + clopidogrel	15.2	4.1–56.5
NSAID + anticoagulant	19.3	8.2–45.3

with the aim of identifying how many of the adverse drug reactions (ADRs) for individual NSAIDs were attributable to liver injury specifically.

Interpretation. In Spain, only 3.38% of all NSAID ADRs were hepatic. This compares with 13.68% of French NSAID reports. Commonly prescribed NSAIDs reporting odds ratios (ROR) include: indomethacin – Spain, 1.02, France, 1.14; ibuprofen – 0.83, 0.75; nabumetone – 0.11, 0.31; celecoxib – 0.64, 0.29; and rofecoxib – 0.17, 0.27.

Comment

The data in this study confirm the high risk of hepatic injury with certain NSAIDs that prompted their withdrawal. A modest number of adverse liver effects were noted for a number of NSAIDs in the years that followed. Differences were seen in France compared with Spain and were thought to be secondary to different reporting rates and differing drug use patterns, along with genetic and environmental factors. This study highlights the importance of the hepatic side-effects of NSAIDs in addition to those of the cardiovascular and upper gastrointestinal systems.

Upper gastrointestinal bleeding associated with antiplatelet drugs

Ibanez I, Vendrell L, Moretti U, *et al. Aliment Pharmacol Ther* 2006; **23**: 235–42

Background. This study set out to establish the risk of major upper GI bleeding associated with various groups of drugs, including in combination with NSAIDs.

Interpretation. A multicentre population-based case–control study for which patients with a first diagnosis of acute upper GI bleed were eligible for inclusion. Those on anticoagulants were excluded from participating. Cases (2813) and their matching control subjects (7193) were reviewed; 20.3% of cases and 11.4% of control subjects were on antiplatelet therapy. A cardioprotective dose of aspirin alone carried an OR of upper GI bleed of 4.0 (95% CI 3.2–4.9) while clopidogrel was associated with an OR of 2.3 (0.9–6.0). When a proton pump inhibitor (PPI) was added, the OR fell to 1.1 and 0.9 for aspirin and clopidogrel respectively. When the combination of any antiplatelet drug

plus NSAID was reviewed, the OR was significantly increased at 17.5 (11.9–25.8). The addition of PPI to this combination reduced the OR to 7.4 (2.2–24.3).

Comment

The data confirm that the risk of upper GI bleed due to the combination of antiplatelet agent and NSAID can be reduced by proton pump inhibition. Clopidogrel is increasingly prescribed in patients with cardiovascular risk; these patients often also have significant risk factors for GI bleeding. Careful consideration should be given to use of concomitant PPIs in such patients.

Upper gastrointestinal mucosal abnormalities and blood loss complicating low-dose aspirin and thrombotic therapy

Taha AS, Angerson WJ, Knill-Jones RP, Blatchford O. *Aliment Pharmacol Ther* 2006; **23**: 489–95

Background. This study was designed to analyse the site of upper GI bleeding lesions in relation to the specific therapies that the patient was taking.

Interpretation. Data from 674 patients presenting to a district general hospital in the west of Scotland with an upper GI bleed were reviewed (Table 1.6). Twenty-eight per cent were found to be on cardioprotective dose of aspirin (75 mg/day) and 12% were on NSAIDs. Overall, 60% were male and 40% of those tested were *Helicobacter pylori* positive.

Comment

A significant association between taking NSAIDs and the presence of gastric or duodenal ulceration at endoscopy after upper GI bleed was confirmed. The study reinforces the fact that low-dose aspirin accounts for a sizeable proportion of serious upper GI bleeds in the community.

Table 1.6 Odds ratios of endoscopic gastrointestinal abnormalities associated with NSAIDs and aspirin

	NSAIDs	Aspirin
Erosive oesophagitis	OR 1 (95% CI 0.29–1) $P = 0.068$	OR 2 (95% CI 1–2) $P = 0.032$
Gastric ulcer	OR 2 (1–3) $P = 0.27$	OR 2 (1–3) $P = 0.15$
Duodenal ulcer	OR 2 (1–4) $P = 0.006$	OR 1 (1–2) $P = 0.093$

The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor

Goldstein JL, Lowry SC, Lanza FL, *et al. Aliment Pharmacol Ther* 2006; **23**: 1489–98

BACKGROUND. The risk of upper GI bleeding associated with aspirin and NSAIDs has long been documented. The newer COX-2 inhibitors have been associated with significantly lower rates of bleeding. Controversy still exists as to whether the GI safety of these drugs persists with concomitant administration of aspirin.

INTERPRETATION. A 7-day multicentre randomized double-blind, double-dummy, placebo-controlled parallel group study was carried out. Patients with a history of positive serology for *Helicobacter pylori*, upper GI erosions, or gastric, pyloric or duodenal ulcer were randomized to aspirin 325 mg daily plus celecoxib 200 mg once daily ($n = 187$), naproxen 500 mg twice daily ($n = 1830$) or placebo ($n = 94$). Other NSAID or COX-2 prescription was strictly prohibited. Initial upper GI endoscopy was performed within 24 h prior to initial administration of study medication, the second performed by the same blinded endoscopist at the end of the 7-day study. A significantly higher proportion of patients in the celecoxib plus aspirin group developed gastric and duodenal ulcers than in the placebo plus aspirin group (RR 2.6, 95% CI 1.2–5.8, $P = 0.008$). A higher incidence of gastric and duodenal ulcers was also observed in the naproxen group compared with the placebo group (RR 3.7, 95% CI 1.8–7.6, $P < 0.001$).

Comment

Fewer endoscopic ulcers were observed in those randomized to celecoxib plus aspirin than in those treated with naproxen plus aspirin. However, COX-2 inhibitor plus aspirin was associated with a higher incidence of ulceration than aspirin alone. The dose of aspirin used in this study is higher than the usual cardioprotective dose (75–81 mg daily) that the majority of our patients will be prescribed. The study shows that, although celecoxib is also associated with gastric and duodenal ulceration, the risk is much less than with a non-selective NSAID, even in the presence of concomitant aspirin therapy.

Conclusion

Selective COX-2 inhibitors continue to be widely used for treatment of pain and inflammation. The SUCCESS-I study is the first large randomized clinical trial to conclusively establish the gastrointestinal safety profile of celecoxib. This is important because a series of large outcome studies have shown no difference in serious gastrointestinal outcomes between etoricoxib and diclofenac |**11**|.

There is considerable evidence to suggest that the GI toxicity profiles of NSAIDs vary widely – drugs such as naproxen have consistently high GI toxicity while diclofenac is relatively less injurious to the GI tract |**12,13**|. Thus, it is important to consider the comparator NSAID while evaluating the GI toxicity of the new COX-2-selective NSAIDs.

It has now been well established that non-COX-2-selective NSAIDs also increase the risk of cardiovascular complications |**14**|. The US Food and Drug Administration (FDA) has required an identical black-box warning on all NSAIDs, both COX-2-selective and non-selective |**15,16**|. The European Agency for the Evaluation of Medicine Products (EMEA) |**17**| and the UK-based Medicines and Healthcare Products Regulatory Agency (MHRA) |**18**| have advised that 'the data is insufficient to warrant changes in current practice'. Thus, decisions regarding selection of an NSAID for chronic treatment must once again be primarily based on the differential gastrointestinal toxicity.

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2

Traditional disease-modifying antirheumatic drugs

HILARY CAPELL, MENG MAY CHEE

Introduction

Over the last decade, there have been a number of promising developments in the treatment of rheumatoid arthritis (RA). While traditional disease-modifying antirheumatic drugs (DMARDs), such as sulphasalazine (SASP) and methotrexate (MTX), remain the mainstay of treatment of RA, there has been further emphasis on a more aggressive approach in the treatment of RA, with early introduction of DMARDs to delay progression of joint damage |**1–5**|. Traditional DMARDs are used singly and increasingly in combination, with parallel 'step-up' or 'step-down' approaches demonstrating efficacious outcomes in several studies |**6–10**|. With the increasing use of biological therapy with anti-tumour necrosis factor α (TNFα), most of the research published over the last year has focused on treatments that include anti-TNFα, their outcomes and side-effects. There have been only a limited number of key publications regarding traditional DMARDs. We aim to review these studies in this chapter.

Trends in DMARD use

The changing use of disease-modifying antirheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database

Edwards CJ, Arden NK, Fisher D, *et al. Rheumatol* 2005; **44**: 1394–8

Background. The United Kingdom General Practice Research Database (UK GPRD) is a national database comprising records of more than 7 million patients from 683 general practices. This is the largest published series of data on DMARD use to date. This study aimed to describe the use of DMARDs and the changing trends in their use over a 15-year period. Patients (*n* = 34 364) with a recorded

diagnosis of RA were identified between 1987 and 2002. The prevalence of RA was 0.5% with an incidence of 0.22% and 71.4% female preponderance, which is comparable with other populations.

Interpretation. In this study, only 50% of patients were prescribed at least one DMARD, with older patients less likely to be treated. The most commonly prescribed DMARD was sulphasalazine (46.3%), followed by methotrexate (31.4%). The relative use of different DMARDs has changed over the 15-year period. Methotrexate use increased more than 17-fold (from 1.8% of all DMARD use in 1988 to 30% in 2002). The reverse trend was seen for gold (13.2% to 2.3%) and penicillamine (14.2% to 2.5%). The use of sulphasalazine and prednisolone has remained fairly stable. The use of combination therapy increased over the study period, reflecting earlier and more aggressive treatment of RA over the last decade. Methotrexate was the DMARD continued for longest, with an estimated median treatment time of 8.1 years.

Trends in disease-modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting rather than by patient disease characteristics

Carli C, Ehlin AGC, Klareskog L, *et al.* for the Swedish Rheumatoid Arthritis Register. *Ann Rheum Dis* 2006; **65**: 1102–5

Background. The study for the Swedish Rheumatoid Arthritis Register aimed to characterize trends and factors associated in DMARD prescription in patients with early RA. Data were obtained from 2584 patients recruited from 19 hospitals (eight university teaching hospitals, six county hospitals and five district hospitals). The associations of DMARD prescription with age, sex, rheumatoid factor, disease duration, type of hospital attended and year of diagnosis were analysed using logistic regression.

Interpretation. In this study, DMARD prescriptions, especially methotrexate, increased in the 5-year study period, independent of patient characteristics. Patients attending district hospitals were less likely to be prescribed DMARDs than those attending university hospitals, independent of confounding factors. However, the association of the DAS28 (Disease Activity Score using 28 joint counts) with the likelihood of DMARD prescription was greater among patients attending district hospitals.

Comment

The UK study provides evidence for a change in pattern of DMARD use over the 15-year period between 1987 and 2002. However, a large number (50%) of patients with a clinical diagnosis of RA have not been appropriately treated, thus highlighting the importance of early referral to specialist care. Patients were identified from primary care records of attendance and, although clinical classification criteria for RA were not used in this data set, it was felt that those patients receiving a DMARD and who attended secondary specialist rheumatological care were likely to have a correct diagnosis. Methotrexate prescription has increased and this is

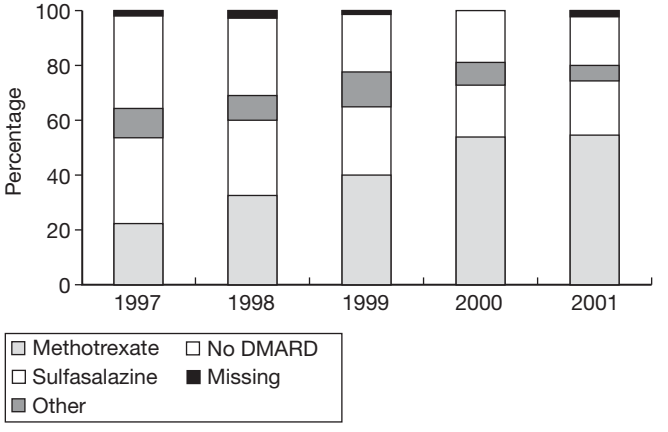

Fig. 2.1 Changing preferences in the type of DMARD prescribed at first consultation in early RA, Swedish Rheumatoid Arthritis Register. Source: Carli *et al.* (2006).

likely to continue. Methotrexate has been shown to be well tolerated given the long median treatment time. Trends will have changed since 2002, when anti-TNFα was introduced, and the UK GPRD will be useful for obtaining further information.

In the Swedish study, there was a trend towards an increasingly aggressive approach to the treatment of early RA from 1997 to 2001 (Fig. 2.1).

In both studies, the use of methotrexate as the first-line DMARD increased throughout the study period, confirming the trend towards more aggressive treatment in RA. It is interesting that in Swedish district hospitals there was greater association between DAS28 and the likelihood of DMARD prescription, but patients attending district hospitals were less likely to be prescribed a DMARD compared with patients attending university hospitals, suggesting that the adoption of research findings in clinical care varies.

Combination therapy

Combination treatment with methotrexate, cyclosporine and intra-articular betamethasone compared with methotrexate and intra-articular betamethasone in early active rheumatoid arthritis (CIMESTRA)

Hetland ML, Stengaard-Pedersen K, Junker P, *et al. Arthritis Rheum* 2006; **54**: 1401–9

Background. This multicentre, randomized, double-blind, placebo-controlled trial aimed to investigate whether disease control in early RA could be achieved and maintained with intensive treatment with methotrexate and intra-articular

steroid, and whether combining with cyclosporine had additional clinical effect or steroid-sparing potential. Patients ($n = 160$) with active RA of less than 6 months, fulfilling 1987 American College of Rheumatology (ACR) criteria for RA, were recruited over 3 years between October 1999 and October 2002. The study consisted of two treatment arms – combination therapy (80 patients) with methotrexate 7.5 mg/week and cyclosporine 2.5 mg/kg/day and monotherapy (80 patients) with methotrexate 7.5 mg/week – and a cyclosporine placebo group. Both treatment groups received intra-articular betamethasone 7 mg/ml in all swollen joints at weeks 0, 2, 4, 6, 8 and every 4 weeks thereafter to week 52. A maximum of four joint injections or 4 ml of betamethasone per visit was allowed. Patients were not allowed oral glucocorticoids. From week 8 onwards, if swollen joints were present, methotrexate was increased by 2.5 mg/week every 4 weeks to a maximum of 20 mg/week. From week 28 onwards, the cyclosporine/placebo dosage was increased by 0.5 mg/day every 4 weeks to a maximum of 4 mg/kg. The primary endpoint was the proportion of patients who achieved American College of Rheumatology 20% (ACR20) improvement criteria responses. The secondary endpoints were clinical remission, the cumulative dose of betamethasone, ACR50 and ACR70 responses and radiographic outcome.

Interpretation. The proportion of patients achieving an ACR20 response at 52 weeks was statistically significantly higher in the combination therapy arm (85%) than in the monotherapy arm (68%) ($P = 0.02$). There were also more patients in the combination therapy arm who achieved ACR50 and ACR70 responses, but the differences were not statistically significant. The median dose of methotrexate at 52 weeks was 12.5 mg/week in the combination group and 15 mg/week in the monotherapy group. In the first 12 weeks, there was no difference in the cumulative dose of betamethasone between the two groups, but from week 12 onwards the cumulative dose was higher in the monotherapy group ($P = 0.03$). The median dose of steroid used was equivalent to < 2 mg of prednisolone per day. Neither treatment arm showed radiographic progression of erosions.

Comment

This was a well-conducted study which showed that aggressive step-up treatment of active early RA with methotrexate and intra-articular corticosteroids, with or without cyclosporine, provided a safe and sustained relief of signs and symptoms of synovitis and delayed radiographic progression. The addition of cyclosporine improved ACR20, but not ACR50 or ACR70, and reduced the need for intra-articular steroid. The results were similar to that achieved with anti-TNFα, which provides further evidence that traditional DMARDs are efficacious, safe and cost-effective.

Combination therapy with sulphasalazine and methotrexate is more effective than either drug alone in rheumatoid arthritis patients with a suboptimal response to sulphasalazine: results from a double-blind placebo-controlled (MASCOT) study

Capell H, Madhok R, Porter D, *et al. Ann Rheum Dis* 2007; **66**: 235-41 [Epub 2006, Aug 22]

BACKGROUND. This randomized controlled study was designed to establish if a combination of the most commonly used DMARDs, SASP and MTX, is superior to either drug alone, as previous studies have not provided firm evidence for this. Patients ($n = 687$) with active RA (DAS > 2.4) and disease duration of < 10 years were recruited between May 1999 and June 2003. In phase I of the study, all patients received SASP 500 mg daily, increasing by 500 mg each week until a target dose of 40 mg/kg/day or maximum tolerated dose was achieved, or maximum dose of 4 g/day. Disease activity was reassessed at 6 months, and those with DAS ≥ 2.4 were offered inclusion into phase II, which was double-blind randomization to three groups: continue SASP with addition of MTX initially 7.5 mg/week (3 × 2.5 mg tablets), increasing by 2.5 mg/month until a maximum permitted dose of 25 mg/week or toxicity occurred; continue SASP with addition of placebo MTX, initially three tablets per week, increasing by one tablet per month until a maximum of 10 tablets per week or toxicity occurred; placebo SASP at previously achieved number of tablets with addition of MTX initially 7.5 mg/week, increasing by 2.5 mg/month until a maximum permitted dose of 25 mg/week or toxicity occurred. Concomitant NSAID and other medications were continued. Intra-articular or intramuscular corticosteroids was permitted, but not within 1 month of 6-, 12- or 18-month assessments. Patients in phase II were then assessed by research nurses every 3 months until 18 months. Radiographs of hands and feet were taken at 6 and 18 months. The primary endpoint was reduction in DAS and secondary endpoints were the proportion of patients achieving a good response (DAS < 2.4 or fall of > 1.2 from baseline) and ACR20, 50 and 70 responses.

INTERPRETATION. At the end of phase I, 137 patients had discontinued SASP, mainly because of side-effects, three had died and 25 failed to attend. Of the remaining 522 patients, 356 were not randomized to phase II as 191 patients were 'too good' with DAS < 2.4, 123 patients declined additional treatment as they were satisfied with progress and 40 patients were considered inappropriate by the physician due to intercurrent illness. One hundred and sixty-five patients were therefore randomized to SASP alone, MTX alone and combination therapy, with 41/55 patients, 38/54 patients and 40/56 patients completing the study respectively (Table 2.1). DAS in the combination arm was significantly better than in either SASP or MTX monotherapy ($P = 0.039$ and $P = 0.023$ respectively). There was no significant difference between SASP alone and MTX alone ($P = 0.79$). The study was not sufficiently highly powered to evaluate radiological progression and radiographic outcomes showed no significant difference in total Sharp scores.

Table 2.1 ACR20,50 and 70 responses in phase II

	Combination ($n = 56$)	SASP alone ($n = 55$)	MTX alone ($n = 54$)
ACR20	48	32	33
ACR50	25	10	7
ACR70	13	7	4

Source: Capell *et al.* (2006).

Comment

More than a third of patients achieved DAS < 2.4 on just SASP alone after 6 months and almost a quarter of patients were satisfied with their progress at 6 months and therefore declined additional treatment. At 18 months, improvement on combination therapy was significantly better than with monotherapy with either SASP or MTX alone. In this study, a combination of SASP and MTX proved safe and more effective than either drug alone in patients with a suboptimal response to SASP after 6 months. This study reflected a 'true-to-life' approach to treatment of RA in a number of Scottish rheumatology centres.

Clinical and radiological outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt Study)

Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, *et al. Arthritis Rheum* 2005; **52**: 3381–90

Background. This Dutch multicentre, randomized clinical trial was designed to compare clinical and radiographic outcomes of four different treatment strategies for early RA to help determine the optimal strategy for preventing long-term joint damage and functional decline. Patients ($n = 508$) were recruited between April 2000 and August 2002 and allocated to the following four strategies. Group 1 (126 patients) received sequential monotherapy starting with MTX 15 mg/week, increasing to 25–30 mg/week if DAS44 > 2.4. If response was insufficient, they were switched to SASP monotherapy, then leflunomide monotherapy, then MTX with infliximab, then gold with methylprednisolone, then MTX with cyclosporine A and prednisolone. In group 2 (121 patients), step-up combination therapy started with MTX 15 mg/week, increasing to 25–30 mg/week if DAS44 > 2.4. If response was insufficient, SASP was added, then hydroxychloroquine (HCQ), then prednisolone. If patients failed to respond on four agents, they were switched to MTX with infliximab, then MTX with cyclosporine A and prednisolone, then leflunomide monotherapy. In group 3 (133 patients), initial combination therapy with tapered high-dose prednisolone started with MTX 7.5 mg/week + SASP 2 g/day + 60 mg prednisolone/day. Prednisolone was tapered over 7 weeks to 7.5 mg/day. If DAS44 was > 2.4, MTX was increased to 25–30 mg/week. If response was still insufficient, MTX with cyclosporine A and prednisolone was substituted, then MTX with infliximab, then leflunomide monotherapy, then gold with methylprednisolone and, finally, azathioprine and prednisolone. If DAS44 was ≤ 2.4, prednisolone was tapered to 0 mg after 28 weeks and then MTX was

tapered to 0 mg after 40 weeks. In group 4 (128 patients), initial combination therapy with infliximab started with MTX 25–30 mg/week plus infliximab initially at 3 mg/kg in weeks 0, 2, 6 and 8. After 3 months, if DAS44 was > 2.4, infliximab was increased to 6 mg/kg, then 7.5 mg/kg, then 10 mg/kg every 8 weeks if DAS44 remained > 2.4 measured before each infusion. If DAS44 was still > 2.4 at an infliximab dose of 10 mg/kg, patients were switched to SASP monotherapy, then leflunomide monotherapy, then MTX with cyclosporine A and prednisolone, then gold and methylprednisolone and, finally, azathioprine and prednisolone. Primary endpoints were functional ability, measured by the Dutch version of the Health Assessment Questionnaire (D-HAQ), and radiographic joint damage, assessed according to the modified van der Heijde–Sharp score.

INTERPRETATION. At 1-year follow-up, more patients in groups 3 and 4 than in groups 1 and 2 remained at the initial stage of treatment, as they had sustained DAS44 of ≤2.4. Seventy-eight per cent of patients in group 3 stopped prednisolone and 50% in group 4 stopped infliximab. Clinical improvement was achieved earlier and by more patients in groups 3 and 4 than in groups 1 and 2. Patients in groups 3 and 4 had less progression of radiographic joint damage than patients in groups 1 and 2, with a statistically significant difference ($P = 0.003$ for group 1 vs. group 3, $P < 0.001$ for group 1 vs. group 4, $P = 0.007$ for group 2 vs. group 3 and $P < 0.001$ for group 2 vs. group 4). There were also more patients from groups 3 and 4 with no radiographic joint damage progression. Patients with early RA treated with initial combination therapy with prednisolone or infliximab had earlier functional improvement with less progression of radiographic joint damage and fewer side-effects than patients who were treated with sequential monotherapy or step-up combination therapy. The step-up approach was superior to sustained monotherapy.

Comment

This study used very complex treatment regimens, which makes the interpretation and generalizability difficult. Anti-TNFα treatment is known to be superior to conventional DMARDs, and having a treatment arm with anti-TNFα may mask the efficacy of the conventional DMARDs in this study. The dose of infliximab used in group 4 (10 mg/kg) was much higher than that permitted in many centres. Ten milligrams per kilogram is three times as expensive as 3 mg/kg and widespread use would have an adverse effect on drug budgets. Longer-term follow-up of this cohort will be of interest.

Comparing the long-term clinical outcome of treatment with methotrexate or sulphasalazine prescribed as the first disease-modifying antirheumatic drug in patients with inflammatory polyarthritis

Hider SL, Silman A, Bunn D, *et al. Ann Rheum Dis* 2006; **65**: 1102–5

BACKGROUND. Previous surveys have suggested that, although MTX is the most commonly preferred first DMARD for inflammatory polyarthritis, SASP remains first choice among some rheumatologists. Both drugs have similar efficacy, but there

are few data comparing the long-term outcome of either drug as the preferred DMARD. This was a prospective cohort study of patients recruited from primary care to compare the clinical, functional and radiographic outcomes at 2 and 5 years in patients with inflammatory polyarthritis who were treated with either MTX or SASP as the first DMARD. Patients ($n = 2659$) from the Norfolk Arthritis Register (NOAR) were recruited between 1990 and 1999, with 331 patients on SASP and 108 patients on MTX included in the study. The outcomes assessed were DAS28, Health Assessment Questionnaire (HAQ), radiological erosions using Larsen score and cumulative mortality at 2 and 5 years. Patients were started on either SASP 2 g/day or MTX 7.5 mg/week. Baseline DAS28, C-reactive protein (CRP) and HAQ scores were similar between the two groups. Patients starting on SASP were younger at diagnosis and had higher swollen and tender joint counts. More patients in the MTX group were co-prescribed steroids. Approximately 75% of patients with inflammatory polyarthritis were treated with SASP. The propensity score was used as a method for adjusting for potential bias in allocation of treatment. Outcomes were compared between treatment groups after adjusting for propensity score.

Interpretation. At 2 years, there were declines in both swollen and tender joint counts and mean HAQ score, which were similar between the two drugs. A higher proportion of patients taking MTX (56%) than of patients taking SASP (50%) had no change in treatment. At 5 years, information was also available for CRP (hence DAS28) and radiological erosions. There were statistically significant larger falls in swollen and tender joint counts in the SASP group than in the MTX group. These joint counts were higher in the SASP group at baseline and, after adjustment for the propensity score and baseline score, there was no significant difference in the change in either joint count between the treatment groups. The proportions or erosive and mean Larsen scores were higher in the SASP group but the differences were not significant. The mean difference in Larsen score after adjustment was 31% lower in the MTX group, although this was not statistically significant. More patients in the MTX group were still taking MTX as their first DMARD (34% vs. 22%), giving a 2.2-fold greater drug survival after adjusting for propensity. A considerable number of patients at both the 2-year and 5-year points were not taking the first DMARD prescribed, some having switched to a different DMARD and some having stopped. Mortality was slightly higher in the MTX group (10%) than in the SASP group (7%), but this may reflect slightly higher age at onset. Forty-one per cent of patients starting SASP had switched to MTX at some stage, but only 13% switched in the opposite direction. Both MTX and SASP are effective agents in the treatment of inflammatory polyarthritis showing similar long-term outcomes. From this study, MTX was better tolerated, with patients twice as likely to remain on MTX as SASP.

Comment

Being an observational study, there would have been unmeasured variables influencing treatment allocation. Treatments were added or discontinued as clinically indicated in relation to the patient's clinical state. There were no data regarding co-prescription of NSAIDs or steroids. However, data were collected to examine 5-year radiological outcomes, which is not easily achievable in clinical

trials. This showed that MTX was better tolerated, thus supporting its use as the initial DMARD. This large cohort study, although observational, does provide wider applicability to normal daily practice.

Joint surgery in the Utrecht Rheumatoid Arthritis Cohort: the effect of treatment strategy

Verstappen SMM, Hoes JN, ter Borg EJ, *et al.* on behalf of the Utrecht Rheumatoid Arthritis Cohort study group. *Ann Rheum Dis* 2006; **65**: 1506–11

BACKGROUND. Joint surgery is seen as an unfavourable outcome measure in the course of RA. It has been estimated that 25% of patients with RA undergo total joint arthroplasty within 23 years of disease onset. This retrospective study of 482 RA patients in Utrecht, the Netherlands, aimed to investigate the prevalence of joint surgery in these patients and prognostic factors leading to joint surgery. Patients were recruited from 1990 until 1998 and randomized to two treatment strategies – an early DMARD strategy vs. a delayed DMARD strategy. In the early DMARD group, at diagnosis, patients were randomly allocated to one of three treatment arms – methotrexate, intramuscular gold or hydroxychloroquine. Patients in the delayed DMARD group did not receive DMARDs but were given NSAIDs at the point of diagnosis. DMARDs were used if necessary during follow-up. Patients were seen every 3 months for the first 2 years and then every 6 months thereafter to assess disease activity. Disease activity was assessed using erythrocyte sedimentation rate (ESR), pain on visual analogue scale (VAS), Thompson joint score (a weighted score including swollen and tender joints), duration of morning stiffness and functional disability using the Dutch Health Assessment Questionnaire. Radiographs of hands and feet were scored at baseline and yearly thereafter using the van der Heijde–Sharp method.

INTERPRETATION. Four hundred and eighty-two out of 590 patients were followed up for at least 2 years; 71% were women and 65% were rheumatoid factor positive. The median age was 56 years and the average disease duration was 7.2 years. One hundred and thirty patients (27%) underwent a total of 240 surgical interventions – 65 patients (50%) had one intervention, 39 patients (30%) two, 15 patients (12%) three, three patients (2%) four and eight patients (6%) had five interventions, which was the maximum per patient. Seventeen per cent were minor interventions, e.g. arthroscopy, carpal tunnel decompression and rheumatoid nodule removal, 53% were intermediate, e.g. arthrodesis, synovectomy, small joint replacement or resection arthroplasty, and 30% were major interventions, e.g. joint replacements of hip, knee, shoulder, elbow, ankle and wrist. Patients in the NSAID/delayed DMARD group were more likely to require surgical intervention ($P = 0.036$). Forty-four per cent of patients in the early DMARD group showed good response to treatment at 1 year compared with 25% in the NSAID/delayed DMARD group ($P = 0.012$). This was less significant after 2 years' follow-up ($P = 0.95$). However, the percentage of patients needing surgical intervention in the entire cohort after 1 year was lower in the group that showed good response (both early DMARD and NSAID/delayed DMARD groups), and this was statistically significant at 2 years ($P = 0.012$).

Comment

This study provides further evidence that good disease control prevents disease progression and structural joint damage by showing that early treatment with DMARDs results in less joint surgery than delayed treatment, and that patients who respond to treatment in the first 2 years are less likely to require joint surgery. This, however, was a retrospective study, with data on joint surgery collected through case records, and the primary indication for joint surgery was not always confirmed. It is possible that some patients may have had surgery performed elsewhere. It does, however, support the already widely accepted evidence that early and aggressive treatment of RA with DMARDs is beneficial and has the potential to reduce need for surgical resources.

Conclusion

Methotrexate and sulphasalazine remain anchor DMARDs in the treatment of RA. Current research interest in the treatment of RA is focused mainly on anti-TNFα therapy. However, there has been evidence showing comparable response to aggressive treatment and tight control of RA with traditional DMARDs |**11**|. The few key studies on traditional DMARDs over the last year have shown a continuing trend towards early use of DMARDs in the treatment of RA, with combination therapy showing more efficacy than monotherapy, without an increase in side-effects. Response to treatment in the CIMESTRA trial showed similar results to that achieved with anti-TNFα therapy. As the long-term side-effects of anti-TNFα therapy are yet to be determined, this finding is encouraging. It confirms that traditional DMARDs are efficacious and are probably more cost-effective than anti-TNFα therapy, hence providing accessible treatments to patients with RA in countries with tight constraints on health budgets.

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3

Biologics

ERNEST CHOY

Introduction

The advent of tumour necrosis factor (TNF) antagonists for the treatment of rheumatoid arthritis (RA) was a major landmark in rheumatology. Since then, the use of biologics has expanded to other rheumatic diseases, especially ankylosing spondylitis (AS) and psoriatic arthritis (PsA). As the numbers of patients treated with biologics have increased, the numbers of primary and secondary non-responders to TNF antagonists have also steadily risen. The therapeutic options for these patients, including switching to another TNF antagonist or alternative biologic, are becoming a clinical dilemma especially with the availability of rituximab and abatacept for treating RA. However, it is unclear which option is best. In the absence of good biomarkers to predict response to biologics, the decision may be decided by healthcare providers based on health economics. In the UK, the National Institute for Health and Clinical Excellence (NICE) has utilized cost-effectiveness analyses on which to base its funding decisions for many years. Similar agencies have been established in Europe. It seems clear that health economics will become increasingly important in determining how biologics will be used in clinical practice.

Anti-TNF therapy

Overview

Although TNF antagonists have been used for treatment of RA since 1999, their long-term safety remains uncertain. National Registries such as the British Society for Rheumatology Biologics Register (BSRBR), which were established to address and monitor safety of TNF antagonists, are starting to provide answers to questions on medium-term toxicity. In 2006, a number of cost-effectiveness studies of TNF antagonists have highlighted some methodological issues, which need to be addressed for future studies.

Cost-effectiveness of biological agents for treatment of autoimmune disorders: structured review of the literature

Fleurence R, Spackman E. *J Rheumatol* 2006; **33**: 2124–31

Background. In the new era of expensive biological treatments, cost-effectiveness analysis has become increasingly used to decide whether such treatments are funded by healthcare providers. This systematic review examines the pharmacoeconomic evidence for TNF antagonists in autoimmune diseases.

Interpretation. This is an important review as it highlighted one of the key methodological issues in cost-effectiveness analyses. The estimate is affected by assumptions. Using different standard cases will affect the result of the modelling. Generating standard reference cases for different diseases will help to standardize this in future.

Comment

Using a threshold of US$50 000 per quality-adjusted life-year (QALY), there was evidence to support the use of TNF antagonists in established RA although there are large variations in precise estimates due to the lack of reference cases.

This study concluded that, in established RA, TNF antagonists are cost-effective, but the lack of standard reference cases resulted in large variations in estimates.

Cost-effectiveness of tumour necrosis factor alpha inhibitors as first-line agents in rheumatoid arthritis

Spalding JR, Hay J. *Pharmacoeconomics* 2006; **24**: 1221–32

Background. This study assessed the cost-effectiveness of TNF inhibitors as first-line treatment for patients with early RA, either as monotherapy or in combination with methotrexate (MTX), vs. MTX based on a US population.

Interpretation. The increment cost-effectiveness ratios (ICERs) of TNF antagonists used as monotherapy for early RA suggest that these drugs may be cost-effective depending on the threshold for cut-off.

Comment

The ICERs for adalimumab, etanercept, adalimumab plus methobrexate and infliximab plus methobrexate were $US63 769, $US89 772, $US194 589 and $US409 523 per QALY respectively.

In combination with MTX, TNF antagonists are not cost-effective. However, etanercept or adalimumab monotherapy may be regarded as cost-effective depending on whether the cost-effectiveness threshold is drawn at $US50 000 or $US100 000/QALY.

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

Chen YF, Jobanputra P, Barton P, *et al. Health Technol Assess* 2006; **10**: 1–248

Background. This systematic review was carried out as part of the Health Technology Assessment for NICE appraisal of TNF antagonists for the treatment of RA.

Interpretation. In established RA, TNF antagonists are cost-effective. In early RA, MTX plus TNF antagonists are superior to MTX monotherapy but the ICER is high. In a study by Spalding *et al.* |**1**|, the ICER of TNF antagonists as first-line treatment in RA was found to be higher than for established RA. However, the exact threshold at which healthcare providers base their decision on whether a treatment is funded is arbitrary.

Comment

This systematic review included 29 randomized controlled trials (RCTs) of TNF antagonists in RA. All three antagonists, either alone or in combination with disease-modifying antirheumatic drugs (DMARDs), were effective in reducing the symptoms and signs of RA in patients with established disease. The numbers needed to treat (95% confidence intervals) are shown in Table 3.1. In early RA, both adalimumab and etanercept monotherapy were more effective than MTX in slowing radiographic joint damage, although improvement in symptoms and signs was similar.

The ICER for etanercept was £24 000/QALY, for adalimumab £30 000/QALY and for infliximab £38 000/QALY. In first-line use as a monotherapy, the ICER for adalimumab and etanercept was around £50 000/QALY. Combination with MTX in early RA generated much higher ICERs, as it precludes subsequent use of MTX, which is cheap.

TNF antagonists are cost-effective treatments for established RA when used in accordance with the 2002 NICE guidance.

Table 3.1 Number needed to treat (95% confidence interval) to achieve different American College of Rhuematology (ACR) response criteria with tumour necrosis factor inhibitors

	ACR20	ACR50	ACR70
Etanercept	2.1 (1.9–2.4)	5.0 (3.8–6.7)	7.7 (6.3–10.0)
Infliximab	3.2 (2.7–4.0)	3.1 (2.7–3.6)	11.1 (7.7–20.0)
Adalimumab	3.6 (3.1–4.2)	4.2 (3.7–5.0)	7.7 (5.9–11.1)

Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis

Bansback NJ, Ara R, Barkham N, *et al. Rheumatology* 2006; **45**: 1029–38

Background. This study examined the effect of etanercept on long-term health status and evaluated the cost-effectiveness in PsA using a model in which etanercept was used after failure of two DMARDs.

Interpretation. This study found etanercept cost-effective for the treatment of PsA, which supported the decision by NICE to approve NHS funding for TNF antagonists for the treatment of PsA in the UK.

Comment

This study found that over the long term etanercept is more likely to produce greater improvement in health-related quality of life (HRQoL). Such improvement is cost-effective when compared with cyclosporine and leflunomide.

Etanercept seems cost-effective for the treatment of PsA.

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation

Woolacott N, Bravo Vergel Y, Hawkins N, *et al. Health Technol Assess* 2006; **31**: 1–239

Background. This study formed part of the technology appraisal by NICE to assess the use of TNF antagonists for the treatment of PsA.

Interpretation. The finding of this study supported the study by Bansback *et al.* |**2**| and concluded that TNF antagonists are cost-effective treatment for PsA.

Comment

The systematic review showed that TNF antagonists improved both arthritis and skin disease. There was also strong evidence that they improved function and that etanercept reduced joint damage. The ICER gained of etanercept compared with palliative care ranged from £14 818/QALY to £49 374/QALY.

This study concluded that etanercept is cost-effective for the treatment of PsA.

Comparison of the response to infliximab or etanercept monotherapy with the response to co-therapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register

Hyrich KL, Symmons DP, Watson KD, Silman AJ. British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; **54**: 1786–94

Background. A previous pragmatic trial |3| suggested that TNF antagonists could be used safely in combination with DMARDs in RA. This study utilized data from the BSRBR to examine the relative efficacy and toxicity of TNF antagonist monotherapy and in combination with DMARDs.

Interpretation. Although the result of this study supports the use of TNF antagonists in combination with DMARDs over monotherapy, the lack of a randomized control trial precludes definitive conclusions to be drawn.

Comment

Based on data from 2711 patients starting treatment with TNF antagonists, it was found that, for infliximab, the likelihood of response was 1.4 (95% CI 0.9–2.0) for the addition of methotrexate and 1.3 (95% CI 0.8–2.1) for other DMARDs vs. monotherapy. Similar results were obtained for etanercept.

Infliximab and etanercept appear to be more efficacious when used in combination with methotrexate or another DMARD than as monotherapy in RA.

Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register

Dixon WG, Watson K, Lunt M, *et al. Arthritis Rheum* 2006; **54**: 2368–76

Background. One of the concerns of TNF blockade is the risk of serious infection. The BSRBR is the only register in which patients with RA taking DMARDs were recruited as control subjects. The study assessed whether the rate of serious infection is higher in RA patients treated with TNF antagonists than in DMARD-treated control subjects.

Interpretation. TNF antagonist treatment increased risk of serious skin and soft-tissue infections, but the overall risk of serious infection was not increased. TNF is important in the immune defence against intracellular pathogens. The data from the

BSRBR suggest that TNF antagonists are associated with an increased risk of bacterial intracellular infection but the absolute risk is small.

Comment

This national prospective observational study compared the incidence of serious infection in 7664 TNF antagonist-treated patients with 1354 DMARD-treated control subjects. The frequency of serious skin and soft tissue infections was increased in anti-TNF-treated patients, with an adjusted incidence rate ratio of 4.28 (95% CI 1.06–17.17). There was no difference in infection risk between the three main anti-TNF drugs; however, 19 serious bacterial intracellular infections occurred, exclusively in patients in the anti-TNF-treated cohort.

TNF antagonist-treated RA patients have an increased risk of serious skin and soft tissue infections, but the overall risk of serious infection is not increased.

Outcomes after switching from one anti-tumour necrosis factor alpha agent to a second anti-tumour necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study

Hyrich KL, Lunt M, Watson KD, *et al.* British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007; **56**: 13–20

Background. With the increasing number of primary and secondary non-responders to TNF antagonists, switching to another TNF inhibitor has become a common practice. This study compared drug discontinuation rates between the first and second courses of anti-TNF therapy using data from the BSRBR.

Interpretation. The cause of discontinuation of first TNF antagonist treatment is a significant predictor of the reason to discontinue the second TNF antagonist.

Comment

Overall, 73% of patients who switched to a second anti-TNF agent remained on the new therapy by the end of follow-up. First drug discontinuation due to inefficacy was associated with a 2.7-fold increase in the rate of second drug discontinuation due to inefficacy. Discontinuation of the first TNF antagonist as a result of toxicity was associated with a doubling in the rate of second drug discontinuation due to toxicity.

Discontinuation of the first TNF antagonist due to inefficacy or toxicity predisposes discontinuation of the second anti-TNF drug for the same reason.

Infliximab

Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus

Aringer M, Steiner G, Graninger WB, *et al. Arthritis Rheum* 2006; **56**: 274–9

Background. Development of autoantibodies was noted during initial clinical trials of infliximab in patients with RA, raising concern over the safety of infliximab. Since then some researchers have reported clinical benefits of TNF antagonists in patients with systemic lupus erythematosus (SLE). This study examined the effect of infliximab on autoantibody titres in SLE patients treated with infliximab.

Interpretation. Transient increases in autoantibody titres were observed in SLE patients treated with infliximab, but these did not correlate with disease activity. Examining the epitopes for these antibodies may help to explain why they are unrelated to disease activity.

Comment

Anti-dsDNA antibodies were increased in five out of seven patients with SLE treated with infliximab plus azathioprine or methotrexate. Antibodies to histone and chromatin, and IgM anti-cardiolipin antibodies were also increased in four, six and four patients, respectively, but fell to baseline levels or lower thereafter. Most patients improved clinically.

A transient increase in autoantibodies was observed in SLE patients treated with infliximab despite clinical improvement after treatment.

Regulation of serum chemokines following infliximab therapy in patients with rheumatoid arthritis

Klimiuk PA, Sierakowski S, Domyslawska I, Chwiecko J. *Clin Exp Rheumatol* 2006; **24**: 529–33

Background. Previous immunohistological study |4| has shown that infliximab reduced expression of adhesion molecules in the rheumatoid synovium. This study examines whether infliximab reduces production of chemokines, which are key mediators of leucocyte trafficking into the synovium.

Interpretation. Chemokines are released by activated monocytes and macrophages to promote leucocyte trafficking, thereby amplifying the inflammatory response. Together with previous study, this supports the notion that one of the key modes of action of infliximab is reducing leucocyte trafficking, although it is possible that reduction in serum chemokine levels merely reflects a general reduction in inflammation.

Comment

Infliximab reduced serum levels of interleukin 8 (IL-8), regulated upon activation, normal T-cell expressed and secreted (RANTES) protein and monocyte chemoattractant protein-1 (MCP-1). The decrease was greatest after the first treatment. Subsequent infliximab treatments also significantly decreased serum chemokines levels, but were less effective.

This study suggested that one mode of action of infliximab is reducing leucocyte trafficking in RA.

Etanercept

Randomized phase II trial of anti-tumour necrosis factor therapy for cachexia in patients with early rheumatoid arthritis

Marcora SM, Chester KR, Mittal G, *et al. Am J Clin Nutr* 2006; **84**: 1463–72

Background. TNF was originally known as cachectin as it was isolated from cancer patients with severe cachexia. It has been assumed that TNF is responsible for the weight loss that is associated with active RA; however, this has not been formally proven. This RCT investigated the metabolic effect of etanercept on body composition in patients with early RA.

Interpretation. This study supports the hypothesis that TNF is a key mediator of weight loss in patients with active RA. Blocking TNF leads to significant increase in weight.

Comment

Twenty-six early RA patients were randomized to treatment with etanercept or methotrexate. Etanercept and methotrexate produced similar suppression of synovitis. Disease activity score was similar in etanercept- and methotrexate-treated patients. Patients treated with etanercept experienced significant weight gain: 44% vs. 14% in the methotrexate group.

Etanercept treatment in early RA leads to a greater increase in weight than methotrexate despite a similar degree of improvement in synovitis.

Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis

van der Heijde D, Da Silva JC, Dougados M, *et al. Ann Rheum Dis* 2006; **65**: 1572–7

Background. This 12-week, double-blind, placebo-controlled study compared the efficacy, pharmacokinetics and safety of etanercept 50 mg once weekly with 25 mg twice weekly and placebo in patients with AS.

Interpretation. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in the treatment of AS. Less frequent injection will be welcome by patients with AS.

Comment

The primary endpoint of this study was Assessment in Ankylosing Spondylitis International Working Group criteria for improvement (ASAS20) response at 12 weeks, which was achieved by 74.2%, 71.3% and 37.3% of patients treated with etanercept 50 mg once weekly, etanercept 25 mg twice weekly and placebo respectively. The incidence of treatment-related adverse events, including infections, was similar among all three groups.

Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in the treatment of AS.

Adalimumab

Clinical assessment of pain, tolerability, and preference of an autoinjection pen versus a prefilled syringe for patient self-administration of the fully human, monoclonal antibody adalimumab: the TOUCH trial

Kivitz A, Cohen S, Dowd JE, *et al. Clin Ther* 2006; **28**: 1619–29

Background. Adalimumab is administered subcutaneously by a ready-to-use, prefilled syringe. This study compared administration of adalimumab by a syringe or an autoinjection pen.

Interpretation. Patients preferred the autoinjection pen to the ready-to-use, prefilled syringe. The former caused less pain and most patients found it more convenient to use. As biologics are often administered by subcutaneous injections, improving the method of drug delivery will greatly benefit patients especially those with significant disability in their hand function.

Comment

This was a multicentre, open-label, single-arm, sequential study in which 52 patients self-administered a standard dose of adalimumab 40 mg subcutaneously every other week on three occasions. The first was administered by ready-to-use, prefilled syringe and the second and third by autoinjection pen. Most patients (76.9%) found the pen less painful. Only 7.7% of patients found the syringe to be less painful. Pain

score was statistically significantly reduced from visit 1 to visit 2 and from visit 1 to visit 3. The majority of patients (88.5%) preferred the pen and over 90% found it more convenient to use.

Administration of adalimumab by autoinjection pen is preferable to administration via syringe.

Interleukin 6

The exact cause of RA is not fully understood; however, proinflammatory cytokines are involved in the development of the disease. These cytokines and their actions are potential therapeutic targets in RA. Interleukin 6 (IL-6) is a pleiotropic inflammatory cytokine that is produced by T-cells, monocytes, macrophages and synovial fibroblasts |**5**|. Raised levels of IL-6 have been found in both serum and synovial fluid in patients with RA, and serum levels of IL-6 correlate with disease activity and radiographic joint damage |**6**|. Administration of mouse monoclonal anti-IL-6 antibody to five patients with RA has been shown to ameliorate disease activity |**7**|.

Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist tocilizumab in European patients with rheumatoid arthritis who had an incomplete response to methotrexate

Maini RN, Taylor PC, Szechinski J, *et al. Arthritis Rheum* 2006; **54**: 2817–29

Background. Recent trials in RA using tocilizumab, a humanized anti-human IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to IL-6 receptor, have shown positive results |8,9|. This multicentre, randomized, double-blind, placebo-controlled trial examined the effect of tocilizumab monotherapy or in combination with MTX in patients with established RA.

Interpretation. Tocilizumab monotherapy or in combination with methotrexate suppressed joint inflammation, and improved symptoms and signs in patients with established RA

Comment

Patients with RA (359) who were partial responders to MTX were randomized to one of seven treatment arms: tocilizumab monotherapy at doses of 2 mg/kg, 4 mg/kg, or 8 mg/kg either as monotherapy or in combination with MTX, or MTX plus placebo. American College of Rheumatology 20% (ACR20) improvement criteria response was achieved by 31%, 61% and 63% of patients receiving 2, 4 and 8 mg/kg tocilizumab monotherapy respectively, and by 64%, 63% and 74% of patients receiving those doses of tocilizumab plus MTX respectively, compared with

41% of patients receiving placebo plus MTX. Clinical and statistical significant improvements were observed from week 4 onward in all patients except those receiving 2 mg/kg of tocilizumab monotherapy. Increases in liver transaminases and non-fasting total cholesterol and triglyceride levels were observed. These were reversible on discontinuation of therapy.

These results indicate that targeted blockade of IL-6 by tocilizumab either as monotherapy or in combination with MTX is efficacious and a promising new therapy for RA (Fig. 3.1).

B-cell depletion

Rituximab was licensed for the treatment of RA in 2006. It is a chimeric anti-CD20 monoclonal antibody that deletes CD20-positive B-cells. CD20 is expressed by

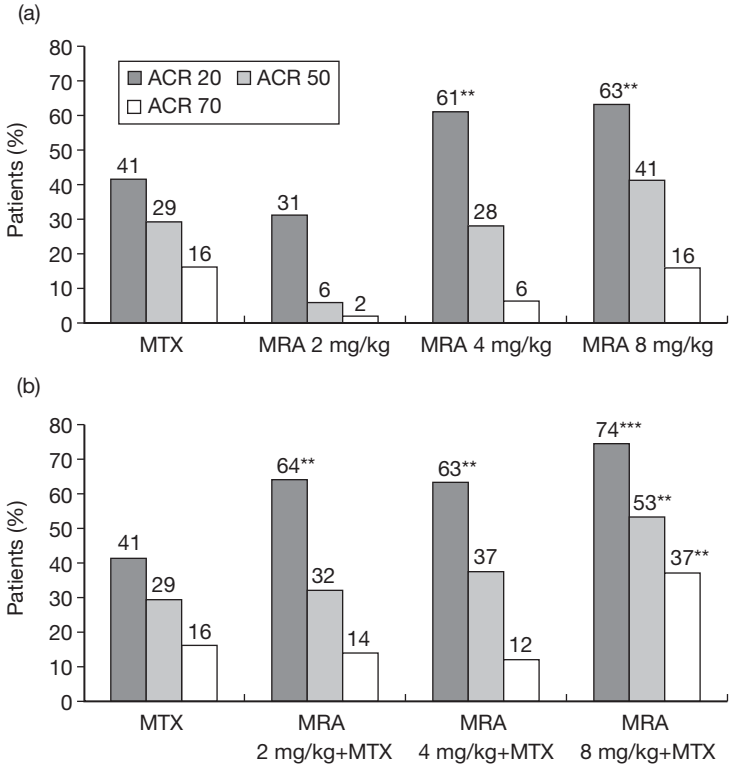

Fig. 3.1 Efficacy end points. American College of Rheumatology 20% (ACR20), 50% (ACR50) and 70% (ACR70) response rates at week 16 in the groups of patients receiving methotrexate (MTX) plus placebo, those receiving MRA (tocilizumab) monotherapy, and those receiving combination therapy with MRA plus MTX. $^{**}P < 0.05$; $^{***}P = 0.001$ versus MTX. Source: Maini *et al.* (2006).

intermediatory B-cells but absent in very early B-cells and plasma cells. Initially developed for the treatment of lymphoma, rituximab selectively depletes CD20+ B-cells |**10**|. In the treatment of lymphoma, rituximab induces disease remission and retreatment is required only when the disease relapses. The infection rate associated with rituximab in lymphoma is low, which has been attributed to the preservation of plasma cells. As the humoral immune response is implicated in many autoimmune rheumatic diseases, many researchers have studied the efficacy of rituximab in many connective tissue diseases, especially SLE.

Rituximab for rheumatoid arthritis refractory to anti-tumour necrosis factor therapy: results of a multicentre, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at 24 weeks

Cohen SB, Emery P, Greenwald MW, *et al. Arthritis Rheum* 2006; **54**: 2793–806

Background. Phase II studies have suggested that B-cell depletion using rituximab is an effective treatment for RA |11|. This pivotal phase III trial seeks to confirm this and examine the tolerability and short-term safety of rituximab in patients for whom TNF antagonists have failed.

Interpretation. In this phase III randomized control trial studying RA patients for whom TNF antagonists have failed, rituximab was an effective treatment. Rituximab may also reduce structural damage.

Comment

The Randomized Evaluation of Long-Term Efficacy of Rituximab (REFLEX) in RA Trial is a multicentre, randomized, double-blind, placebo-controlled, phase III study in 520 patients for whom at least one TNF antagonist has failed. They were randomized to receive either two intravenous infusions of rituximab or placebo, in combination with MTX. ACR20 response, the primary endpoint, was achieved in 51% and 18% of rituximab- and placebo-treated patients, respectively, at 24 weeks. Improvements in function, fatigue and generic health status were also observed. There was also a trend towards less progression in radiographic damage as measured by the Genant score.

This study shows that in TNF antagonist-refractory patients, rituximab is an effective treatment (Fig. 3.2).

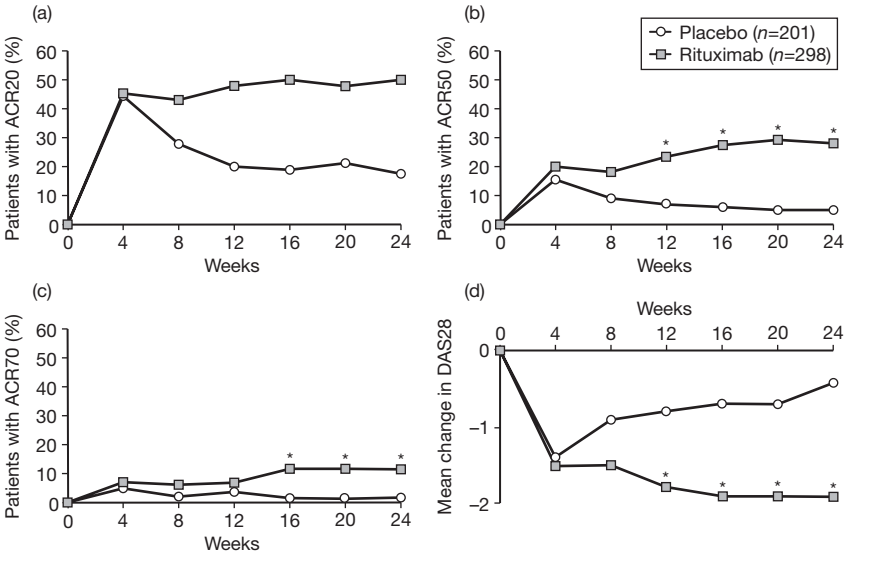

Fig. 3.2 (a–c) Percentages of patients achieving a response according to the American College of Rheumatology 20% improvement criteria (ACR20), 50% improvement criteria (ACR50) and 70% improvement criteria (ACR70), respectively, and (d) changes in scores on the Disease Activity Score 28-joint assessment for swelling and tenderness (DAS28) over the 24-week study period in the intent-to-treat population. *$P < 0.0001$ versus the placebo group, by two-tailed test. Source: Cohen *et al.* (2006).

The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial

Emery P, Fleischmann R, Filipowicz-Sosnowska A, *et al. Arthritis Rheum* 2006; **54**: 1390–400

Background. Hitherto, the rituximab dosing regime used to treat RA has been based on that used in lymphoma. This includes the use of glucocorticoids, which may explain and confound the therapeutic efficacy observed in previous clinical trials. This study aims to determine whether the efficacy of rituximab in RA occurs with or without glucocorticoids.

Interpretation. This multicentre, randomized, placebo-controlled trial showed that the efficacy of rituximab is independent of concomitant glucocorticoids.

Comment

Rheumatoid arthritis patients (465) taking MTX were recruited and randomized into nine treatment groups: three rituximab groups and groups receiving 500 mg

or 1000 mg placebo on days 1 and 15 in addition to either placebo glucocorticoids, intravenous methylprednisolone premedication or intravenous methylprednisolone premedication plus oral prednisone for 2 weeks. Over 50% of the patients who received rituximab achieved an ACR20 response at week 24 compared with 28% in the placebo-treated patients ($P < 0.0001$). Intravenous glucocorticoid premedication reduced the frequency and intensity of infusion-related reactions, but taking glucocorticoids did not influence efficacy.

Rituximab in combination with MTX is effective in the treatment of RA. Glucocortocid premedication reduced infusion-related reactions, but oral corticosteroid is not necessary to achieve therapeutic benefit.

Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years

Strand V, Balbir-Gurman A, Pavelka K, *et al. Rheumatology* 2006; **45**: 1505–13

Background. Whilst clinical trials have shown that rituximab is an effective treatment for RA, the sustainability of clinical response is important in assessing its cost-effectiveness and its impact on routine clinical care.

Interpretation. This study showed that rituximab leads to sustained improvement in the symptoms and signs of RA.

Comment

This study reported the long-term follow-up of patients who were recruited to a randomized controlled trial comparing MTX alone, rituximab alone or rituximab in combination with cyclophosphamide or MTX over 2 years. Forty-five per cent of patients receiving rituximab plus MTX completed 2 years' follow-up without further treatment compared with 15% in the group receiving methotrexate alone, 10% in the group receiving rituximab alone (10%) and 22% in the rituximab plus cyclophosphamide group. This was accompanied by improvement in functional capacity as measured by the Health Assessment Questionnaire (HAQ).

A single course of treatment of rituximab in combination with MTX provides sustained benefit to some patients with RA for at least 2 years.

Co-stimulation blockade

The role of T-cells in the pathogenesis of RA is a controversial issue. The therapeutic failure of depleting anti-T-cell monoclonal antibodies in clinical trials has cast doubts over their importance in maintaining synovitis. As proliferation and full activation

of an effective antigen-specific T-cell require signalling from a T-cell receptor and at least one additional co-stimulatory signal provided by an antigen-presenting cell, blocking co-stimulatory signals can effectively inhibit T-cell activation. There are a number of co-stimulatory molecules, but one of the major pathways involves interactions between the CD28 and CTLA4 molecules on T-cells and their ligands, CD80 (B7-1) and CD86 (B7-2) molecules on the surface of antigen-presenting cells |**12**|. CD28 is constitutively expressed by all CD4 and some CD8 T-cells, whereas CTLA4 is expressed only on activated T-cells. Monocytes and dendritic cells express CD86 constitutively but other antigen-presenting cells express CD86 only when activated. CD80 is expressed primarily on activation. Binding of CD28 to CD80 or CD86 stimulates T-cell growth. Conversely, binding of CTLA4 to CD80 or CD86 suppresses T-cell activation. Abatacept is a CTLA4–Ig fusion protein. In the USA, abatacept was licensed for the treatment of RA in 2006. Its European licence is anticipated in 2007.

Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial

Kremer JM, Genant HK, Moreland LW, *et al. Ann Intern Med* 2006; **144**: 865–76

Background. In a phase II study |13|, abatacept improved symptoms and signs in RA patients with active disease. This pivotal phase III study examines the therapeutic efficacy including effect on structural joint damage and tolerability of abatacept in patients who have active disease despite treatment by MTX.

Interpretation. Abatacept is an effective disease-modifying treatment for RA patients who have an inadequate response to MTX.

Comment

This double-blind, placebo-controlled trial recruited 652 patients with active RA despite MTX treatment and randomized them to monthly infusion of either 10 mg/kg abatacept or placebo in a ratio of 2:1. At 6 months, ACR20, ACR50 and ACR70 responses were 68%, 40% and 20% for abatacept vs. 40%, 17% and 7% for placebo respectively. At 1 year, abatacept slowed the progression of structural joint damage when compared with placebo; the difference was statistically significant. The rate of infection was higher with abatacept (2.5%) than with placebo (0.9%). Infusion reaction occurred in 8.8% of patients.

Abatacept statistically significantly reduced disease activity in patients with RA who are partial responders to MTX (Fig. 3.3).

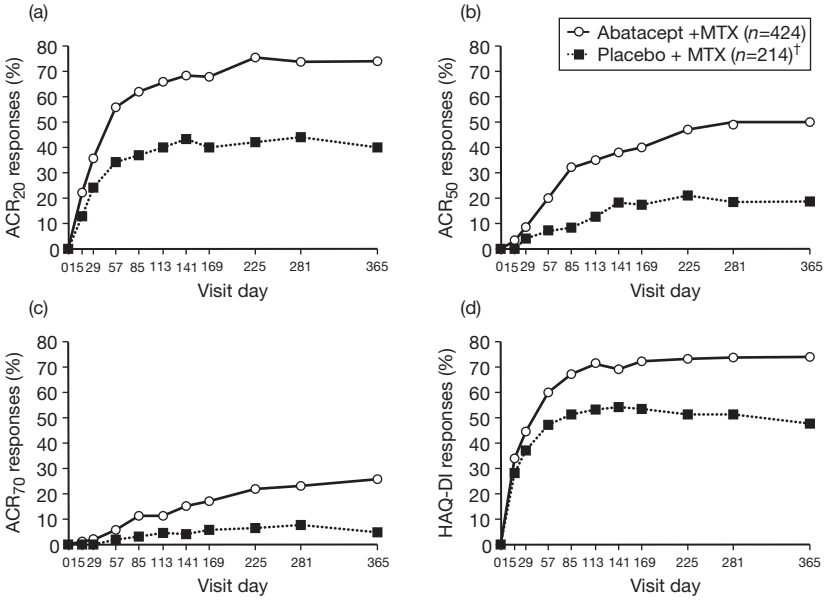

Fig. 3.3 American College of Rheumatology (ACR) 20% (ACR20) (a), ACR50 (b) and ACR70 (c) responses over 1 year in all patients who received at least one dose of the study medication. (d) The percentage of patients who achieved a Health Assessment Questionnaire Disability Index (HAQ-DI) response (0.3-unit improvement from baseline in HAQ-DI) was determined over 1 year. MTX, methotrexate. *Intention-to-treat population where all dropouts were considered to be ACR non-responders subsequent to their dropout. †Because of adherence issues identified during the study, patients from one site were excluded from all efficacy analyses before unblinding but were included in the analysis of safety. Source: Kremer *et al.* (2006).

Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life (HRQoL)

Emery P, Kosinski M, Li T, Martin M, *et al. J Rheumatol* 2006; **33**: 681–9

Background. This study examined the effect of abatacept on the HRQoL of patients with RA.

Interpretation. In combination with MTX, abatacept 10 mg/kg improved HRQoL in patients with RA.

Comment

Patients with RA (339) who were taking MTX were randomized to abatacept 2 mg/kg, abatacept 10 mg/kg or placebo. HRQoL was measured using the Short-Form 36 Health Survey (SF-36). After 12 months of treatment, patients treated with

abatacept 10 mg/kg showed improvement in SF-36 in all eight domains compared with placebo-treated patients. Differences in SF-36 change scores between abatacept 10 mg/kg and placebo groups reached statistical significance on all eight domain scales of SF-36. Improvement in HRQoL correlated with clinical response.

Abatacept plus methotrexate improved HRQoL in patients with RA.

Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial

Westhovens R, Cole JC, Li T, *et al. Rheumatology* 2006; **45**: 1238–46

Background. Given patients with RA for whom TNF antagonists have failed may have more resistant disease, this study reported the HRQoL outcome in a double-blind placebo-controlled trial in patients for whom at least one TNF antagonist had previously failed.

Interpretation. In this phase III randomized controlled trial in patients for whom TNF antagonists have failed, abatacept improved HRQoL.

Comment

Patients (258) for whom at least one TNF antagonist had previously failed were randomized to receive abatacept 10 mg/kg plus DMARDs or placebo and DMARDs. The abatacept group improved significantly more than the placebo group on seven out of eight domains of the SF-36, the HAQ and fatigue score measured by the visual analogue scale (VAS).

Abatacept improved HRQoL in RA patients even when they had previously failed anti-TNF therapy.

Safety of the selective co-stimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and non-biologic disease-modifying antirheumatic drugs: a 1-year randomized, placebo-controlled study

Weinblatt M, Combe B, Covucci A, *et al. Arthritis Rheum* 2006; **54**: 2807–16

Background. As abatacept has shown therapeutic promise in early phase II RA study, this paper reports its safety and tolerability in combination with DMARDs or biologic agents.

Interpretation. Abatacept is well tolerated when used in combination with traditional DMARDs but biologic agents should be avoided as this leads to higher incidence of serious adverse events.

Comment

Rheumatoid arthritis patients with active disease who were receiving at least one traditional DMARD or biologic agent for at least 3 months prior to enrolment into the study were recruited. They were randomized to receive abatacept (10 mg/kg) or placebo in a 2:1 ratio. Overall, the rates of adverse events (90% and 87% respectively), serious adverse events (13% and 12% respectively) and discontinuations due to adverse events (5% and 4% respectively) were similar in the abatacept and placebo groups. Serious infections were more common in the abatacept group than in the placebo group (2.9% vs. 1.9%). However, patients receiving abatacept and a biologic agent experienced more frequent serious adverse events (22.3%) than other subgroups (11.7–12.5%).

Abatacept plus traditional DMARDs seems to be well tolerated. However, abatacept when combined with a biological agent increased the rate of serious adverse events. Therefore, abatacept should not be used in combination with other biological therapy.

CTLA-4IG suppresses reactive oxygen species by preventing synovial adherent cell-induced inactivation of Rap1, a Ras family GTPase mediator of oxidative stress in rheumatoid arthritis T-cells

Remans PH, Wijbrandts CA, Sanders ME, *et al. Arthritis Rheum* 2006; **54**: 3135–43

Background. Oxidative stress contributes to the inflammatory properties of T-cells in RA. This study was undertaken to assess production of reactive oxygen species (ROS) and oxidative stress in RA T-lymphocytes before and after co-stimulation blockade by abatacept.

Interpretation. This study showed that one of the mechanisms of action of abatacept may be through the inhibition of ROS production by synovial fluid T-cells.

Comment

Reactive oxygen species production in RA synovial fluid T-cells was compared with that in peripheral blood T-cells from RA patients and healthy donors. This study showed that cell–cell contact between T-cells and RA synovial adherent cells mediates ROS production in T-lymphocytes following exposure to inflammatory cytokines. Blockade of co-stimulation by abatacept prevented induction of ROS.

Abatacept reduced ROS production by synovial fluid T-cells in patients with RA.

Conclusion

TNF antagonists have been in routine clinical use for many years. Although they are expensive, pharmacoeconomic studies have confirmed that they are a cost-effective treatment in RA and PsA. Their medium-term safety data from national registries are reassuring, but clinicians need to remain vigilant. As the number of patients treated by TNF antagonists has increased, so has the number of non-responders and partial responders. There are several therapeutic options: increase dose or reduce frequency of TNF antagonists, switch to another TNF antagonist or change to alternative treatment. The last option has been made more feasible as rituximab and abatacept are now licensed for the treatment of RA. The number of patients with rheumatic diseases treated by biologics is set to continue to increase in the coming years.

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4

Vascular morbidity in rheumatic diseases

NAVEED SATTAR

Introduction

The excess risk of vascular disease in rheumatoid arthritis (RA) has been known for many decades |**1**|, but, at the clinical level, coronary heart disease (CHD) or global cardiovascular disease (CVD) risk assessment and related preventative treatment in RA has been less well characterized. Increasing awareness over the last decade of inflammation as a novel player in the origin of CVD in the general (non-RA) population |**2**| has stimulated resurgent interest in potential mechanisms underpinning excess CVD risk in RA.

Early studies attempted to determine the extent of excess vascular risk in RA. Numerous studies have now addressed this question. For example, Solomon *et al.* |**3**| compared incidence rates of myocardial infarction and stroke in subjects with and without RA among the 114 342 women in the Nurses' Health Study. They observed an adjusted relative risk of myocardial infarction in women with RA compared with those without of 2.0 [95% confidence interval (CI) 1.23–3.29]. Women who had RA for at least 10 years had a relative risk for myocardial infarction of 3.10 (95% CI 1.64–5.87). In keeping with a near twofold increased risk, investigators in Malmö |**4**| reported a standardized morbidity ratio (SMR) of 176 for myocardial infarction in their RA patients compared with the general population. Relevant evidence from all studies suggests CHD risk is equally elevated in men and women with RA and increases with disease severity and evidence of extra-articular disease, and with disease duration |**3,5**|. A precise estimate of the level of this excess risk is not possible but it would appear to be somewhere around 1.5- to 2.0-fold higher |**6**|. This risk is somewhat lower than the excess risk of CVD seen in subjects with type 2 diabetes, although previous comparisons of the CVD risk in the two conditions have been made |**7**|.

More recent research has tried to define at what point during the disease course vascular risk in RA commences, and whether presentation of vascular risk differs in patients with RA compared with those without inflammatory conditions. Equally, increasing attention is being focused on the effects of differing anti-inflammatory modalities on this risk in RA patients. Relevant recent studies are reviewed.

Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study

Maradit-Kremers H, Crowson CS, Nicola PJ, *et al. Arthritis Rheum* 2005; **52**: 402–11

BACKGROUND. Mechanisms underlying the excess risk of clinical CHD in patients with RA compared with age- and sex-matched non-RA subjects, are not entirely clear. Equally, when such risk begins is not well examined. This study by an experienced group examined these issues. To do this, the researchers examined medical records including data on myocardial events and related risk factors of 603 individuals who developed RA over a 40-year period.

INTERPRETATION. The results indicated that during the 2-year period immediately prior to fulfilment of the American College of Rheumatology (ACR) criteria RA patients were significantly more likely to have been hospitalized for acute myocardial infarction (MI) [odds ratio (OR) ~ 3] or to have experienced unrecognized MI (OR ~ 6), and around 40% less likely to have a history of angina pectoris compared with non-RA subjects (Table 4.1). After the RA incidence date, RA patients were twice as likely to experience unrecognized MIs [hazard ratio (HR) 2.13, 95% CI 1.13–4.03] and sudden deaths (HR 1.94, 95% CI 1.06–3.55) and less likely to undergo coronary artery bypass grafting (HR 0.36, 95% CI 0.16–0.80) compared with non-RA subjects. Adjustment for the CHD risk factors did not alter these findings. Thus, elevation in CHD risk in RA patients precedes

Table 4.1 Prevalence of coronary heart disease in rheumatoid arthritis (RA) and non-RA subjects at index date (Rochester, Minnesota, 1955–95)

	Observed, no. (%)		Odds ratio (95% confidence interval	
Characteristic	**RA cohort (*n* = 603)**	**Non-RA cohort (*n* = 603)**	**Age- and sex-adjusted***	**Multivariable-adjusted***
Hospitalized myocardial infarction	17 (2.8)	5 (0.8)	3.40 (1.25–9.22)†	3.17 (1.16–8.68)†
Unrecognized myocardial infarction	11 (1.8)	2 (0.3)	5.50 (1.22–24.81)†	5.86 (1.29–26.64)†
Angina pectoris	27 (4.5)	43 (7.1)	0.59 (0.35–0.99)†	0.58 (0.34–0.99)†
Revascularization procedures	6 (1.0)	6 (1.0)	1.00 (0.29–3.45)†	1.04 (0.30–3.60)†

*Conditional logistic regression analyses were used for both the age- and sex-adjusted and the mutivariable-adjusted odds ratio estimates. Multivariable-adjusted logistic regression models included age, sex, smoking status, body mass index, and the presence or absence of diabetes.
†$P < 0.05$ between cohorts.
Source: Maradit-Kremers *et al.* (2005).

the ACR criteria-based diagnosis of the condition. In addition, RA patients are less likely to report symptoms of angina and more likely to experience unrecognized MI and sudden cardiac death, and such risks cannot be explained by an increased incidence of traditional CHD risk factors in RA patients.

Comment

The results of this study are of considerable interest and the use of medical records to identify CHD risk both before and after diagnosis of RA is novel. However, some caution is required. The population number and number of events were modest, and this accounts the large confidence intervals for many of the endpoints. Furthermore, adjustment for traditional risk factors was based on categorical rather than continuous adjustment of risk factors, and this lends itself to residual confounding. That said, there is consistency in the findings, with a lower frequency of angina, in keeping with greater proportion of unrecognized MI. The results suggest that ischaemia is less well perceived in patients with RA. These findings reiterate the need for wider CHD risk-screening in patients with RA to enable better identification and treatment of established CHD risk.

Increased case fatality rates following a first acute cardiovascular event in patients with rheumatoid arthritis

Van Doornum S, Brand C, King B, Sundararajan V. *Arthritis Rheum* 2006; **54**: 2061–8

BACKGROUND. Among patients with RA, cardiovascular mortality is increased compared with the rate among unaffected peers. In this study, 30-day mortality rates following a first acute cardiovascular event (MI or stroke) were compared between RA patients and the general population. To achieve this, the authors tracked all cases of a first acute cardiovascular event between 1 July 2001 and 30 November 2003 in Victoria, Australia, from hospital discharge data. Individuals were classified as having RA by standardized criteria. Thirty-day mortality rates were determined from linkage to the state death registry.

INTERPRETATION. RA patients have around an 80% increased risk of 30-day case fatality following MI compared with non-RA patients. Risks after stoke were not different between RA and non-RA subjects. The higher death rates post MI remained significant after adjustments for a list of potential confounders (Table 4.2).

Comment

The above findings are of interest in terms of both results and the methodology of exploiting existing registries data, a process others could replicate. Replication would be useful as in the present study only a modest number of individuals with RA (359) had a first cardiovascular event compared with the much larger number

Table 4.2 Mortality risk following a first acute cardiovascular event in rheumatoid arthritis (RA) patients*

Event type	Crude OR (95% CI)	Adjusted OR (95% CI)†
All index events		
30-day mortality, all cause	1.7 (1.3–2.2)	1.5 (1.1–2.0)
30-day mortality, cardiovascular	1.8 (1.3–2.3)	1.6 (1.2–2.2)
Myocardial infarction		
Presence of CHF during admission	1.6 (1.2–2.1)	1.2 (0.9–1.7)
30-day mortality, all cause	2.3 (1.6–3.1)	1.8 (1.3–2.6)
30-day mortality, cardiovascular	2.3 (1.7–3.2)	1.9 (1.3–2.7)
Stroke		
30-day mortality, all cause	0.9 (0.6–1.6)	1.0 (0.6–1.8)
30-day mortality, cardiovascular	1.1 (0.6–1.8)	1.2 (0.7–2.0)

*Reference group is patients without RA.
†Adjusted for age, sex, risk factors (diabetes, hypertension, smoking, hyperlipidaemia), type of intervention after cardiac event (percutaneous transluminal coronary angioplasty, coronary artery bypass graft) for acute myocardial infarction only, admission as an emergency to an intensive care unit, comorbidities, congestive cardiac failure, hospital type, accessibility of goods and services, ethnicity and socio-economic factors.
CHF, coronary heart failure; CI, confidence interval; OR, odds ratio.
Source: Van Doornum *et al.* (2006).

of non-RA subjects. In addition, it was not clear if medications were considered as potential confounders with RA subjects potentially receiving less cardioprotective agents: for example, statin use may be less common in RA patients as cholesterol levels are commonly found to be lower in RA patients |**8**|.

If the results from other registries support the study findings, more work on the mechanisms – e.g. arrhythmia/sudden deaths – underlying the higher short-term mortality in RA subjects would be needed. If we accept the results, the implications point once again to a need for comprehensive CHD risk screening in most patients with RA to enable better identification and treatment of established CHD risk to reduce likelihood of vascular events.

Patterns of cardiovascular risk in rheumatoid arthritis

Solomon DH, Goodson NJ, Katz JN, *et al. Ann Rheum Dis* 2006; **65**: 1608–12

Background. The pattern of CHD risk in RA patients of differing age, sex and prior CHD status is unclear. This study therefore investigated the relative risk of MI, stroke and CVD mortality in adults with RA compared with adults without RA across age groups, and by prior CVD status. The authors conducted a cohort study among all residents aged > 18 years residing in British Columbia between 1999 and 2003. Subjects with RA were compared with matched patients without RA for the primary composite endpoint of a hospital admission for MI, stroke or CVD mortality.

Interpretation. The rate ratio for any CVD event was around 60% higher in RA subjects. However, this ratio decreased with age, from 3.3 in patients aged 18–39 years to 1.6 in those aged > 75 years (Table 4.3). The absolute rate difference was 1.2 per 1000 person-years in the youngest age group and increased to 19.7 per 1000 person-years in those aged > 75 years (Fig. 4.1). Among patients with a prior CVD event, the rate ratios and rate differences were not increased in RA. This study confirms that RA is a risk factor for CVD events and shows that the rate ratio for CVD events among subjects with RA is highest in young adults and those without known prior CVD.

Comment

The authors of this study had access to a large dataset to examine CVD risk in RA subjects across different ages. The headline figure of a 60% higher CVD event risk is comparable with a wealth of other related data. The particular novel aspect of the present study is the finding that the ratio (similar to relative risk) is much higher in younger RA subjects than in older subjects. However, as absolute CVD event risk is higher in older subjects, the number of absolute excess CVD events caused by RA is much greater in older subjects. This observation underlines the difference between relative and absolute risk. Of interest, Solomon and colleagues also noted a higher 30-day mortality rate (1.89, 95% CI 1.56–2.30) in RA patients following a CVD event, consistent with data reported above from Van Doornum and colleagues. Furthermore, if RA patients survived through this post-CVD event period, their subsequent vascular risk was not elevated compared with non-RA subjects. Such observations merit further investigation.

Effects of tumour necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study

Sattar N, Crompton P, Cherry L, *et al. Arthritis Rheum* 2007; **56**: 831–9

Background. The existing data of effects of TNF blockade on CVD risk factors are weak, coming mostly from small uncontrolled studies. The Glasgow group

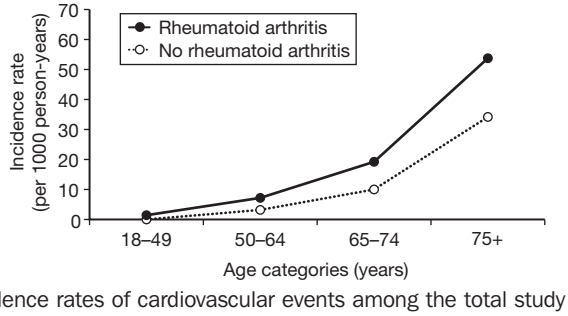

Figure 4.1 Incidence rates of cardiovascular events among the total study population. Source: Solomon *et al.* (2006).

Table 4.3 Cardiovascular events among subjects with and without rheumatoid arthritis, by age

	RA				Non-RA					
	n	**Events**	**Person-years**	**Rate**	***n***	**Events**	**Person-years**	**Rate**	**Rate difference (95% CI)**	**Rate ratio (95% CI)**
All patients	25385				252976					
MI		375	71384	5.3		2022	709166	2.9	2.4 (1.9–2.9)	1.8 (1.7–2.0)
Stroke		363	71260	5.1		1902	709489	2.7	2.4 (2.0–2.9)	1.9 (1.7–2.1)
CV death		437	70612	6.1		3478	738212	4.7	1.4 (0.9–1.9)	1.3 (1.2–1.4)
Any CV event		1042		14.8		6428	706059	9.1	5.7 (4.9–6.4)	1.6 (1.5–1.7)
Age category (any CV event)										
18–49 years	6873	35	19900	1.8	68754	109	201873	0.5	1.2 (0.7–1.7)	3.3 (2.4–4.5)
50–64 years	8178	175	23473	7.5	80617	784	232648	3.4	4.1 (3.1–5.0)	2.2 (1.9–2.5)
65–74 years	5664	309	15735	19.6	56990	1617	159256	10.2	9.5 (7.6–11.3)	1.9 (1.7–2.1)
75+ years	4488	623	11414	54.6	46615	3918	112281	34.9	19.7 (16.0–23.4)	1.6 (1.5–1.7)

CV, cardiovascular; MI, myocardial infarction; RA, rheumatoid arthritis.
The rate is events per 1000 person-years. The rate difference is the absolute difference (excess) in events per 1000 people-years between patients with RA and those without RA. The composite outcome refers to MI, stroke or cardiovascular death.
Source: Solomon *et al.* (2006).

had an opportunity to conduct a larger, double-blind, placebo-controlled study on the back of a clinical trial. They examined effects of tumour necrosis factor (TNF) modulation on concentrations of traditional and novel cardiovascular disease risk factors. Patients with psoriatic arthritis and active psoriasis (127) were randomized to one of three treatment arms [placebo, onercept (a recombinant human TNF-binding protein 1) 50 mg, or onercept 100 mg for 12 weeks]. Biochemical risk factors were evaluated at baseline and at the end of the treatment period.

Interpretation. Onercept at a dose of 100 mg induced significant ($P < 0.002$) reductions in the levels of C-reactive protein (CRP), lipoprotein(a) [Lp(a)] and homocysteine and an increase in the sex hormone-binding globulin (SHBG) concentration (Table 4.4). The 100-mg dose of onercept was also associated with significant ($P < 0.05$) increases in the level of circulating apolipoprotein A-I (Apo A-I). However, levels of apolipoprotein B (Apo B) and triglycerides also increased significantly. This study is the first to demonstrate that targeting the TNF pathway can significantly decrease Lp(a) and homocysteine levels and elevate Apo A-I and SHBG concentrations. However, TNF blockade-induced increases in triglyceride and Apo B levels were unexpected and suggest that it is not possible, on the basis of biochemical changes in isolation, to suggest that cardioprotection would necessarily follow.

Comment

The findings from this study significantly improve our knowledge of the effects of TNF blockade on CVD risk factors. The data support an important precursor role for high-grade inflammation in modulating several putative risk parameters. Most of the changes with the TNF-blocking agent used are certainly in keeping with a lower CVD risk, but not all. Thus, the conclusion that it may be difficult to make predictions on the net vascular effects of TNF blocking agents based solely on a panel of biochemical parameters would appear to be correct. It will be of interest to examine whether direct indicators of atherosclerosis progression, such as carotid intima–media thickness (IMT) or plaque, can be measured in the context of sufficiently powered randomized TNF-blocking (or other biologic) trials, and, if so, whether such measures are helpful.

Antirheumatic drug use and the risk of acute myocardial infarction

Suissa S, Bernatsky S, Hudson M. *Arthritis Rheum* 2006; **55**: 531–6

Background. There is a need to better understand and assess the risk of acute myocardial infarction (AMI) associated with the use of disease-modifying antirheumatic drugs (DMARDs) and other medications commonly used in RA. This study set out to gather relevant information using a nested case–control analysis within the context of an existing database.

Table 4.4 Changes over time in C-reactive protein and IL-6 concentrations and biochemical cardiovascular risk factors in the three study groups*

Risk factor	Placebo ($n = 42$)	Onercept, 50 mg ($n = 42$)	P†	Onercept, 100 mg ($n = 42$)	P†
C-reactive protein (mg/l)	6.50 ± 21.9	–12.8 ± 21.8	< 0.001	–13.93 ± 27.5	< 0.001
Interleukin 6 (pg/ml)	3.71 ± 35.4	–3.03 ± 46.9	< 0.001	–25.80 ± 73.1	< 0.001
Cholesterol (mmol/l)	0.01 ± 1.10	–0.12 ± 0.46	0.98	–0.11 ± 1.62	0.13
HDL cholesterol (mmol/l)	–0.03 ± 0.14	–0.03 ± 0.22	0.78	–0.02 ± 0.16	0.98
Triglycerides (mmol/l)	0.04 ± 1.01	0.02 ± 0.75	0.08	0.09 ± 1.37	0.02
Apolipoprotein A-I (mg/dl)	–5.59 ± 15.4	–2.58 ± 18.2	0.17	3.98 ± 17.2	0.002
Apolipoprotein B (mg/dl)	–0.40 ± 14.2	3.00 ± 10.1	0.19	6.31 ± 11.7	0.042
ICAM-1 (ng/ml)	6.07 ± 49.8	–4.41 ± 55.3	0.71	–15.58 ± 51.9	0.12
Lipoprotein(a) (mg/dl)	1.52 ± 7.7	–2.02 ± 8.4	0.048	–3.11 ± 6.5	0.002
SHBG (nmol/l)	–1.31 ± 9.0	2.47 ± 15.9	0.054	4.32 ± 8.8	0.002
Homocysteine (μmol/l)	0.34 ± 4.2	–0.72 ± 2.7	0.014	–1.72 ± 2.6	< 0.001

*Values are the mean ± SD.
†Versus placebo, by analysis of covariance on ranks.

HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; SHBG, sex hormone-binding globulin.
Source: Satter *et al.* (2007).

Interpretation. The authors reported lower AMI rates (20% lower) with the current use of any DMARD (Table 4.5). This effect was consistent across all DMARDs, including methotrexate (MTX), leflunomide and other traditional DMARDs, but not biological agents. AMI rate increased with the use of glucocorticoids but not with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase 2 (COX-2) inhibitors. The authors' main conclusion was that DMARD use is associated with a reduction in AMI risk in patients with RA.

Comment

This study, like others discussed herein, makes use of an existing database to try to decipher the CVD effects of antirheumatic drugs. Whilst this approach is useful, there is always the potential for residual confounding due to inability to adjust for some potential confounders. The authors readily admit this possibility in their discussion. They attempted to get at and adjust for some potential confounders (such as comorbidity), but it was not possible to adjust for disease severity, which is an obvious confounder. Clearly, subjects who would be prescribed biological agents

Table 4.5 Crude and adjusted rate ratios of acute myocardial infarction (AMI) for current use of disease-modifying antirheumatic drugs (DMARDs) and other antirheumatoid arthritis (RA) medications

				Adjusted*	
	AMI cases (*n* = 558)	**Control subjects (*n* = 5580)**	**Crude RR**	**RR**	**95% CI**
DMARDs (current use)					
No current use (reference)	416	3945	1.00	1.00	Reference
Current DMARD use	142	1695	0.78	0.80	0.65–0.98
Methotrexate monotherapy	60	697	0.84	0.81	0.60–1.08
Leflunomide	6	194	0.30	0.28	0.12–0.65
Biologic agents†	42	324	1.33	1.30	0.92–1.83
All other DMARDs‡	34	479	0.69	0.67	0.46–0.97
Other anti-RA drugs (current use)					
NSAIDs	82	827	0.99	1.05	0.81–1.36
COX-2 inhibitors	92	840	1.12	1.11	0.87–1.43
Glucocorticoids	84	671	1.31	1.32	1.02–1.72

*Adjusted for one another as well as for age, ischaemic heart disease, peripheral arterial disease, other cardiovascular disease, diabetes and respiratory illness.
†The biological agents available at the time were infliximab, etanercept and anakinra.
‡The traditional DMARDs include hydroxychloroquine, sulfasalazine, auranofin, aurothioglucose, gold, sodium thiomalate, minocycline, penicillamine, chlorambucil, cyclophosphamide and cyclosporine.
AMI, acute myocardial infarction; CI, confidence interval; COX-2, cyclo-oxygenase-2; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RR, rate ratio.
Source: Suissa *et al.* (2006).

would tend to have more severe disease than other groups, and this may account for the absence of any apparent benefit of biological agents. Nevertheless, the results on all DMARDs appeared consistent and, with respect to MTX, concur with prior data |**9**|. The higher CVD risk in those taking steroids is of interest and concurs with another recently published study on a similar topic with similar design |**10**|, and with evidence from a carotid ultrasound study |**11**|.

Differences in atherosclerotic coronary heart disease between subjects with and without rheumatoid arthritis

Aubry MC, Maradit-Kremers H, Reinalda MS, *et al. J Rheumatol* 2007; **34**: 937–42

Background. There is considerable interest in determining whether the features of CHD differ in RA patients compared with non-RA counterparts, but a scarcity of relevant data. Aubry and colleagues therefore compared the histological features of coronary artery disease (CAD) in patients with RA and non-RA control subjects. They used autopsy material from patients with RA and control subjects with a similar age, sex, history of CVD and autopsy date. The grade of stenosis was evaluated in each artery. The numbers of vulnerable plaques and acute coronary lesions were counted. The composition of a representative stable and vulnerable plaque from each vessel was evaluated.

Interpretation. The authors noted that RA subjects with CVD were far less likely to have grade 3–4 lesions in the left main artery (7% vs. 54%) than were control subjects with CVD, but that vulnerable plaques were much more apparent (Fig. 4.2). Inflammation in both the media of the left circumflex ($P = 0.005$) and the adventitia of the left anterior descending (LAD) artery was also more common in RA patients than in control subjects. Thus, there was less histological evidence of atherosclerosis but greater evidence of inflammation and instability in RA patients than in control subjects. These differences suggest that the mechanisms responsible for cardiovascular morbidity and mortality may be different in patients with RA.

Comment

This study is important as it provides some evidence that CAD may differ in its characteristics in RA patients compared with non-RA subjects. The greater burden of vulnerable plaques and tissue inflammation but less severe vessel stenosis is perhaps in keeping with expectations. In other words, it appears that, in RA subjects, the greater systemic inflammation may push the balance towards vulnerable plaques far more quickly than in non-RA subjects. It would be of tremendous interest to confirm and extend these findings in living patients with CVD using novel imaging techniques, which can now give some indication of plaque composition.

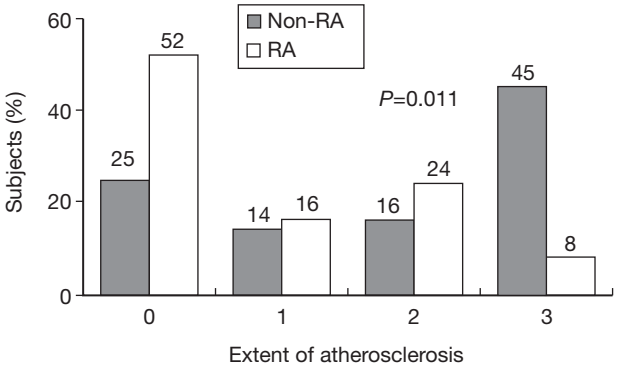

Fig. 4.2 Proportion of study subjects with extent of atherosclerosis among 25 rheumatoid arthritis (RA) patients with global cardiovascular disease (CVD) risk and 51 control subjects with CVD. Source: Aubry *et al.* (2007).

Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis

del Rincon I, Freeman GL, Haas RW, *et al. Arthritis Rheum* 2005; **52**: 3413–23

Background. It is always important to remember that vascular risk in RA is almost certainly an interaction between traditional risk factors and aspects of RA systemic inflammation. The present study attempted to estimate the contribution of cardiovascular (CV) risk factors and RA disease manifestations to atherosclerosis in RA, as measured by carotid IMT and plaque content.

Interpretation. The contribution of demographic factors, CV risk factors, and RA manifestations to IMT and plaque varied depending on the patients' age stratum. Demographic features explained 11–16% of IMT variance, CV risk factors explained 4–12%, and RA manifestations explained 1–6%. The greatest contribution of RA manifestations occurred in the youngest age group, while that of CV risk factors occurred in the older age groups. Results for carotid plaque were similar. There was a significant interaction between the number of CV risk factors present and the erythrocyte sedimentation rate (ESR), suggesting that the ESR's effect on IMT varied according to the number of CV risk factors (Fig. 4.3). Thus, the authors concluded that both established CV risk factors and manifestations of RA inflammation contribute significantly to carotid atherosclerosis in RA, and may modify one another's effects.

Comment

The findings of this paper are exactly in keeping with expectations in that CVD risk in RA subjects, at least as estimated from carotid ultrasound findings, appears to be due both to established CVD risk factors and the degree of systemic inflammation

in RA |8|. Carotid IMT measurements are considered the best surrogate vascular test – because best validated – and thus the results have some credibility, but it should be noted that there is no agreed definition of what constitutes a carotid plaque on ultrasound. In addition, the authors did not assess all traditional CV risk factors and the absence of high-density lipoprotein (HDL) cholesterol is significant as low-HDL cholesterol is often the major lipid abnormality in RA subjects, and HDL

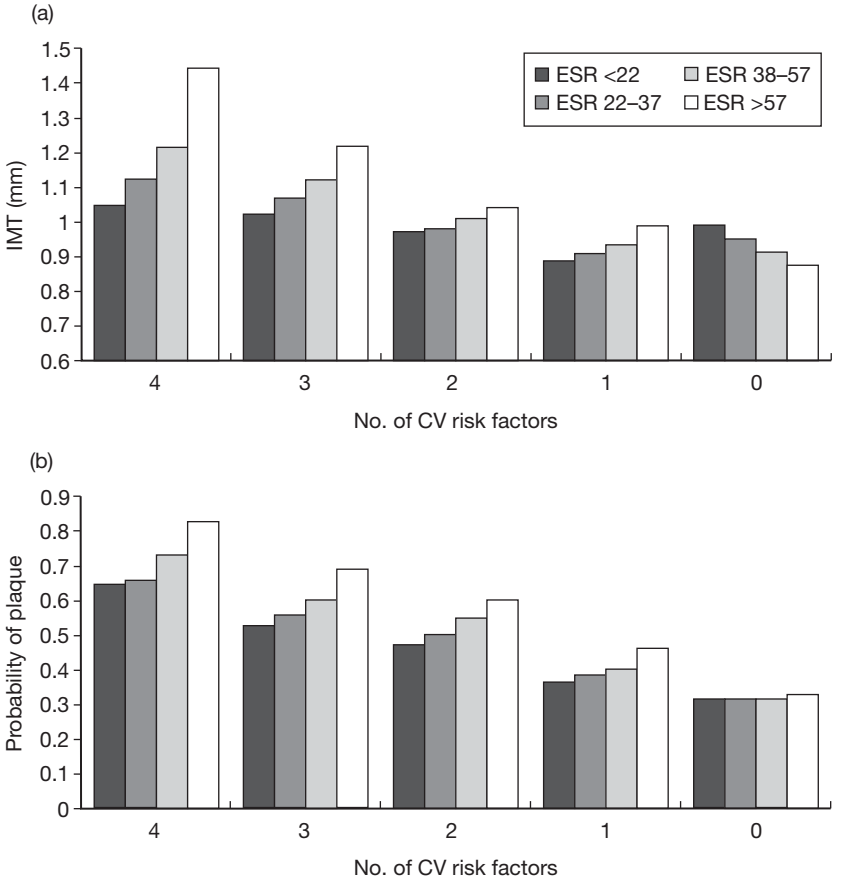

Fig. 4.3 Age- and sex-adjusted mean carotid intima–media thickness (IMT) and probability of carotid plaque, as functions of the number of cardiovascular (CV) risk factors and erythrocyte sedimentation rate (ESR) quartiles (mm/h). The number of CV risk factors and the ESR were each significantly associated with both dependent variables (P for trend ≤ 0.001 for each). There was a significant interaction between the ESR and the number of CV risk factors (P for the product term ESR × number of CV risk factors ≤ 0.001). The interaction suggested that the effect of ESR on IMT varied according to the number of CV risk factors. In the case of carotid plaque, the effect of ESR was significant, without evidence of interaction. Source: del Rincon *et al*. (2005).

cholesterol correlates inversely with the degree of inflammation |**8**|. Nevertheless, the results appear to confirm the need to address both established CV risk factors in RA and the degree of systemic inflammation to slow progression of atherosclerosis in RA subjects.

Conclusion

Whilst there is now clear evidence of excess CVD risk in RA subjects from a variety of reports, studies in recent years have improved knowledge on the pattern of CVD risk in RA. It is apparent from the reports considered in this review that excess CVD risk may begin early in the course of the disease. Moreover, it appears that the CVD risk is greater with more severe systemic disease and longer duration of RA. Furthermore, this excess vascular risk appears to manifest differently in RA compared with non-RA subjects with less angina, but more sudden deaths and unrecognized MIs. Finally, there is now emerging evidence for a higher 30-day case fatality after a CVD event in RA vs. non-RA subjects.

Of interest, many of the above data were gathered from analyses of existing databases. Whilst these can accumulate data on many thousands of patients, it is important to remember the potential for residual confounding, with an inability to adjust for all potential confounders. Nevertheless, consistency of the evidence is emerging and in keeping with the current knowledge on the interaction between inflammation and atherosclerosis.

The implications of the above findings are clear. They strengthen the need to determine CVD risk in RA subjects, with the aim of reducing this risk with established modalities – statins or antihypertensives – in those deemed at sufficiently high risk. In this respect, emerging evidence indicates that statins may have dual effects in RA, with a modest disease-modifying effect (requiring confirmation) and a significant lipid-lowering effect, equivalent to the magnitude of lipid reduction in non-RA subjects |**12**|. The latter finding is particularly important as extrapolation of data from all statin endpoint trials suggests that the extent of low-density lipoprotein (LDL) cholesterol reduction accounts for the majority of statin clinical benefit |**13**|.

CVD risk screening in RA subjects would involve minimal additional tests (blood pressure and non-fasting lipids in majority) and use of available risk factor charts |**14**|. As the majority of RA patients continue to exhibit significant systemic inflammation despite potent therapy, it would seem sensible to multiply risk levels derived from such charts by a factor of around 1.5 to derive the likely level of risk in RA subjects |**6**|. This conservative adjustment factor represents a balance between reported excess CVD risks in a variety of studies, on the one hand (e.g. |**3–5**|), and the lack of prospective RA studies that have measured and adjusted properly for the full range of traditional risk factors, on the other. Finally, it is very important to appreciate that it is the CVD risk level and not the cholesterol level in isolation which dictates whether statin treatment is applicable. The time has come when rheumatologists would benefit from training on CVD risk assessment.

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5

Seronegative spondyloarthropathies

MARTIN PERRY, IAIN MCINNES

Introduction

The seronegative spondyloarthropathies are characterized by inflammation and consequent damage to the axial skeleton together with peripheral joints and entheses. Distinct associations with inflammation of other tissues including skin (psoriatic arthritis), eye (uveitis) and gut (inflammatory bowel disease) are described commensurate with common pathophysiological pathways |**1**|. There has been remarkable recent progress in understanding such pathways, especially in skin and in peripheral joints, by examining the tissue lesion directly via biopsy and *ex vivo* analysis |**2–4**|, and through the application novel imaging modalities including high-resolution ultrasound and magnetic resonance imaging (MRI) |**5,6**|. The data arising from these studies continue to inform the development of new therapies |**7,8**|. However, in the last year, the major advances have occurred in refinement of the use of existing therapeutics, particularly of the biological agents that target tumour necrosis factor (TNF). This review will focus primarily on those clinical studies reported that usefully inform clinical practice.

Psoriatic arthritis

We have selected studies published in the last year that reflect three areas of ongoing importance in the investigation and treatment of psoriatic arthritis (PsA). Initially we report on the ongoing efforts to properly define the disease in a manner that is useful for clinical trials and in practice. Thereafter we report on a variety of studies addressing the use of TNF blockers in the disease. Although it is clearly established that TNF blockade confers therapeutic advantage in patients with PsA |**9**|, details are now available concerning their impact on radiographic progression and on measures of social and societal function that will become central to cost-effectiveness analyses in future. Finally, novel biological targets are now being explored based in part on the shared pathogenetic features perceived to exist between skin and joint disease in PsA.

Classification criteria for psoriatic arthritis: development of new criteria from a large international study

Taylor W, Gladman D, Helliwell P, *et al.*, CASPAR Study Group. *Arthritis Rheum* 2006; **54**: 2665–73 |**10**|

Background. This important study aimed to compare the accuracy of existing classification criteria for the diagnosis of PsA and to construct new criteria from observed data. Consecutive clinic attendees with PsA and other inflammatory arthropathies were recruited prospectively by seven criteria. Sensitivity and specificity were compared using conditional logistic regression analysis. Latent class analysis was used to calculate criteria accuracy in order to confirm the validity of clinical diagnosis as the gold standard definition of 'case'-ness. Classification and regression trees methodology and logistic regression were used to identify items for new criteria, which were then constructed using a receiver operating characteristic curve.

Interpretation. A total of 1124 patients were recruited, including 588 patients with PsA and 536 control subjects. The latter included patients with rheumatoid arthritis ($n = 384$), ankylosing spondylitis ($n = 72$), undifferentiated arthritis ($n = 38$), connective tissue diseases ($n = 14$), and other diseases ($n = 28$). The specificity of each set of criteria was high. The sensitivity of the Vasey and Espinoza method (0.97) was similar to that of the method of McGonagle *et al.* (0.98) and greater than that of the methods of Bennett (0.44), Moll and Wright (0.91), the European Spondylarthropathy Study Group (0.74), and Gladman *et al.* (0.91). The CASPAR (classification criteria for psoriatic arthritis) criteria consisted of established inflammatory articular disease with at least three points from the following features: current psoriasis (assigned a score of 2; all other features were assigned a score of 1), a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxta-articular new bone formation, rheumatoid factor negativity and nail dystrophy. These criteria were more specific (0.987 vs. 0.960) but less sensitive (0.914 vs. 0.972) than those of Vasey and Espinoza |**11**|.

Comment

The authors highlight a significant problem in the field of PsA; several different classification criteria exist and it is unclear which is most sensitive and specific for the diagnosis of 'true' PsA. The study focused on establishing classification criteria for the purpose of clinical research rather than clinical diagnosis. In this regard the data will be of most value to academia at present. The study is to be commended for the diversity of centres involved, including 13 different countries, thus reducing cultural bias or centre bias. The Vasey and Espinoza approach is generally regarded as the optimal existing criterion set. These authors recommend the CASPAR method primarily because of its simplicity and higher specificity. The Vasey and Espinoza method, however, demonstrates higher sensitivity, and the relative merits of the two approaches will require comparative evaluation in new cohorts.

Adalimumab improves joint- and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT)

Gladman DD, Mease PJ, Cifaldi MA, *et al. Ann Rheum Dis* 2007; **66**: 163–8 |**12**|

Background. The objective of the study was to evaluate the effect of adalimumab on patient-reported outcomes of joint- and skin-related functional impairment, health-related quality of life (HRQoL), fatigue and pain in patients with PsA. The design was a 24-week randomized controlled trial in which 313 patients with moderate to active PsA were either treated with adalimumab 40 mg every second week or placebo. Four outcome measures were used: the Health Assessment Questionnaire Disability Index (HAQ DI), the Short-Form 36 Health Survey (SF-36), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) and the Dermatology Life Quality Index (DLQI).

Interpretation. Significant differences between placebo- and adalimumab-treated groups were noted in all four outcome measures assessed at 24 weeks. The HAQ DI showed significant changes (–0.4 vs. –0.1, $P < 0.001$) at both 12 and 24 weeks. Significant improvements in the SF-36 domains of physical functioning, physical role, bodily pain, general health, vitality and social functioning, as well as the physical component summary score, were observed when comparing adalimumab and placebo ($P < 0.01$) at 24 weeks. Significantly more patients in the adalimumab-treated group than in the placebo-treated group experienced complete resolution of functional loss (HAQ DI = 0) and dermatologically related functional limitations (DLQI = 0) at 12 and 24 weeks ($P = < 0.001$). Again, at both 12 and 24 weeks, adalimumab led to significantly greater improvements in FACIT-Fatigue scores, pain scores and disease activity measures ($P < 0.001$ for all).

Comment

Adalimumab is a fully human monoclonal anti-TNF antibody widely used in the treatment of RA. Patients with PsA have a significantly reduced quality of life compared with the general population. These patients have a reduced rate of employment and often experience adverse emotional and psychosocial effects. The authors appropriately highlight the economic impact on both individuals and society of maintaining patients in employment. The ADEPT study has shown the effectiveness of adalimumab in improving joint and skin disease whilst also inhibiting radiological progression |**13**|. This paper confirms that adalimumab also confers significant improvement on indices of quality of life. There is a broad concurrence across the different outcome measures suggesting that the benefit of being on treatment provides broad clinical and functional benefit. Although the duration of the study is short (24 weeks), these initial results are encouraging in that long-term alteration in patient-centred outcome can be achieved.

Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from IMPACT2

Kavanaugh A, Krueger GG, Beutler A, *et al. Ann Rheum Dis* 2007; **66**: 498–505 |**14**|

Background. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) showed benefit of infliximab for both articular and dermatological manifestations of psoriatic arthritis |15|. The objective of IMPACT2 was to evaluate both the efficacy and safety of infliximab over 1 year in patients with PsA in a double-blind, randomized, placebo-controlled trial. Two hundred patients with active PsA were randomized to receive infusions of infliximab 5 mg/kg or placebo at weeks 0, 2 and 6, and every 8 weeks thereafter for 1 year. Active disease was defined by five or more swollen joints and five or more tender joints, with either a C-reactive protein level of at least 15 mg /l or morning stiffness lasting 45 min or longer. Concomitant methotrexate (MTX) therapy was allowed but was not mandatory. Patients with persistent disease activity could enter early escape at week 16, and all remaining placebo-treated patients crossed over to infliximab at week 24. Infliximab-randomized patients who had no response or who lost response could escalate their dose to 10 mg/kg starting at week 38. Outcome measures included American College of Rheumatology 20% (ACR20) improvement criteria, Psoriasis Area and Severity Index (PASI) 75 and the ACR70 (the last has not previously been assessed in PsA).

Interpretation. ACR20 was achieved by 58.9% and 61.4% of patients in the randomized infliximab and infliximab/placebo groups, respectively, at week 54. Corresponding PASI 75 scores at week 54 were 50.0% and 60.3%; however, a major clinical response was achieved by only 12.1% of the patients in the infliximab group. The effect of dose escalation from 5 mg/kg to 10 mg/kg in 15 patients who had not achieved ACR20 at week 38 was such that nine of these patients subsequently achieved ACR20 by week 54. Health Assessment Questionnaire (HAQ) scores by week 54 were markedly better than at baseline, with 58.9% in the combined infliximab group and 53% in the placebo/infliximab group achieving significant change in HAQ. The safety profile of infliximab until week 54 was consistent with that observed until week 24. Twenty-two patients (11.5%) in the infliximab combined group experienced serious adverse events, which included infections and altered liver function tests. Two malignancies occurred: basal cell skin cancer (placebo) and stage 1 Hodgkin's lymphoma (infliximab).

Comment

This important trial over a 1-year period has confirmed the benefit of infliximab in the treatment of PsA. However, the effects are variable, with at least 30% of patients not achieving an ACR20. The small numbers of patients suitable for dose escalation make this part of the trial difficult to interpret. Skin responses are more impressive: the fact that 42% of patients achieved a PASI90 response is an important factor when considering the impact of this aspect of the condition on psychological

health. Safety issues remain notable and require rigorous ongoing review in practice and in the context of registries.

Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis

Kavanaugh A, Antoni C, Krueger GG, *et al. Ann Rheum Dis* 2006; **65**: 471–7 |**16**|

Background. As noted above, the IMPACT2 trial evaluated the effect of infliximab in PsA. As part of the study, the effect of infliximab on HRQoL and physical function in patients with active PsA was determined. The trial methods are described above. HRQoL was assessed using the SF-36 at weeks 0, 14 and 24. The SF-36 has eight multi-item scales. Two summary measures of the scales, the physical component summary (PCS) and the mental component summary (MCS,) are derived by aggregating the eight scales as factor components. Functional disability was assessed using the HAQ at every visit until week 24. Associations between changes in quality of life (SF-36) and articular (ACR) and dermatological (PASI) responses were examined.

Interpretation. At week 14 the infliximab group achieved a mean percentage improvement in HAQ from baseline of 48.6%, compared with a worsening of 18.4% in the placebo group ($P < 0.001$). Furthermore, 58.6% and 19.4% of infliximab- and placebo-treated patients, respectively, achieved a clinically meaningful improvement in HAQ (that is a decrease of ≥ 0.3 unit) at week 14 ($P < 0.001$). Increases in PCS and MCS scores and all eight scales of the SF-36 in the infliximab group were greater than those in the placebo group at week 14 ($P \leq 0.001$). These benefits were sustained until week 24. Patients achieving ACR20 and PASI75 responses showed the greatest improvements in PCS and MCS scores.

Comment

A common problem in interpreting clinical studies for use in clinical practice is the relative paucity of data concerning function and quality of life. The IMPACT2 trial included these outcomes and, although the duration of data collection was short, significant functional improvement occurred across HAQ and SF-36 scores. Interestingly, the change in scores was the same whether patients received methotrexate at baseline or whether they received infliximab alone. It remains unclear what further benefit can be obtained from fixed combination of these agents. This has been clearly demonstrated in RA populations |**17**|. Both psoriasis and local arthritis responses are important from a patient's perspective. Maximal improvement in HRQoL was observed in those patients who achieved both a skin and joint response. There remain challenges in interpreting the dichotomous responses in skin and articular compartments – in particular it is unclear whether TNF blockade can be justified on the basis of improvements in one compartment when the other remains active, particularly if the latter was the indicating tissue lesion.

Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis

Kavanaugh A, Antoni C, Mease P, *et al. Rheumatology* 2006; **33**: 2254–9 |**18,19**|

BACKGROUND. The objective of this study was to examine the effect of infliximab on employment status, time lost from work and productivity. A double-blind, placebo-controlled study of patients with active PsA was undertaken. A total of 200 patients with PsA were randomized to intravenous infusions of either infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14 and 22, with early escape at week 16. Employment status, workdays missed and productivity were assessed at baseline and at week 14. The effect of PsA on daily productivity was assessed using a visual analogue scale (VAS).

INTERPRETATION. The baseline employment characteristics were similar between placebo and treatment groups: similar percentages of each group were employed, similar percentages missed workdays and mean productivity scores were also similar. At week 14, median productivity increased significantly in the infliximab group compared with the placebo group (67.5% vs. 9.2%; $P < 0.0001$). Patients in the infliximab group had improved employment status from unemployed at baseline to employed at week 14 (11.5% vs. 0%; $P = 0.084$) and from part-time to full-time employment (30.0% vs. 10.0%; $P = 0.582$). There was also a tendency for patients in the infliximab group to have missed fewer workdays in the 4 weeks prior to week 14.

Comment

It is difficult to attempt to show a change in employment status in a trial, especially with a study duration of 14 weeks. It is, however, a crucial question as a major component of the decision making by institutional and national healthcare providers is made on the basis of cost and clinical effectiveness in the longer term. Thus, societal costs will become an important component of the evaluation of biological agents in general and will remain an issue for TNF blockers in particular in the foreseeable future. This study has shown an improvement in employment status for patients with PsA, once treated with infliximab. The improved productivity correlates with similar findings discussed in this chapter for ankylosing spondylitis patients (see below). The present study must be extended to a longer term and should include the impact of other components of effectiveness including, for example, toxicity and attrition of the use of an individual agent.

Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept

Mease PJ, Kivitz AJ, Burch FX, *et al. Rheumatology* 2006; **33**: 712–21 |**19**|

Background. The aim of this study was to evaluate the clinical and radiographic responses in patients with PsA treated for up to 2 years with etanercept. Patients were previously randomized to receive placebo or etanercept in a double-blind study and chose to participate in the current open-label extension phase. All patients received etanercept 25 mg twice weekly. Radiographic progression was determined at baseline, 1 year and 2 years using the Sharp method modified to include joints frequently affected in PsA. Arthritis and psoriasis responses were determined using ACR20 improvement criteria, PsA response criteria (PsARC) and the PASI.

Interpretation. Initially 205 patients were randomized, with 169 subsequently continuing into the open-label part of the study. Of the latter, radiographic data were available for 141 [71 randomized to receive placebo (placebo/etanercept) and 70 randomized to receive etanercept (etanercept/etanercept)] at 2 years. ACR20 criteria, PsARC and PASI50 criteria were met by 64%, 84% and 62%, respectively, of etanercept/etanercept patients at the end of the 48-week open-label period. Placebo/etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63%, 80% and 73%). Radiographic progression was inhibited in the etanercept/etanercept patients (mean adjusted change in total Sharp score of –0.38 from baseline to 2 years). In placebo/etanercept patients, disease progression was inhibited once patients began receiving etanercept (mean adjusted change of –0.22 from 1 year to 2 years). One serious adverse event occurred in the etanercept group.

The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year

Kavanaugh A, Antoni CE, Gladman D, *et al. Ann Rheum Dis* 2006; **65**: 1038–43 |**20**|

Background. The aforementioned IMPACT trial was employed also to determine the effect of infliximab on structural damage in PsA. The study design is described earlier in this chapter. Hand and feet radiographs were obtained at weeks 0 and 50 and total radiographic scores determined using the PsA modified van der

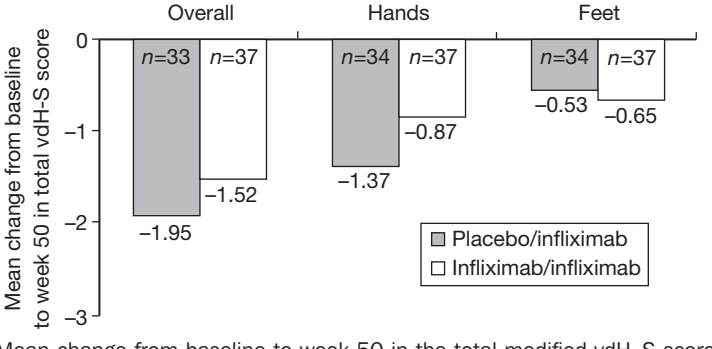

Fig 5.1 Mean change from baseline to week 50 in the total modified vdH–S score. Source: Kavanaugh *et al*. (2006).

Heijde–Sharp (vdH–S) score (Fig. 5.1). Projected annual rate of progression was calculated by dividing the radiograph score by disease duration (years).

Interpretation. Sixty-five per cent of infliximab-treated patients compared with 10% of placebo-treated patients achieved an ACR20 response at week 16 ($P < 0.001$). At week 50, 69% of patients achieved an ACR20 response. Both baseline and week 50 radiographs were available for 72/104 patients. The baseline estimated mean annual rate of progression was 5.8 modified vdH–S points/year. Mean (median) changes from baseline to week 50 in the total modified vdH–S score were –1.95 (–0.50) for placebo/infliximab and –1.52 (–0.50) for infliximab/infliximab patients (*P* not significant). At week 50, 85% and 84% of patients in the placebo/infliximab and infliximab/infliximab groups, respectively, had no worsening in the total modified vdH–S score.

Comment

Progressive joint destruction leads to disability and reduced life expectancy. Understanding the effect of TNF blockers on joint integrity may therefore have prognostic value. The two studies highlighted above show that both infliximab and etanercept are capable of modifying erosive progression in PsA. The 2-year follow-up data support the previous observations made by Mease *et al.* with etanercept over 1 year |**21**|. The evidence that infliximab is also effective in this regard is therefore unsurprising, but nevertheless reassuring. Note, however, that radiologically most patients do not progress to further erosive disease and that similar proportions of patients in each group had no worsening of scores. It is also noteworthy that the placebo/infliximab group had received infliximab for half as long as the infliximab/infliximab group. Although the results reached statistical significance, it is doubtful if the study is adequately powered. Radiographic progression to disability and deformity have been very significantly delayed in RA practice by the aggressive use of TNF blockers – discrepancies exist between inflammation suppression and modification of articular damage. Similar investigations will be of interest in the PsA patient cohort – the assumption that this will be reproduced should be made only with caution as there are distinct radiographic and, therefore, presumably, pathophysiological pathways operating in the two diseases.

Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study

Mease PJ, Gladman DD, Keystone EC, Alefacept in Psoriatic Arthritis Study Group. *Arthritis Rheum* 2006; **54**: 1638–45 |**22**|

Background. The aim of this double-blind, randomized, placebo-controlled clinical trial was to evaluate both the efficacy and safety of alefacept in combination with MTX for the treatment of PsA. Inclusion criteria included age 18–70 years, active PsA (three or more swollen joints and three or more tender joints) despite treatment with MTX for ≥3 months. Alefacept (15 mg) or placebo

was administered intramuscularly once weekly for 12 weeks in combination with MTX, followed by 12 weeks of observation during which only MTX treatment was continued. The primary efficacy endpoint was the proportion of patients achieving an ACR20 response at week 24.

Interpretation. A total of 185 patients were included in the study, with 123 randomized to receive alefacept plus MTX, and 62 to receive placebo plus MTX. At week 24 after initiation of the study, 54% of patients in the alefacept plus MTX group achieved an ACR20 response, compared with 23% of patients in the placebo plus MTX group ($P < 0.001$). Mean reductions in tender and swollen joint counts in patients receiving alefacept plus MTX were –8.0 and –6.3 respectively. Significant skin improvements were also noted in many patients. In the alefacept plus MTX group, the incidence of serious adverse events was low (1.6%), and no opportunistic infections or malignancies were reported.

Comment

This study is the first phase II clinical trial using MTX and alefacept for the treatment of PsA. Previous phase I data have shown some preliminary signs of benefit in both cutaneous and articular compartments |**23,24**|. Alefacept was the first biological drug to be used for the treatment of chronic plaque psoriasis, and is believed to act by inhibiting T-cell activation, blocking CD2 lymphocyte function-associated antigen-3 (LFA-3) interactions. Treatment duration was only 12 weeks, which perhaps accounts for the fact that the ACR50 and ACR70 responses appear reduced towards 24 weeks. That said, however, co-stimulator blockade has been associated with accrual of responders throughout and after treatment periods in other co-stimulatory blockade studies, reflecting the kinetics of the role played by T-cells in the pathogenesis of disease as an upstream pathological event. No radiological data or functional scores were reported. Moreover, the initial results are significant but modest compared with alternative biological drugs now available and described above. The dose of alefacept used was 15 mg i.m., selected on the basis of that used for psoriasis, and it would be interesting to investigate if this dose is optimal. The safety profile appears satisfactory, although it is of some concern that CD4+ T-cell counts dropped in 7% of patients in the alefacept group to $< 250\,mm^3$. A larger study including dose titration and inclusion of radiological data is now required. It is likely that there will be accrual of non-responders to TNF blockade over time, and as such it is important that novel therapeutic approaches are now developed. Given the apparent effectiveness compared with placebo of alefacept in psoriasis and in this preliminary study in PsA, further studies appear warranted.

General comments

The foregoing studies define the clear advantages to be found in the use of TNF-blocking agents in the treatment of PsA. Future efforts are now required to identify those patients most likely to benefit from such intervention and when such agents should be optimally used. For example, it is unclear whether the remarkable benefits found in early intervention in RA can be reproduced in the PsA population |**25,26**|.

Moreover, there is the intriguing possibility that early intervention may prevent disease emerging in an additional tissue compartment – this can best be examined in the treatment of psoriasis patients in whom the onset of arthritis can be carefully documented on an ongoing basis. Whether the event rate will be high enough to garner such information in the short term is unclear. Finally, it will be mandatory to collect appropriate safety data for this patient group to ensure that there is no unexpected toxicity emerging beyond that observed in registries recoding outcomes in the RA population. Closure of the latter as RA cohorts are achieved may endanger this requirement and merits detailed consideration of the establishment of disease-specific registries, perhaps on an international basis.

Ankylosing spondylitis

The major recent advance in the treatment of ankylosing spondylitis (AS) is the advent of TNF-blocking agents. Previous studies have demonstrated the beneficial effects of infliximab and etanercept |**27–32**|. The review of 2006 publications demonstrates further evaluation of the benefits of these agents and confirms that adalimumab is also effective in AS. Other studies of note include an evaluation of the relative merits of sulphasalazine in AS, formal testing of the role of exercise in AS, long held to be of prime importance, and also one paper alluding to the potential for novel biomarkers for disease activity and tissue damage.

Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicentre, randomized, double-blind, placebo-controlled trial

van der Heijde D, Kivitz A, Schiff MH, *et al.*, ATLAS Study Group. *Arthritis Rheum* 2006; **54**: 2136–46 |**33**|

Background. The study aim was to evaluate the safety and efficacy of adalimumab in patients with active AS. The design was that of a multicentre, randomized (2:1 ratio), double-blind, placebo-controlled study to evaluate a subcutaneous injection of adalimumab, 40 mg every second week, compared with placebo for 24 weeks. The primary efficacy endpoint was the percentage of patients with a 20% response according to the Assessment in Ankylosing Spondylitis International Working Group criteria for improvement (ASAS20) at week 12 (Fig. 5.2). Secondary outcome measures included the ASAS20 at week 24 and multiple measures of disease activity, spinal mobility and function, as well as ASAS partial remission.

Interpretation. At week 12, 58.2% of adalimumab-treated patients (121 of 208) achieved an ASAS20 response, compared with 20.6% of placebo-treated patients (22 of 107) ($P < 0.001$). More patients in the adalimumab group (45.2%, 94 of 208) than in the placebo group (15.9%, 17 of 107) had at least a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at week 12 ($P < 0.001$). Significant

improvements in the ASAS40 response and the response according to the ASAS5/6 criteria at weeks 12 and 24 were also demonstrated ($P < 0.001$). Partial remission was achieved by more adalimumab-treated patients than placebo-treated patients (22.1% vs. 5.6%; $P < 0.001$). Adalimumab-treated patients reported more adverse events (75.0% vs. 59.8% of placebo-treated patients; $P < 0.05$), but there was no statistically significant difference in the incidence of infections. Most adverse events were mild or moderate in severity.

Comment

This well-designed trial was well powered and showed satisfactory retention of patients, with 296 of 315 patients remaining in the study at week 24. It demonstrates the benefit of adalimumab therapy for treatment of AS. A wide range of outcome measures demonstrated improvement, including Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI, patients' and physicians' global assessments of disease activity, C-reactive protein levels and lumbar side flexion. One area not included in the study was radiological assessment of bone oedema by MRI scanning – such studies will be of interest in future. There were no major adverse events and the safety profile appeared similar to that reported in comparative studies in RA and PsA.

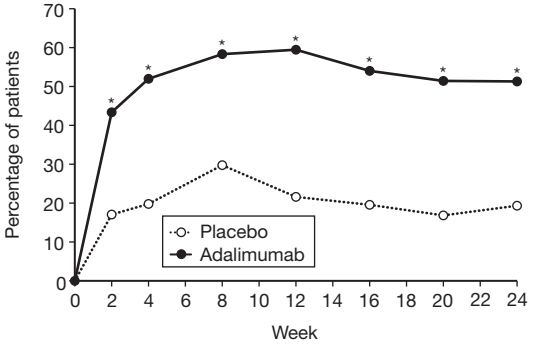

Fig 5.2 Percentage of patients who achieved a 20% response over time according to the Assessment in Ankylosing Spondylitis International Working Group criteria for improvement. *$P < 0.001$ versus placebo, based on an intention-to-treat analysis using non-responder imputation. Source: van der Heijde *et al*. (2006).

Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis

van der Heijde D, Da Silva JC, Dougados M, *et al.*, Etanercept Study 314 Investigators. *Ann Rheum Dis* 2006; **65**: 1572–7 |**34**|

Background. Etanercept is used in a twice-weekly 25 mg dose in patients with AS. This study aimed to compare the efficacy, pharmacokinetics and safety of using etanercept 50 mg once weekly in AS patients with twice-weekly etanercept

25 mg and placebo. Trial design was of a randomized, double-blind, placebo-controlled trial for 12 weeks. Patients (356) with active AS were recruited. A visual analogue scale was used to determine active AS. The primary outcome measure was the proportion of patients achieving an ASAS20 response at week 12. Secondary outcomes included the proportion of patients who achieved ASAS40 and ASAS5/6, BASDAI and patient and physician global assessments of disease activity. Baseline characteristics were similar among all three groups.

Interpretation. ASAS20 response at 12 weeks was achieved by 74.2% of patients treated with etanercept 50 mg once weekly and 71.3% of those treated with etanercept 25 mg twice weekly, in both cases significantly higher than the response rate in patients taking placebo (37.3%, $P < 0.001$). The ASAS40 response followed a similar pattern (58.1%, 53.3% and 21.6% respectively; $P < 0.001$). Moreover, even at 2 weeks significant improvement was seen in measures of disease activity, back pain, morning stiffness and C-reactive protein level ($P < 0.05$). Serological detection of etanercept was similar between the etanercept groups. There were no differences in side-effects between all groups.

Comment

It has been shown that patients with RA have similar responses to etanercept when given as once-weekly 50 mg or as 25 mg twice weekly |**35**|. This study was designed to assess if this is also true in the AS population. The potential advantages of a once-weekly preparation include improved compliance, a reduction in the severity or frequency of local skin reactions, and ease of storage and distribution. Non-inferiority of the weekly etanercept was demonstrated, and secondary outcomes such as BASDAI and CRP have confirmed the benefit from ASAS criteria. It can be concluded that 50 mg of etanercept weekly is an effective drug in the treatment of AS. This has implications for the daily use of this agent pending local approval for this formulation.

Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a 54-week study

Cantini F, Niccoli L, Benucci M, *et al. Arthritis Rheum* 2006; **55**: 812–16 |**36**|

Background. One of the important questions arising in the treatment of AS, as in other rheumatic disorders, is how to treat the patient in whom one TNF-blocking agent is no longer efficacious or who has problems tolerating the drug. This study looked at the effect of switching to once-weekly 50 mg etanercept in patients who had failed to achieve or maintain an ASAS20 response, or who had withdrawn from infliximab therapy due to intolerance or adverse events. Patients were recruited over 24 weeks and the trial design was that of a 54-week, open-label prospective study. The primary outcome was the percentage of ASAS20

responders at 54 weeks, with secondary outcomes including ASAS20 at week 24, ASAS50 and ASAS70 at weeks 24 and 54, change in BASDAI from baseline, the number and severity of etanercept-related adverse events, and the percentage of patients who were able to reduce or interrupt corticosteroid, NSAID or analgesic intake.

Interpretation. Twenty-three patients were recruited. In 18 of these patients, the reason for switching to etanercept was lack of effect of infliximab. No serious adverse events occurred during the study. At week 24 ASAS20 was achieved by 18 (78%) of the 23 patients, ASAS50 by 12 patients (52%) and ASAS70 by 9 (39%) of 23 patients. At week 54, ASAS20 was recorded in 17 (74%) of 23 patients, ASAS50 by 14 (61%) of 23 and ASAS70 by 9 (39%) of 23. The mean ± SD BASDAI score fell from 6.9 ± 1.3 at baseline to 3.1 ± 1.5 at week 24 ($P = 0.001$). It had decreased significantly to 2.9 ± 1.7 at week 54 ($P < 0.001$). Withdrawal of corticosteroids was possible in 9 of 10 patients, and a 50% reduction in dose was achieved in one patient. NSAID and analgesic interruption was recorded in 19 of 20 patients.

Comment

Do patients respond to a different biological drug targeting the same biological target once the initial biologic used has lost effect |**37**|? This study attempts in part to answer that question for the AS population in whom treatment with infliximab is no longer beneficial. This study concludes that AS patients may respond in numbers similar to those observed in biologic-naive cohorts. Important provisos should be noted – the number of patients is small and the study is open-label. Nevertheless, the data suggest that the mode of action of these agents in AS pathogenesis may not be consistent across all patients. Alternatively, there may be important pharmacokinetic differences between these agents in a subset of AS patients. It will be important to perform the reverse experiment in which etanercept partial or non-responders are subsequently exposed to infliximab.

Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial

van der Heijde D, Han C, DeVlam K, *et al. Arthritis Rheum* 2006; **55**: 569–74 |**38**|

Background. Ankylosing spondylitis can lead to disability and loss or reduction in employment. This is particularly important in this condition, which often has an onset in the early decades of life, when patients are likely to be in employment. The trial aimed to examine whether clinical benefits observed after treatment with infliximab were accompanied by improvement in productivity and reduction in time lost from work in a randomized, double-blind, placebo-controlled, multicentre trial of patients with AS. The Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) confirmed previous studies showing that

infliximab reduced the signs and symptoms of AS. Adults with active AS receiving standard anti-inflammatory treatment were randomized to receive infusions of placebo or 5 mg/kg infliximab at weeks 0, 2 and 6 and every 6 weeks thereafter until week 24. Physical function was measured using the BASFI. The impact of disease on productivity was measured using a visual analogue scale (range 0–10). Self-reported employment status and time lost at work before and during the trial were collected. Spearman's correlation coefficient was used to examine factors associated with productivity.

Interpretation. Patients treated with infliximab experienced a more significant reduction in limitations of work and daily activity due to physical or emotional problems than patients treated with placebo. Of the subset of patients employed full time, patients in the infliximab group had a significantly greater improvement in productivity as early as week 6 than did the placebo group. The median change from baseline in the productivity score at week 24 was 0.7 (median change 11%) in the placebo group compared with 2.1 (62%) in the infliximab group ($P < 0.05$). Daily productivity was significantly correlated with physical function and disease activity at baseline and week 24.

Comment

This trial has confirmed that the impact of physical and emotional health on work and daily activity is significantly reduced in patients treated with infliximab. Disappointingly, however, patients who were previously unemployed remained so, and the study really demonstrates that those who were already in employment had fewer 'sick days'. Note also that many data are based upon self-reporting and should be interpreted with some caution. For example, it was noted that patients who had physical or emotional problems at baseline were more likely to be unemployed and tended to miss more workdays. The trial duration is comparatively short to determine such outcomes, but suggests that future analyses should include such measures. This will be of particular importance as the relevant health economic models are tested to evaluate the cost-effectiveness of biological agents in AS in the longer term.

Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicentre, randomized, double-blind, placebo-controlled magnetic resonance imaging study

Braun J, Landewe R, Hermann KG, *et al.*, ASSERT Study Group. *Arthritis Rheum* 2006; **54**: 1646–52 |**39**|

Background. The study aim was to determine whether the effects of anti-TNFα in reducing the signs and symptoms of AS coincide with a reduction in spinal inflammation as detected by MRI. The study design was that of a multicentre, randomized, double-blind, placebo-controlled study. Pre- and post-gadolinium T1 and short TI inversion recovery (STIR) magnetic resonance images of the spine

were acquired at baseline and at week 24 in patients with AS who participated. Patients were randomly assigned at an 8:3 ratio to receive infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2 and 6 and then every 6 weeks thereafter. MR images were obtained and evaluated independently by two readers who were blinded to the treatment allocation and time sequence of the images.

Interpretation. A total of 194 patients in the infliximab group and 72 patients in the placebo group had evaluable images at baseline and week 24. About 80% of the patients had at least one active spinal lesion at baseline, as assessed by MRI. The improvement in the MRI activity score after 6 months was significantly greater in the patients who received infliximab (mean 5.02, median 2.72) than in those who received placebo (mean 0.60, median 0.0) ($P < 0.001$). Almost complete resolution of spinal inflammation was seen in most patients who received infliximab, irrespective of baseline activity.

Comment

This study, the largest of its kind yet performed, has convincingly demonstrated the role of TNF in spinal inflammation. By imaging the spine with MRI scanning, significant differences in the degree of spinal inflammation have been shown when patients are treated with infliximab. These radiological findings confirm clinical findings from previous studies |**5**|. It remains to be seen to what extent TNF-blocking drugs can prevent radiographic progression in addition to reducing spinal inflammation.

An international study on starting tumour necrosis factor-blocking agents in ankylosing spondylitis

Pham T, Landewe R, van der Linden S, *et al. Ann Rheum Dis*. 2006; **65**: 1620–5 |**40**|

Background. This paper looked at determining the type and proportion of patients with AS whom rheumatologists consider to be candidates for treatment with TNF-blocking agents, and to what extent this is in agreement with the ASAS international working group recommendations on initiation of treatment with anti-TNF agents. Participants were rheumatologists from 10 different countries, who were considered to be experts in treating patients with AS and in the use of anti-TNF treatment, but were unaware of the ASAS recommendations (unpublished at the time of study in 2003). The first 10 consecutive patients with AS seen by the rheumatologist were evaluated as to whether they were candidates for anti-TNF treatment. Thereafter, a metrologist assessed the patients for disease activity and severity, and collected data on demographics and treatment.

Interpretation. Complete data were available for 1207 of the 1284 patients and were used for analysis. Overall, the rheumatologists indicated that they would initiate TNF-blocking agents in 49.3% of patients, ranging from 37.2% patients in Canada to 78.3% in Australia. These candidates had higher disease activity, higher levels of acute-phase reactants, worse spinal mobility, worse function, a greater frequency of hip involvement and a higher prevalence of sick leave. Of all patients considered to be candidates, 40%

did not fulfil ASAS recommendations with respect to previous use of NSAID (at least two NSAIDs) or BASDAI (≥4). Conversely, 36% of patients who did not fulfil the NSAID or BASDAI recommendations were still considered to be candidates for TNF-blocking treatment. Objective variables such as C-reactive protein, erythrocyte sedimentation rate (ESR) or magnetic resonance activity were considered less important than disease activity in the decision on starting TNF-blocking drugs. The only important objective criterion was rapid radiographic progression.

Comment

The discrepancy between the rheumatologists' opinions and the recommendations of the ASAS group are unsurprising and reiterate the importance of having available reliable and validated clinical guidance to ensure consistency of use of biological agents across a given population. Many other variables, however, will impinge upon the treatment decision, including comorbidity and local and national clinical guidelines and restrictions or those otherwise placed by the healthcare providers and funding agencies.

Increased disease activity is associated with a deteriorated lipid profile in patients with ankylosing spondylitis

van Halm VP, van Denderen JC, Peters MJ, *et al. Ann Rheum Dis* 2006; **65**: 1473–7 |**41**|

Background. The aim of this study was to explore the association between disease activity and lipid profile in patients with AS. Cardiovascular mortality is increased in patients with AS. A possible explanation might be a more prevalent atherogenic lipid profile in patients with AS than in the general population. It has been postulated that inflammation 'deteriorates' the lipid profile, thereby increasing cardiovascular risk. Disease activity parameters for AS and lipid levels [total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides] were measured in 45 patients with AS for 6 months after starting treatment with leflunomide or placebo. Findings in this treatment group were compared with those in 10 patients with AS treated with etanercept. Blood samples for lipid measurement were taken after overnight fast at weeks 2, 4, 6, 9, 12, 16, 20 and 24. A specialized regression model, adjusting for repeated measurements, age and sex, was used to assess the influence of the disease activity variables on the lipid levels.

Interpretation. Forty-five patients were recruited with mean age of 42 years. Multilevel regression analyses showed significant associations between disease activity parameters and lipid levels, for instance higher CRP and ESR levels were significantly associated with lower total cholesterol ($P < 0.001$), with regression coefficients of –0.01 and –0.01 respectively. BASDAI confirmed that those patients with clinically active disease had lower total cholesterol levels, with triglyceride levels having an

inverse relationship with disease activity. Both serological and clinical data therefore demonstrated a higher atherogenic index for those patients with active disease. Similar significant associations were found between other disease activity parameters and lipid levels.

Comment

This relatively small study was designed to investigate potential surrogates explaining the higher mortality due to cardiovascular death in AS. Increase in disease activity was associated with decreases in lipid levels. The effect was sustained across both patient groups, i.e. those taking etanercept and leflunomide. It should be noted that the investigators did not exclude from the trial patients who were taking statin medication despite the potential impact of these drugs on lipid profile. The inclusion of patients on leflunomide is also noteworthy – one of its recognized side-effects is hyperlipidaemia. The findings are in keeping with those of other studies in inflammatory disease which have found altered lipid profiles compared with control populations |**42,43**|. It would be advisable for the clinician to be assiduous in treating adverse lipid profiles in AS until formal clinical guidelines can be formulated.

One-year follow-up of two exercise interventions for the management of patients with ankylosing spondylitis: a randomized controlled trial

Fernandez-de-Las-Penas C, Alonso-Blanco C, Alguacil-Diego IM, Miangolarra-Page JC. *Am J Phys Med Rehabil* 2006; **85**: 559–67 |**44**|

Background. Exercise has been a cardinal component of the management of AS. This study aimed to assess the long-term effects on functional and mobility outcomes of two exercise interventions for the management of patients with AS. In an extended 12-month follow-up of a randomized controlled trial, 40 patients were diagnosed with AS according to the modified criteria of New York and randomized to control or experimental groups. The exercise programme was performed at least three times per month. The control group was treated during 15 sessions with a conventional exercise regimen in AS, whereas the experimental group received 15 sessions of exercises based on the treatment of the shortened muscle chains following the guidelines described by the Global Posture Re-education method. These patients were followed up and assessed again 1 year after entering the study. Outcome measures included scores for Bath Ankylosing Spondylitis Metrology Index (BASMI; tragus to wall distance, modified Schober test, cervical rotation, lumbar side flexion, and intermalleolar distance), BASDAI and BASFI.

Interpretation. The intra-group comparison between follow-up and post-intervention data showed that clinical and functional measures decreased in both groups during the follow-up period. Lumbar side flexion and intermalleolar distance measurements reached significance (control: $P = 0.001$; intervention: $P = 0.002$). Intra-group differences between follow-up and pre-intervention assessments revealed that improvements in all mobility measures of the BASMI index and in the BASFI index were partially maintained

at the 12-month follow-up in the experimental group but not in the control group. The inter-group comparison (unpaired *t*-test analysis) between changes on each outcome during the long-term follow-up (post follow-up and pre-follow-up) showed no significant differences in the decrease between post-intervention and follow-up data between the study groups. On the other hand, the inter-group comparison between pre-intervention and follow-up data revealed significant differences in almost all mobility measures of the BASMI index (except for cervical rotation) and in the BASFI index, in favour of the experimental group.

Comment

Patients who have been given exercises based on the shortened muscle chains seem to retain better mobility. The study validates the use of these exercises as an alternative to the conventional exercise regimen used in AS |**44,45**|. Assuming that there are no differences in drug therapy between the groups, this study is a reminder of the need to optimize all aspects of patients' care that contribute to improved function. It would be hoped that physiotherapy advances could be optimized, especially for the patient in whom non-steroidal anti-inflammatory medication or biologics are contraindicated.

Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity

Chen CH, Lin KC, Yu DT, *et al. Rheumatology (Oxford)* 2006; **45**: 414–20 |**46**|

Background. It has been suggested that matrix metalloproteinases (MMPs) could be used as a potential marker of disease activity in AS. These endopeptidases are involved in the maintenance of the extracellular matrix, and MMP-3 has been elevated in AS patients with high BASDAI scores. The objective of the study was to submit serum levels of MMPs and tissue inhibitors of metalloproteinases (TIMPs) to statistical analyses to test their exact degrees of clinical usefulness as biomarkers for detecting high disease activity in AS, comparing them with ESR and CRP. Serum levels of MMP-1, -3 and -9 and TIMP-1 and -2 were measured in 42 AS patients and 20 healthy control subjects. The BASDAI provided the gold standard for measuring disease activity. Patients with BASDAI ≥4 were regarded as having high disease activity. The results were compared with results for a separate cohort of 41 AS patients.

Interpretation. Only MMP-3 levels were significantly higher in AS patients than in healthy control subjects ($P < 0.001$). Among AS patients, MMP-3 levels were also higher in patients with high disease activity than in those with low disease activity, and correlated significantly with BASDAI ($r = 0.366$, $P = 0.017$) and functional indices ($r = 0.344$, $P = 0.026$). The correlation with BASDAI was stable in a 1-year follow-up

($r = 0.464$, $P = 0.095$) and reproducible with two different enzyme-linked immunosorbent assays. The BASFI of functional impairment also correlated with MMP-3 levels in patients with high disease activity. The sensitivity and specificity of MMP-3 level was 69.2% and 68.8% respectively. Most importantly, using receiver operating characteristic plots to analyse the two cohorts, MMP-3 was more accurate than ESR and CRP in detecting AS patients with high disease activity ($P = 0.01$ and $P = 0.009$ respectively).

Comment

There is currently considerable interest in the advent of novel biomarkers of disease activity, and particularly of biomarkers that might relate to underlying tissue damage and remodelling. The paper defines a possible new marker of disease activity in AS. The authors have convincingly shown acceptable sensitivity and specificity of MMP-3; it appears not to be inferior to conventional serological measures of disease activity. The study numbers are not large, and so findings need to be treated with caution. Other studies have reported variable results in comparing MMP-3 levels and disease activity. If confirmed, developing an assay to use in clinical practice will be a helpful adjunct in patient assessment.

Efficacy of sulphasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre, randomized controlled trial

Braun J, Zochling J, Baraliakos X, *et al. Ann Rheum Dis* 2006; **65**: 1147–53 |**47**|

Background. In this study, the aim was to assess the effect of sulphasalazine (SASP) on inflammatory back pain (IBP) due to active undifferentiated spondyloarthritis (uSpA) or AS in patients with symptom duration < 5 years. Patients (230) with IBP and a BASDAI > 3 from 12 centres were randomized and treated for 24 weeks with placebo or SASP 2 g/day. The primary outcome variable was the change in BASDAI over 6 months. Secondary outcomes included measures of spinal pain, physical function and inflammation. Radiographic evaluation was done including of the vertebral column and sacroiliac joints if the patient had symptoms of disease in these regions at baseline.

Interpretation. Patients were aged 18–64 years (50% male) and at baseline 67% were positive for human leucocyte antigen B27 (HLA-B27+ve). Enthesitis was found in 50% and peripheral arthritis in 47% of the patients. No difference was present in treatments between the groups. The mean (SD) BASDI was markedly reduced in both groups: by 3.7 (2.7) and 3.8(2.4) for the SASP and placebo groups respectively. Patients with IBP and no peripheral arthritis experienced significantly ($P = 0.03$) greater benefit with SASP [BASDAI 5.1 (1.3) to 2.8 (2.3)] than with placebo [5.2 (1.6) to 3.8

(2.4)]. Spinal pain ($P = 0.03$) and morning stiffness ($P = 0.05$) improved with SASP in these patients, but other secondary outcomes were not markedly different.

Comment

This is a study which has been long overdue given the frequent use of SASP for peripheral arthritis associated with the spondyloarthropathies. The authors attempt to answer the important question of whether SASP improves spinal inflammatory back disease. Interestingly, there was no difference between the AS and uSpA group as a whole and the placebo group at 24 weeks, but the significant benefit of SASP in the uSpA group with no peripheral arthritis is an interesting finding. The latter group has not previously shown any benefit from SASP, although CRP and morning stiffness have been found to be improved. The investigators point out that in retrospect the BASDAI may not be the best outcome measure as it has not been validated in uSpA. However, it is difficult to see what alternative measure would be used, and it has been well validated for AS patients. The control group may have received higher doses of NSAIDs, which could further complicate interpretation of the outcome of the trial. Given the familiarity that most clinicians have with SASP and its cost advantage over anti-TNF treatments, it should be considered for uSpA patients with inflammatory back symptoms.

Conclusion

Like RA, the seronegative arthropathy field is dominated by the advent of biological therapeutics. Significant challenges remain. Despite the long-known association with HLAB27, and the recognition of a large variety of components of innate and adaptive immune responses in the synovial membrane and enthesial compartments, it is unclear what future biological interventions may comprise or offer. Considerable interest lies in the biology of interleukin 17 (IL-17) and IL-23 in this respect. Similarly, the co-stimulation blockers may offer long-term promise as tolerance-inducing agents. Progress may be possible in other directions however. The advent of disease activity-focused/strategic approaches in RA has brought about considerable improvements in outcomes – similar approaches should be attempted in the spondyloarthropathies. An increasing evidence base is required to justify or otherwise the use of traditional DMARDs such as MTX and leflunomide. Together the relative merits of these agents in combination with biologics, particularly TNF-blocking agents, should also be better clarified. Finally, biomarker-based evaluation of disease activity and improved disease outcome measures will be necessary to optimize treatment and in due course promote patient-centred therapeutics and eventually personalized medicine.

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6

Education developments in rheumatology

JOANNE BURKE, MAX FIELD

Introduction

Alterations to medical education have occurred over the past few decades, but really developed when the General Medical Council (GMC) issued the document *Tomorrow's Doctors* in 1993, which charged medical schools in the UK with the task of reforming undergraduate training |**1**|. This document identified the reasons for change and described the generic skills required for the practice of medicine. It also defined the necessary philosophical principles involved and suggested some values that could guide faculty staff in their approach to the challenge. Medical schools were asked to reduce factual knowledge by defining a core curriculum, to reassess discipline-based teaching in isolation by encouraging integration of subjects, and to discourage rote learning by stimulating students to analyse information and make decisions on their own. These changes were designed to promote student-centred learning, stimulate curiosity, develop critical thinking and encourage a more adult method of study that could form the basis for continued learning after graduation.

Over the last 15 years postgraduate training has also changed significantly, with two factors altering attitudes. First, the move towards specialist registrar as a unified middle grade reduced the number of years of training |**2**| and, second, the new FY1/FY2 training grade and changes resulting from run-through training have meant a further alteration in the programmes after *Modernising Medical Careers* |**3**|. These moves have been driven in part by harmonization across Europe because staff have the option to travel across national boundaries, and in part in response to the persistent drive to reduce working hours to comply with the European Working Time Directive. In addition, amendments at an undergraduate level have produced an initiative to review what training occurs as a postgraduate and how best to build on that which takes place during the undergraduate years. Whatever the cause, the reduction in clinical contact time is increasingly recognized as a significant influence, and this has resulted in training at all levels having to be restructured.

This article explores the impact of these changes on undergraduate and hospital-based postgraduate medical education, particularly in the sphere of rheumatology. Despite guidelines at a European level, there is little published information about

what is included in individual medical school curricula in the UK or Europe. It is on this basis that this chapter describe the changes that have occurred in Glasgow as an example of the problem-based learning that has been instigated in undergraduate education as part of the new development in medical school courses. This is used to provide an illustration of what can be included in an integrated programme to increase exposure in rheumatology and orthopaedics over the 5 years of any course. In addition, postgraduate education in the context of secondary care is described and, because this is already more proscribed by the Joint Committee for Higher Medical Training (JCHMT), the possibilities for development in light of recent changes to training programmes are discussed.

Undergraduate training

The GMC recommendations for undergraduate medical education provided far-reaching guidelines for curriculum change |**1**|. Much of the early discussion about teaching in rheumatology was published before or just after these changes |**4,5**|. Subsequent review of the practice in the UK, 10 years later |**6**|, provided increased information about undergraduate education in rheumatology and showed that, although the number of hours devoted to rheumatology had fallen, training in musculoskeletal system diseases had become more widespread across the UK curricula. In light of the GMC recommendations, there have been calls to make any curriculum development compatible with the format of student-centred learning |**7**|, and for a standard curriculum to be developed to support the students |**8**|, but to date, although the European League against Rheumatism (EULAR) has suggested some guidelines |**9**|, there is no one programme specifically set for the UK needs.

In most cases, the UK medical schools have made amendments to their course in response to the GMC |**10**|, but it would be fair to say that some have been more far-reaching than others. One example of what can be achieved as a result of reform to the traditional course is that which has been developed in Glasgow. Traditionally, students were subjected to lectures based on individual subjects in a classical 'preclinical' format prior to entering a clinical phase of the course in a purely hospital-based environment. The present course now integrates learning across the years using a problem-based learning (PBL) approach.

The first 3 years

The response of Glasgow Medical School to *Tomorrow's Doctors* was a radical change in the medical curriculum based on the model implemented at the University of Limburg in Mastrich |**11**|. The launch of this course took place in October 1996 and, as in some other UK medical schools, PBL was a core element. In the first 3 years of the new course, small groups of students work through patient-centred scenarios. These were originally designed by teams of experts, and covered concepts necessary for understanding of each topic. The student groups initially reactivate their prior knowledge, as part of the initial review of the scenario, when, under the

guidance of a trained facilitator, they discuss what the group understands about the subject. They then establish what their limitations are concerning this scenario and what questions they need to address to extend their background understanding. Subsequently, they use resources from the library such as books, journal articles and the internet to extend their background knowledge. This is supported by timetabled events such as expert-led workshops, laboratories and plenary reviews on the topics under investigation. This provides an integrated learning experience that is finally subject to one further review by the student group and their facilitator to ensure that an adequate core knowledge has been achieved. This is based on the learning objectives recommended by the specialist team to ensure that their requirements are fulfilled.

Some scenarios relate to the musculoskeletal system and their manifestations as well as management issues. The core for the musculoskeletal system in the first 3 years of the course is outlined in Table 6.1. In the first year, a series of scenarios involves casualties from a car and bicycle accident. Areas covered include the bones

Table 6.1 Details of MSS training for Glasgow medical students from years 1 to 3

	Year 1	Year 2	Year 3
Spine	Structure/function spinal cord, nerves and vertebral column	Back pain, sciatica, spinal reflexes, pain management	
Upper limb	Anatomy, bony landmarks, shoulder dislocation, immunology	Muscle biology, ligament injuries and Colles fracture	Inflammatory joint disease Management of RA
Lower limb	Anatomy, bony landmarks, fractures of femur and pelvis	Muscle biology, joint anatomy and architecture, acute ligament injuries	Degenerative joint disease Management of OA
Fractures	Fractures, complications and investigations	Colles fracture osteoporosis, bone structure/function and healing	Metabolic bone disease, X-rays
Disability	Chronic disability, neuromuscular disability, chronic joint disease and multiple fractures		
Ethics	Consent, legal issues, perspectives on autonomy and competence, public health, prioritization of healthcare		
Profession	Communication skills, medical legal issues, interactions with professionals, PAMs and alternative therapies		
Clinical skills	Range of joint movements using locally developed video	History and examination of normal MSS using GALS system and video	History and examination of MSS using normal and MSS patients

GALS, gait, arms, legs and spine; MSS, musculoskeletal system; OA, osteoarthritis; PAMs, professions allied to medicine; RA, rheumatoid arthritis.

of the limbs and the joints, features of fractures and their complications, imaging, treatment principles and the role of the rehabilitation team. In year 2 the emphasis of the scenarios moves towards a molecular and cellular approach, with the structure and function of bones, muscles and ligaments being investigated. At this time the students are encouraged to learn about pain physiology and management, ligament injuries, fracture healing and osteoporosis. In year 3 there is more of a clinical emphasis, with differential diagnosis, investigations and interpretation of results being a major component of the training. The scenarios are set around inflammatory joint disease, degenerative joint disease and metabolic bone diseases and their management, although, when appropriate, basic science knowledge from earlier years is also revisited.

Vocational studies and clinical skills

In parallel with this core, students begin to develop their clinical skills, communication skills and topics relating to professional development during the first 3 years of their course as part of the vocational studies element. In terms of clinical skills, hospital staff and general practitioners act as vocational tutors to supervise the students' training in clinical examination techniques from the first year onwards and history-taking expertise from year 2. The students learn the recommended examination skill for each system by watching relevant CDs of each clinical ability.

In the context of the musculoskeletal system, students in year 1 study joint movement by watching an instructional CD made to demonstrate the range of movements that each joint can perform. Physiotherapists and medical staff supervise these sessions and students are encouraged to demonstrate the movements on one another. In year 2 students extend this experience by examining a CD resource covering the gait, arms, legs and spine (GALS) system developed by Docherty and colleagues |**12**| for the Arthritis Research Campaign (ARC) to provide them with an instruction on how to start to examine the musculoskeletal system in more detail. This is followed by two sessions in which students practise the GALS examination skill on normal individuals, guided by their tutor to reinforce this learning. By observing and performing these clinical skills in patients with musculoskeletal system problems in hospital and general practice settings, the students develop this further, and in the third year the GALS examination system is put in the context of patients with musculoskeletal system diseases. Two further CDs based on the GALS have been developed by our students; using patients with single-joint (shoulder and hip) problems, these CDs show how the use of GALS can help identify damaged joints. We are extending this range of examples by asking our students to generate more CDs in patients with back problems and various polyarthritides to show that the GALS examination can be a useful screening technique across a variety of disorders and symptoms.

Nevertheless, the first 3 years of the course were designed to provide a core competence in each of the specialties, which is further enhanced during the final 2

years of the course, when students deal with patients with a spectrum of diseases. In the context of the musculoskeletal system this programme from year 1–3 provides a base from which to build.

The final years, years 4 and 5

In the final 2 years of the course, students are attached for 5-week blocks to clinical units in teaching and general hospitals. This part consists in a series of clinical attachments in the specialties of medicine, surgery, psychological medicine, child health, obstetrics and gynaecology, and general practice. The model of teaching and learning has been developed significantly from the earlier conventional course, to capitalize on, and reinforce, the PBL skills developed in the first 3 years. Students now select their own patients being guided by a handbook containing a wide spectrum of 150 clinical problems. This list of core problems was designed to provide the student with a curriculum for the final 2 years so that the students have a list of subjects about which questions can be asked at finals. As part of their assessment a portfolio of 40 patient cases is built up over the final 2 years selected from the 150 clinical problems given to each student. Each must conform to a standard format, including a clinical history of the problem, a complete clinical examination, differential diagnosis, and initial and long-term management plan. Finally, students complete a reflective commentary, detailing what they have learned as a result of the case. However, the students select each written portfolio case, so that they can develop the direction of their own learning. The students' educational supervisor reviews each portfolio case, and provides feedback to the students so as to assist the students' learning.

In terms of the musculoskeletal system and related manifestations, there are nine clinical categories designed to cover problems that can occur in adult and childhood rheumatology and orthopaedics practice. These include a single acutely painful joint, multiple joint pains and more specific localized problems including hip pain, the painful shoulder, and neck and back pain. In addition, chronic immobility covers some aspects of disability, cold exposure covers Raynaud's phenomenon and its associated causes, and short stature encourages the student to address some specific childhood problems.

Students are given a variety of causes of these problems. For example, in the acute swollen single joint the causes are listed as crystal arthropathy, septic arthritis, reactive arthritis and trauma. Students who choose to write a portfolio case on this subject are expected to read about all these problems as part of their learning and include what they have gleaned in their reflective commentary. A review of the portfolio cases |**13**| has shown that, given the choice, students select two or three cases from this list of problems with a musculoskeletal system theme so that virtually all do gain some understanding about the problems associated with diseases of the musculoskeletal system.

Student-selected modules (components)

The GMC recommendations for change in the medical curriculum also include the suggestion that, to complement core learning and related activities, students should be given the opportunity to study subjects of their own choice in considerable depth. These blocks, initially called 'special study modules' in *Tomorrow's Doctors*, were renamed 'student-selected components' (SSCs) in the 2002 version, and in Glasgow consist of uninterrupted 5-week blocks. The aim is that students will have the opportunity and support to explore ideas that they find of particular personal interest, or relevance, to a level that is both demanding and intellectually satisfying. The study area chosen could range from exploring a core subject to a greater depth or studying a subject completely new and possibly unrelated to the core.

The need for SSCs with a basis in musculoskeletal system training has been reviewed and advice given as to how to recruit interested students |**14**|. Over the 5 years of the University of Glasgow medical curriculum, seven sessions (~22% of the course) are devoted to SSCs, with the first module starting in year 2. Thereafter, there are two each in years 3, 4 and 5. The electives, at the end of years 3 and 4, are also considered to be SSC-like activities, but provide an extra opportunity to experience other training opportunities within and outwith the UK. In years 2 and 3 the SSCs tend to be more proscribed, with students selecting from a list of opinions offered by university and clinical departments. Popular subjects include principles of pharmacology, pathogenesis of bacterial infection, pathogenesis of breast cancer and genetic analysis, but SSCs can cover areas as diverse as languages. However, pain management, the anatomy and structure of limbs, head and neck, and the physiology of motor control clearly have a musculoskeletal system element in their module. In the final 2 years, students have the option to choose any subject from a broad variety, so that over 1000 projects are offered over the 2 years of this part of the course. In addition, students have the opportunity to approach any member of staff (covering clinical, science or related topics) requesting supervision of self-proposed modules, which can be instigated following approval by the medical faculty.

A recent audit of SSCs undertaken during the final 2 years of the Glasgow course reveals that, in 2004/5, 90 modules had a musculoskeletal component. These cover a variety of topics, as outlined in Table 6.2, and include subjects undertaken with a bias towards medical education, audit and shadowing pre-registration house officers (PRHOs) on rheumatology wards. In addition, some are purely clinically based attachments in sports medicine, rheumatology and orthopaedic surgery. Similar numbers of SSCs were offered in 2005/6.

However, to date there is no information about what SSCs are offered by rheumatologists across the UK. A bank of rheumatology-based SSCs held by a central organization would be valuable for provision of an attractive way of setting up projects, saving a lot of effort in the preparation and providing an environment for cross-fertilization of ideas that could only encourage staff and students to participate.

Table 6.2 List of musculoskeletal system based SSCs (student selected components) selected by University of Glasgow medical students

Primary content areas	Number of students
Sports medicine	12
Shoulder injuries and disease	4
Human healing	6
Assessment of the musculoskeletal patient	8
Audit of spinal osteotomy for spinal ankylosis	1
Rheumatology general	10
Making GALS screen CD for Glasgow University	5
PRHO shadowing rheumatology ward	2
Audit anti-TNF therapy in RA in north Glasgow	2
Upgrading RA and OA fixed resource session	6
Exam question setting for rheumatology	6
Orthopaedic surgery	6
Homeopathic medicine	3
Sports trauma/knee surgery	7
Principles of orthopaedic surgery	1
Orthopaedics general	1
Orthopaedic surgery	6
Miscellaneous	4
Total	90

GALS, gait, arms, legs and spine; OA, osteoarthritis; PRHO, pre-registration house officer; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Formative and summative assessment

It is well recognized that the form and content of assessment has a strong influence on students' learning |**15**|. Therefore, the structure, content and process of assessment should be designed to reflect the specific objectives of each stage of the course. Assessment serves the purpose of feedback to students (formative) as well as certification (summative). Table 6.3 summarizes the role and purpose of assessment.

Formative assessment is intended to enable students to judge how well they are doing at various stages of the course and to identify strengths and weaknesses, and is best done in anodyne conditions. Most methods of formative assessment are informal and ongoing, with no formal record of results being kept. Specific formative assessment of medical students in terms of the musculoskeletal system can involve feedback from a vocational studies (VS) tutor about competency in taking a history and examination using the GALS screening protocol, or from a PBL facilitator and peer group members on accuracy of factual content of a rheumatology-related scenario. Alternatively, it can take the form of the completion of 'mock' assessment material either by answering written questions

Table 6.3 Summary of the main purpose of and role of student assessment (adapted from |**15**|)

Main purpose of summative assessment
To pass or fail students
To grade or rank students
To allow progress to the next phase
Main purpose of formative assessment
To provide feedback to students
To identify students' strengths and weaknesses
To encourage and motivate students
To help students to develop self reflection

or by demonstrating clinical skills. These tasks can provide students with guidance on progress and learning and encourage self-reflection.

In contrast, summative assessment is necessary to show that students are fit to progress to the next stage of their course. It is a formal requirement of most universities, and results are recorded. Musculoskeletal summative assessment can be adopted in a number of examinations in order to analyse factual knowledge and practical skills. For factual knowledge, modified essay questions (MEQs), short note questions and extending matching questions (EMQs) have been used successfully in Glasgow and elsewhere. MEQs are particularly useful as they can test knowledge at different levels as well as exploring an unfolding clinical situation in the test setting, while short note questions can assess in-depth knowledge and understanding. The newly adopted EMQs are now becoming widely used in both undergraduate and postgraduate examinations. They are based around a theme, such as a symptom, sign, diagnosis, set of investigations or a topic in basic sciences and provide a measure of the student's ability to process and evaluate information. Following an ARC education conference in 2003, a bank of such questions was stored with the ARC for use by any interested faculty staff. Analysis of responses across different universities to these questions could provide a 'standard series' of questions that could be used for benchmarking purposes in the sphere of musculoskeletal system diseases.

For examining practical skills, communication skills and competencies, an objective structured clinical examination (OSCE) tends to be used. Glasgow students rotate through a number of stations, at each of which they must complete one or more tasks. Typical musculoskeletal stations have been designed for the students to demonstrate prowess in the use of the GALS to examine the arm, leg and spine. In year 2 OSCEs these tend to be performed using healthy subjects (often students) as volunteer patients, with examiners checking that technique is adequate. By the end of year 5 the OSCE station is more extensive, with the examination technique being incorporated in a broader OSCE station where students are also expected to make clinical judgements about patients. Similar assessments have been developed and validated in other schools |**16**|, and in Glasgow OSCE stations have been used

to show an effect of teaching interventions such as peer-assisted learning (PAL) |**17**|. A bank of musculoskeletal system-based OSCEs would be valuable for provision of an attractive way of standard setting across any region or in a more widespread assessment to demonstrate the effect of any intervention in teaching.

Evaluation of medical education

All medical schools perform some form of evaluation of their medical education programme. This provides an opportunity to improve the quality of teaching and learning. Table 6.4 summarizes the role and purpose of evaluation. This can take many forms, including student/staff questionnaires, individual student/staff interviews or information gleaned from assessment. Questionnaires are valuable for obtaining information from large number of students or staff about the learning process and the ability of the staff to execute appropriate level learning; however, the data may not provide specific reasons for poorly or well-rated sessions. Interviews with students and staff can provide specific information regarding why a session was poorly or well rated, as well as exploring potential ways for improvement. Fourth-year students from the Glasgow course have successfully implemented changes to the year 3 scenario about rheumatoid arthritis (RA) and osteoarthritis (OA) and have generated a film of a patient with RA in which disability is a significant theme. Information from student assessments is useful for finding out if the students have achieved the learning outcomes of a curriculum. A problem in the course could be highlighted if there is a consistent downward tendency in performance over several years.

Over the past decade, the use of the computer in medical education has transformed the process of evaluation with online form completion and new developments in data storage and retrievals. This has meant that data can be disseminated and used by course coordinators and medical faculty committees to provide guidance on course content, teaching methods and professional development to our teaching faculty.

Our initial data comparing the traditional curriculum and the PBL course have shown that the students perceive that PBL is based less on rote learning and memorizing details, and more on gathering and analysing information |**18**|. In addition, students feel that thinking independently, decision-making on their own, problem solving and integrating subjects in order to encourage problem-solving are more in the PBL ethos, and as such this course seems to develop the life-long learning skills that the GMC was keen to develop.

Table 6.4 Summary of main purpose and role of student evaluation

To provide feedback to teachers and facilitators on student learning
To provide feedback to students and faculty on student learning
To evaluate an event's strengths and weaknesses
To improve teaching and learning
To monitor standards over time

Evaluation of the musculoskeletal system in Glasgow

In terms of medical students' knowledge of the musculoskeletal system and its manifestations, requirements are specifically highlighted by the GMC |**1**|. Musculoskeletal disorders are common both in general practice and in hospital settings and consume great amounts of healthcare resources |**19**|. Therefore, irrespective of the medical path followed, a comprehensive knowledge of this area is important. However, there is evidence (from a number of medical schools) that

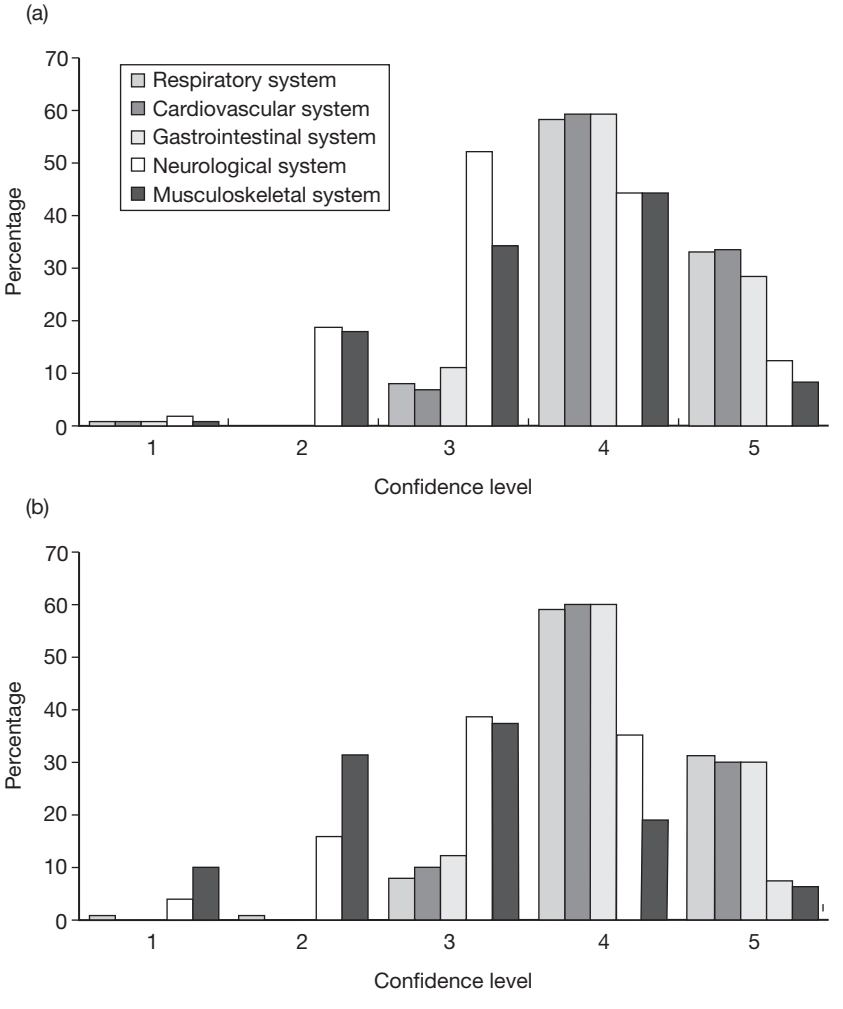

Fig. 6.1 Results of the final year student questionnaire enquiring about students' assessment of their ability (a) to take a history and (b) to examine patients with problems in each of the five major systems: respiratory system, cardiovascular system, musculoskeletal system, gastrointestinal system and neurological system. Confidence was assessed using a five-point Likert scale from 1 (not confident) to 5 (very confident).

current medical student training is inadequate to meet these clinical demands |**6,20**|. Furthermore, a study of the musculoskeletal system component of the Glasgow curriculum also supports the observation that the musculoskeletal system is not as well covered as the other systems.

In this study, a questionnaire was distributed to graduating students. They were asked to assess their ability in taking a history and performing a clinical examination of the musculoskeletal system. The results shown in Figure 6.1 delineate their ability on a five-point Likert scale (from 1, not confident, to 5, very confident). The students appear fairly confident in their ability, with the majority of students (75%) grading their ability to take history from a musculoskeletal system (MSS) patient, in grades 3 to 5. A similar percentage (61%) feel they can carry out the relevant MSS clinical examination with similar grades of confidence (grade 3–5).

The results from the questionnaire concerning the MSS were compared with results for the other four main systems, namely respiratory (RS), cardiovascular (CVS), gastrointestinal (GIS) and neurological systems. When comparing the students' confidence in the individual specialties (Fig. 6.1), it can be seen that they are less confident in both taking a relevant history and performing a relevant clinical examination for the MSS and neurological system than they are in the more acute specialties (grades 2–4 rather than 3–5 respectively). When analysed using a chi-squared test, the students were statistically less confident in doing an MSS history and examination than they were covering the CVS, RS and GIS ($P < 0.0001$).

These data show that students at the completion of their course are relatively confident in their ability to take a history and undertake a clinical examination in all the systems. It is not clear whether this relates to a lower priority that the students give to patients with musculoskeletal system problems or whether the limited availability of musculoskeletal system cases makes these diseases more difficult to learn about in this setting. In either case, the student's exposure is at best patchy because not all hospital attachments have rheumatology services, and indicates that there are areas for improvement in further curriculum design.

Musculoskeletal system education in the UK and elsewhere

Kay and colleagues performed a survey of undergraduate rheumatology teaching in the UK |**6**|. This involved sending out a three-page questionnaire to the lead rheumatology teachers at the 26 medical schools in the UK. As this questionnaire had also been used in 1990, results were compared between the two surveys. Questions about rheumatology teaching included exposure, time allocation, learning methods and assessment techniques. In the first study |**5**|, responses were obtained from all medical schools, in comparison with 23 out of the 26 medical schools for the second survey. It transpires that 16 of the 26 medical schools had implemented a new curriculum since 1990 and a further five schools planned to implement change in 1998.

In most of the medical schools (18), students were exposed to some rheumatology training; however, in five, up to 50% of students received no rheumatology training

at all; in comparison, only two schools reported offering no rheumatology training in 1990. This equates to 9 of the 23 schools offering rheumatology teaching during the first 2 years, a similar number to that reported in 1990, while in the later years only five medical schools confined their teaching to one year, commonly year 3, compared with 17 schools in 1990, with teaching in the remaining 18 schools being spread across the clinical years. Alarmingly, analysis of time devoted to rheumatology teaching (although not easy to perform due to fragmentation) revealed that this had fallen from a median of 4 weeks (120 h) to just over 2 weeks (69 h) when comparing the two surveys. In terms of the learning methods, these appeared to be quite diverse, with large- and small-group learning as well as problem-based learning and self-directed learning (18, 23, 16 and 18 schools respectively).

All schools used some form of ARC resource to support rheumatology learning: reports, patient information booklets or video clips. The wide use of this material indicates the appropriateness and usefulness of these valued resources, which have the added advantage of providing some form of uniformity across the schools, a problem that has been highlighted by a recent focus group study from a Newcastle group |**21,22**|. Indeed, one of the reasons for developing the GALS screening system for musculoskeletal system examination was to enable a standard training module to be developed across the UK and, hence, it was validated by ARC in the first place. This has concentrated the clinical skills examination of the musculoskeletal system into a short screening process and has led to the development of the new Regional Examination of the Musculoskeletal System (REMS) as an extension of this |**23**|, which has also been endorsed by the ARC. It has been suggested that REMS should be the way forward in terms of providing a more comprehensive standard training programme in the musculoskeletal system for medical students across the UK.

A wide variety of assessment techniques are used to examine musculoskeletal system. These include multiple choice and written papers, and long and short cases, as well as objective structured clinical examinations. Clinical skills were tested using at least one method in 14 schools, a threefold increase in comparison with 1990. Some form of rheumatology assessment was a requirement for reaching or passing the final examinations in all but five schools, a significant increase (greater than threefold) from 1990.

Concern about undergraduate education covering the musculoskeletal system has not been restricted to this country. Reports from several parts of America |**24,25**|, Africa |**26**| and Australia |**27**| and several Asian countries have also highlighted these concerns, but there is only a limited consensus as to how to resolve these issues |**28**|. Nevertheless, the revolution in medical school training for students has altered the course content at an undergraduate level, and will by necessity force some amendments to the newly developing postgraduate training.

In summary, it is reassuring to see that the results in this UK survey show a change in the course structure, diversity of learning and assessment techniques, which reflects the GMC guidelines |**1**| and other prominent educational bodies. However,

concerns about the reduction in time spent on studying the musculoskeletal system must be highlighted and addressed given the existing high rate of patients with these disorders attending GPs, together with the projected increase in the older population of 25% in the next 15 years |**29**|.

New ideas are forthcoming about undergraduate education in musculoskeletal diseases. Training for students, traditionally the realm of the medical staff, can equally well be delivered by paramedical staff |**30**|, and patient educators have been used successfully in training medical students |**31**|. The approach of peer-assisted learning (PAL) has the potential to help teach the necessary skills. PAL has been defined as 'one group of students helping another learn while themselves gaining from that experience', and this technique has been beneficial in training students in the necessary techniques for general clinical examination |**17**| and particularly for examining the musculoskeletal system |**18**|. In addition, novel interactive learning tools such as *jointzone*, again endorsed by the ARC, and others |**32,33**| can also be valuable to standardize training in musculoskeletal diseases. If these new techniques are linked to a curriculum that spans the UK, with appropriate assessments (formative and/or summative), then these can only encourage learning in our subject and hopefully enhance recruitment into this specialty as a result.

Postgraduate training

The aim of postgraduate training is to establish an appropriate level of staffing of suitably trained specialists. For patients with musculoskeletal problems there is an established workload in general practice, particularly in areas of social deprivation |**34**|, where, estimates suggest, up to 25% of patients have a rheumatology problem. In addition, up to 60% of disability pensions result from musculoskeletal system problems |**28**|. As the present health trends change and demography alters to one of an increasing aged population over the next few years, this load is hardly likely to decrease. Again, this is not a problem restricted to the UK but is a worldwide phenomenon.

Staffing levels in secondary, hospital-based care are generally regarded as inadequate given the workload in the UK |**35**|, but this is not unique to rheumatology or the UK, rather being a problem in the Western world |**36**|. The British Society of Rheumatology (BSR) estimates that there should be one full-time equivalent rheumatologist for every 80 000 people, but clearly in most areas of the UK the numbers fall well below this figure, with an average nearer to one per 200 000 people, and with increasing commitments for general medicine making posts effectively part-time in their relevant specialty, the numbers needed will be proportionately higher. Hence, there is a need to increase staff numbers to an adequate level |**35**|, but any staff appointed after training should reach a set level of competence |**37**|.

Hospital-based training

Although the quantity of clinical staff in rheumatology is far from adequate, we should be sure of the quality of the product, and this can be assessed by the standards of care that are offered in rheumatology as a specialty. In 1995, a survey of hospital notes showed that senior house officer (SHO) and registrar staff do not examine the MSS as part of a routine patient examination in the context of the acute medical setting |**4**|. This is despite evidence that over 10% of admitted patients have MSS problems, a situation that has been confirmed in studies from Australia, where MSS examination is equally underperformed |**27**|. Sadly, there has been little improvement over the ensuing decade, with a more recent study finding that MSS symptoms are recorded in only 50% of patients and that the MSS is examined in only 20% |**38**|. Unfortunately, this is an acute problem in the general medical setting and in long-term hospital patients despite the fact rehabilitation could be important in facilitating early discharge. The situation is no different for children, with a recent study showing that examination of the MSS in children is similarly poor |**39**|, with similar implications for children with joint diseases.

This implies that the failure of clinical staff to devote sufficient time to dealing with MSS problems is a general problem. The aetiology of this is probably multifactorial, resulting in part from a lack of time in the busy acute setting and possibly a lack of confidence and training in MSS skills |**38**|, but also from the perception that this aspect of care is less important. In a study by Coady and colleagues |**22**|, trainers in the undergraduate curriculum reported that limitations in students' anatomical knowledge, lack of agreement about what students should learn, and the perception amongst physicians that rheumatology is a marginal specialty are relevant factors limiting undergraduates' learning in rheumatology. In addition, the increasingly specialized nature of orthopaedic surgery, the limited reinforcement of training in the MSS and limitations in clinician and patient time were also important factors. All these factors must apply equally to staff in postgraduate training, and especially the lack of reinforcement at a postgraduate level. Reassuringly, further opportunities for learning about the MSS using GALS as a standard guide improved SHO confidence in understanding about the MSS |**38**|, showing that there is potential to improve on the existing situation. Whatever the cause, it is clear that there will be a multifactorial approach to improving the skills necessary, and a persistent need for adequate in-hospital experience and training.

Proposed training opportunities following Modernising Medical Careers

In the UK a 2-year foundation training following university graduation was implemented from August 2005. The aim of the FY1/FY2 programme is to provide the junior staff with rotating positions, giving a secure position of longer duration than that presently offered from which to develop their career. This will provide experience in various areas across the spectrum of medicine, and is designed to standardize all training to both teaching and peripheral hospitals, but once again the rationale is not to train by experience but to provide opportunities that can be

built upon during higher training. Various programmes are being set up, including ones with an academic bias, to try and recruit candidates interested in academic medical subjects as a career option.

The generic skills required for the curriculum have been defined |**3**|, driven by the Department of Health, the Royal Colleges and the GMC. As such, this builds on the ideals of undergraduate education in *Tomorrow's Doctors* |**1**| and *The Scottish Doctor* |**40**| and is developed in part from the *Good Medical Practice* guidelines |**41**|. Its aims are to 'develop generic skills, knowledge, competences and attitudes to provide the highest professional performance and conduct' using the outline shown in Figure 6.2. Successful completion of the training during the first year will lead to full registration with the GMC, and will enable the trainee to enter the FY2 year programme prior to entering a specialist training programme.

From the point of view of training based on any single subject, the Department of Health document is not proscriptive – much as one might expect. However, in addition to the generic skills, the trainees are expected to be able to manage the duties involved in acute receiving (on-take), initiate and follow care for acutely ill patients, and plan for discharge. This does not specifically include medical MSS problems as causes of acute hospital admission, even though these are estimated to account for ~5% of these problems. Of some concern to orthopaedic surgeons, it even excludes trauma as a reason for being brought into hospital. Nevertheless, it does include management of acute presentations of chronic diseases, appropriate pain control (including large joint and back injuries) and liaising with members of the multidisciplinary team, most of which rheumatologists (and members of certain

Fig. 6.2 A description of the design of the foundation year programme covering the skills required to maintain adequate safety of patient care (Department of Health 2003, www.dh.gov.uk).

other specialties) are well able to offer their patients and trainees. In addition, the requirement for FY2 to aspirate large joints is a valuable skill necessary for the management of acute rheumatological problems. Hence, rheumatologists can have a significant input into their local programme, but it may be difficult to design a training caseload given the pressures of the more acute problems that seem to drive this syllabus.

Assessment is also raised as an issue for the FY1/FY2 year programme, and the usual methods are suggested, including observed clinical skills, case discussions and peer and team assessment, as well as objective assessments such as mini-clinical evaluation exercises |**42**|. In the past, during assessment of PRHO skills the trainees themselves felt that their ability to examine the MSS was the poorest of their clinical skills, and this was supported by the fact that none of the 22 attained a pass in the OSCE evaluation of this skill. By comparison, 93% attained a pass in the RS examination. On the principle that assessment drives learning, it behoves rheumatologists to ensure that theoretical and practical subjects are adequately represented in any assessment of progress if we wish to see recruits coming into our specialty.

Specialist registrar training

Higher medical training in most subjects has, until recently, been a process dependent on the deanery in which training has taken place, with only limited guidance for trainees. Changes in specialty training have altered from training based on clinical exposure, with Calman and colleagues |**2**| developing and initiating the specialist registrar (SpR) grade. The requirements for training and assessment of rheumatology SpRs have been outlined by Paice and Dacre |**43**|. Training now lasts 4–5 years, and is designed to replace the longer apprenticeships and to fast-track training of new consultants. As part of this process, selection of suitable trainees has improved by providing defined entry criteria to post. This has taken into account the reduction in hours resulting from the European Medical Directive, and it is now mandatory to obtain a Certificate of Completion of Specialist Training (CCST) before application to consultant posts.

In the rheumatology context, the main hurdles to training students have in the past been the lack of clarity in what to teach and the limited ability of non-specialists to train undergraduates and postgraduates in this area |**21**|. The JCHMT for Rheumatology (2003) (www.jchmt.org.uk/rheum) provided guidance in one area for the registrar trainees and generated a syllabus to guide their learning. This includes details on medical knowledge, clinical skills requirements and management experience, but also guidance on training methods to allow the trainee to gain these skills, and very much builds on similar documents from Canada |**44**| and the USA |**45**|, and is the basis for similar guidance being generated for Australia (L. Schreiber, personal communication). In addition, the JCHMT paper gives trainees guidance on optional modules, including laboratory or imaging experience, analysis of specialist investigation such as EMG investigations

and sports medicine. The schedule also includes manipulation, which is more a feature of training within the EU. However, any training opportunity remains just that, namely only an opportunity for participation and not a guarantee that the trainee can take part. The challenge remains to balance employer requirements and trainees' needs in the provision of service.

A recent survey of SpRs in rheumatology shows that they now perceive that clinical workload has overtaken learning development in the day-to-day priorities of hospital life, particularly if they are undergoing dual training in rheumatology and general medicine |**46**|. Nevertheless, the SpRs generally rate their training highly, and feel that there is good support from their senior colleagues. In addition, despite the JCHMT syllabus, there are regional variations even within the UK, with little uniformity in training. The formal teaching time varies, with a median of 2–3 hours per week devoted to training, with two-thirds of trainees attending 70% of the sessions. However, this does suggest that one-third fail to attend, implying that for a significant number more time could and probably should be made available.

Cutting training in the business sector reduces service commitment, has adverse effects on customer satisfaction and even reduces share prices. Hence, many millions are spent maintaining staff training, particularly in the service sector. In the context of rheumatology, trainees complain that their ability to attend training days is hampered by heavy clinical commitments |**46**|. It is important to realize that the business approach should apply equally to NHS training – a short-term answer cannot provide a long-term solution. The solution is not difficult – if training is to take place as approved by the statutory bodies then it should be a requirement for trainees to attend a certain percentage of the sessions in order to attain CCST certification. One advantage of this would be that the necessary funds would have to be found to facilitate this process because failing to do so could become the subject of litigation.

Along with these changes came further developments based on *Modernising Medical Careers* (MMC). These developments are in the process of being implemented but will essentially amalgamate the SHO positions with SpR programmes. The new positions will be named specialist training registrars (StRs), and as this chapter is being written applicants are applying for 4-year rotating posts for training some general specialties (medicine, surgery, etc.), which will be covered in all 4 years of the programme. In the context of specialty training in rheumatology, the first 2 years will concentrate on general medical training and that for the specialty development will occur in the second phase. This system will no doubt be subject to considerable scrutiny as the present applicants move on in their careers. The challenge is now to find stimulating ways in which training can be developed to excite those desirous of being involved, deliver what is required for their training and produce a high-quality product that can be seen to be capable of providing a specialist service for the NHS.

Table 6.5 Relative proportions of subjects covered in the Internal Medicine Examination Board examinations for rheumatology certification in the USA

Primary content areas	Relative proportion (%)
Rheumatoid arthritis	14
Other rheumatic and connective tissue diseases	14
Systemic lupus erythematosus	10
Systemic diseases, non-rheumatic	9
Basic science	8
Osteoarthritis	8
Soft tissue disorders	7
Vasculitides	7
Infectious arthritis	6
Crystal-induced arthropathies	5
Spondyloarthropathies	4
Metabolic bone disease	4
Miscellaneous	4
Total	100

Source: Internal Medicine Examination Board (www.abim.org/cert/ssrheu.shtm).

Assessment

Although only 50% of the UK specialist registrar trainees agreed that an exit examination should be required as part of training |**46**|, the American Board of Medical Specialists (ABMS) certify USA trainees |**47**|, and part of this accreditation involves passing an exit examination. All specialist trainees in rheumatology must pass their internal medicine examination first before being eligible for the rheumatology examination. The latter consists of best answer questions and subjects are covered in varying proportions, with rheumatoid arthritis and connective tissue diseases predominating (Table 6.5). The examination covers normal anatomy, immunology, genetics, biochemistry and mechanisms and pathways of inflammation. In addition, use of laboratory tests, imaging studies and relevant pathology, pharmacology, epidemiology, biostatistics and ethics can be assessed. All candidates are expected to have working knowledge of the role of joint and soft-tissue injections.

In the UK an exit examination remains to be put in place. However, a pilot study using a different approach has been employed using an OSCE format as a possible template |**48**|. This was based on the JCHMT core curriculum, and included a more practical content but with some stations using patient scenarios and radiological interpretation and pathological material, and some having sections including time for discussion on patient management. This was well received by staff and trainees, and when patients were involved was not too onerous for them. Costs were also justifiable at less than £10 000 per session.

The SpRs generally performed well in this pilot, and examiner review showed that the staff found this valuable for the trainees' annual appraisal. This confirms

the suggestion that clinical experience correlates with performance in US exit examinations. Nevertheless, the exit examination is an area about which trainees in general have some concerns, with only 50% agreeing that this would be a valuable tool in training |**46**|. However, having taken part in an OSCE-based examination, only two candidates out of 12 found it too anxiety provoking |**49**|, indicating that many concerns may be allayed by actually taking part.

Clearly, with validation issues being at the forefront of the GMC agenda, this could be a very useful format for formally assessing trainees in individual deaneries prior to obtaining the CCST. In addition this format could possibly be validated at all levels of training to provide supervisors with information about progress and guide future learning. Although this is a pilot project, it could be expanded to include more relevant stations in a practical examination. Assessment in specialty is increasingly likely to become more competence-based and less likely to be related to time devoted to the specialty given the restrictions in time attributed to specialty training in the StR programmes. This assessment could also be broadened to add a theoretical examination along the style of the board exams, which could assess more of the knowledge-based aspects if perceived appropriate.

The way forward for training

Medical student training and postgraduate training programmes have been reorganized, albeit independently. The opportunity now arises to develop a seamless training curriculum that can produce university graduates with basic experience in the musculoskeletal system and its diseases. This could be the basis from which to build postgraduate training in any subject, but which would hopefully produce interested students who wish to become the specialists of the future following further training.

Given the evidence that medical students seem to lack confidence in musculoskeletal topics, medical schools may wish to consider increasing their training in this area. However, as these problems appear to apply to junior house staff as well |**37**|, these deliberations should apply equally to postgraduate training. It is inappropriate for those schools with no musculoskeletal system education not to wish to add this to their curricula, and the remainder may want to increase the duration of courses that contain MSS training. Ongoing problems include:

1. standardization in core teaching of curricula;
2. the scarcity of accepted teaching materials;
3. the recruitment and retention of willing and able staff.

Core curriculum content

A set of agreed standards for undergraduate MSS education that is recognized and widely accepted by all is required. This would go at least some way to ensure that

tomorrow's doctors undergo the similar training and therefore are equally confident and competent in assessing MSS disorders. Attempts to do this have been made by Doherty and Woolf |**9**| and include three main domains:

1 competencies in clinical assessment and diagnosis;
2 knowledge of the main characteristics and principles of rehabilitation;
3 core knowledge supporting diagnosis and management.

These principles have been included in the postgraduate curricula developed by the JCHMT and have formed a valuable basis on which qualified trainees can build their development. The British Orthopaedic Association and the BSR have produced core curriculum recommendations |**50**|, with a key goal being to influence training in musculoskeletal disorders in medical schools and improve appropriate referral patterns after graduation. This matter extends wider than Britain and appears to be an international issue. The International League Against Rheumatism (ILAR) Undergraduate Medical Education in Rheumatology (UMER) 2000 project highlights the value of basic clinical skills and the need for international collaboration in promoting undergraduate training in musculoskeletal system diseases |**51**|. However, so far, there are no studies to confirm whether such a core curriculum is being followed in medical schools.

Appropriate and accepted learning material

A number of reports have identified a need to improve and extend the accepted teaching material |**22,52**|. A good example of a valuable teaching aid is the GALS locomotor screen developed in 1992 |**12**|, an example of a training adjunct that the GMC suggests should be included in the UK curriculum. This screening examination is quick, easy to perform and detects important abnormalities in the locomotor system. Previous to this, medical students saw the musculoskeletal system as complex and difficult to examine, one reason underlying the poor performance in junior house officer (JHO) and SHO evaluations |**4,38**|. Furthermore, the introduction of GALS screen teaching to medical students and SHOs resulted in performance of a musculoskeletal assessment to a level similar to that of the other major systems |**38,53**|. This also provides uniformity and removes the element of confusion that can arise as a result of inconsistency in staff approaches to and during clinical examinations. A similar consensus across schools with regard to what should be included in the undergraduate curriculum would help standardize the training in the UK to the benefit of students and educators alike. It is to be hoped that the development of REMS will not alter that situation of aiming towards a standardized clinical skills programme across the UK, and indeed could help set up the basis for a more standard undergraduate syllabus in general.

While the UK medical schools widely use other high-quality materials supported by the ARC, tutors request additional resources to assist with musculoskeletal system teaching. These include development and dissemination of teaching materials, more

learning support as well as funding |**6**|. This endorses the need for more acceptable resources available for teachers and learners. Once again this situation is not unique to undergraduate training: rheumatology postgraduate trainees are also keen to have the use of extra resources |**46**|.

One area which necessitates future development is computer-based learning |**54**|. Computers are not a universal requirement for postgraduate training, and there is evidence of only limited use even in areas such as musculoskeletal radiology, where computers are a valuable adjunct to practice |**55**|. However, all undergraduates now have access to computers for personal and professional development and most medical schools now undertake training in computer skills |**54**|. The internet provides a transglobal service, and a list of websites from local, national and international facilities are available. The ARC has the interactive rheumatology website, *jointzone,* training facility for undergraduates as well as postgraduates (www.jointzone.org), which, if it became the subject of standardization in training, would provide consistency for trainees at all levels. Computer-based material available on licence can also be used for education such as computer-generated models of human anatomy, the virtual reality human beings |**32,56**|, which could be useful for all training grades where there are areas of limited knowledge. However, as yet it remains to be seen what uptake there is of these opportunities in UK schools or in postgraduate training programmes.

Appropriate and accepted assessment material

The ARC has generated a bank of musculoskeletal examination questions for use by UK medical schools for summative assessment. Furthermore, the development of common musculoskeletal OSCE stations could be encouraged. A number of medical schools in the south-east of the UK have used similar stations covering communication skills in medical subjects to assess whether these could be used across different medical schools. Although there was some inconsistency in the marking schedules between schools, the idea was well received, and these approaches would encourage standard setting and an agreed level of competency in examination that could equally be applied to the musculoskeletal system. The OSCE that has been used in the UK for postgraduate assessment |**48**|, and which has also been piloted in the USA, could form the basis of training assessment and collaborations in undergraduate appraisal. Previous studies have shown that patients with rheumatic diseases are very willing to help in this situation, and the patients' partners programme |**57**| has been a useful source of recruits. The ease with which assessment tools provide information for formative evaluation makes this an attractive option for a more general examination to assess progression through training, as well as an exit examination.

A solution to problems of staff recruitment and retention

The GMC recognizes that doctors should be professionally skilled teachers as well as doctors |**1**|, and there is an increasing awareness among medical teachers of the

importance of principles of teaching and learning |**49**|. However, restrictions on time for programmed activities are reported to have limited the examiner recruitment for postgraduate examinations. Rheumatology trainees are keen to have the use of extra resources, particularly tutor time, but again this is frequently not available |**46**|. One solution to this problem is to ask for assistance from suitably trained allied health professional personnel, who can be helpful in both training and assessment of undergraduates, and some have successfully trained postgraduates in joint and soft-tissue injection techniques. One possible way of increasing time for training could lie in expanding the numbers of trainers across professions to relieve strain on hard-pressed staff, as has been undertaken in undergraduate training |**30**|. In addition, this has a potential for offering interprofessional training opportunities, which could well be beneficial.

However, at an undergraduate level, students have been used as facilitators of learning, and this practice is becoming increasingly well recognized as making use of a largely untapped and expanding resource, namely student knowledge. Topping |**58**| suggests that well-constructed and supported PAL schemes are successful in a wide range of educational settings. Such PAL schemes could, therefore, be ideal in a medical school setting, as they could be used to train the medical student in the skills of teaching, as well as in clinical skills.

Such an initiative was set up and evaluated at the medical school at Glasgow University |**59**|. This programme was designed to enable fourth- and fifth-year medical students (trainers) to practise the principles of small-group tutoring, and to encourage first-year and second-year students (trainees) to improve their clinical examination skills. This study illustrates that PAL for clinical examination skills could be incorporated alongside present training in medical school curricula and offers widespread benefits to both student trainers and trainees. Indeed, some trainees are now becoming trainers in their own right, so, if this process were to be applied to all medical training, PAL could potentially be of benefit in postgraduate education in all specialties, relieving some of the burden of valuable tuition staff. If all staff were involved in training the group just beneath them in experience, then this would not only spread the training load but also enable staff to gain more expertise in teaching – another of the GMC objectives in good medical practice |**41**|.

Conclusion

There is increased awareness of the MSS as a source of clinical problems in the population at large. In general, there is limited provision for this need in primary and secondary care, and it would be appropriate for planners to address this. The demographic changes in the community and the ever-increasing rates of obesity in the population at large can only increase the likelihood of more patients having MSS problems, with implications on the service that the NHS provides.

Previously, training in any subject was based on clinical exposure and 'osmosis' from senior clinical staff, and experience was regarded as synonymous with aptitude. To a certain extent this was the rule for undergraduate and postgraduate training. Various influences have forced this approach to be replaced with more structured training, bearing in mind an increased awareness of the principles behind teaching and learning for students, trainees and their trainers. This process will now commence in medical schools, expand through FY1/2 training, develop during the training grades and continue for consultant staff, and will necessitate regular assessments at all levels so that the public can be reassured of the quality of knowledge, experience, clinical skill and overall care.

The new foundation years and StRs introduced as part of *Modernising Medical Careers* |**3**| have been designed to bridge the gap between undergraduate and senior practitioner. This could provide a unique opportunity to set a process in motion, and undergraduate training and assessment should provide the basis for this development. This requires the community to ensure that the basic undergraduate programme is more standardized – a difficult proposition given the variety of sites where this is delivered. The Glasgow experience has been designed from scratch in the new mould of PBL training to provide a core-integrated basic programme in musculoskeletal disease. Comparisons between the courses across the UK would at least provide a benchmarking between them and facilitate integration to provide the required initial standard training level.

Consultant staff can also have an expanded role not only to continue professional development supervised by their employers, but also, for those with junior staff, in training as educational supervisors. Many have identified education as a potential source for extra training in its own right, and the availability of certification of training from courses such as *Physicians as Educators* (www.rcplondon.ac.uk, www.rcpsglasg.ac.uk). In the rheumatology context, the biannual ARC conference should help increase awareness of training as an important issue and provide a source of continuing professional development for the NHS and academic staff involved. However, there is no reason why this should just be limited to senior staff. This could provide an opportunity for all trainees to develop their own teaching skills, which would allow them to be applied at all levels of training as undergraduate and postgraduate – a significant investment in the future of our subject for the benefit of our patients.

There are multiple areas in rheumatology that could be included in training, many of which could be implemented without very much change to practice and at low cost. Rheumatology is leading the way in clinical medicine with the increased use of specifically targeted therapies. These have been developed as a result of increased understanding of patients' problems and the disease processes involved. The solutions have been designed to resolve the problems that result from inflammatory autoimmune diseases, thereby limiting the patients' 'dis-ease' and preventing long-term disability.

In the same way, it is up to the community to rise to the challenge that has been set in the education sphere. Increased understanding of the problems can lead to a concerted approach to training, starting with medical students and developing through their postgraduate development. Generic skills have now been defined and are being implemented and, although there could possibly be more harmony in different medical schools, curricula covering rheumatology training are developing. If we can capitalize on the changes to training, using them as a tool to encourage learning in our area, then we can ensure the continued recruitment of trainees interested in rheumatology who are adequately prepared for the job.

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Part II

Osteoarthritis and gout

7

Osteoarthritis

NISHA MANEK

A recent projection of the prevalence of arthritis and associated activity limitations in the USA estimates that the number of adults with arthritis and its associated activity limitation will increase substantially by 2030, resulting in a large impact on individuals, the healthcare system and society in general |**1**|. Therefore, in the coming decades, osteoarthritis (OA) will become an even greater public health concern. Research into understanding OA continues to increase substantially, and the past year has seen much progress in many areas of OA.

Research in OA has traditionally focused on three major areas: epidemiology, including the incidence, prevalence and associations of joint damage; clinical studies, with a focus on symptomatic OA; and basic science, which has been heavily dominated by biochemical studies of articular cartilage. Fortunately, these basic areas of enquiry are broadening out. For example, there has been a remarkable broadening of the basic science agenda, which now includes extensive studies of bone, synovium and ligament changes in OA, as well as attempts to link biochemistry to clinical outcomes. The well-known association of obesity and knee OA appears to be more complex than previously predicted, and OA may be a systemic disorder rather than a local joint one. Proteomics is a brand-new tool and OA research will very likely benefit from this emerging powerful technique. Animal models in OA have yielded potential new gene targets in humans. Although these basic science advances will take years to benefit patients with primary OA, the reality of OA is that it is a disease of older people, most of whom have other health problems in addition to their joint failure. Advances in our understanding of the biomechanics of lower-extremity OA provide therapeutic approaches, especially if joint surgery is not an option. Furthermore, there are preliminary data utilizing intra-articular injections of *Botulinum* toxin A in difficult inflammatory and degenerative arthritis. The first large-scale trial of the neutraceuticals glucosamine and chondroitin sulphate was also published. New approaches to assess pain and disability, the two main consequences of OA, allow a better and more comprehensive assessment in clinical work and evidence-based medical studies, and this chapter will discuss a new framework for disability, the International Classification of Functional Disability, and Health. The papers I have selected will, I hope, give the reader and practitioner some practical applications and at the same time an idea of the potential research avenues.

Self-report measures of activity limitation associated with OA

The assessment of disability associated with osteoarthritis

Pollard B, Johnston M. *Curr Opin Rheumatol* 2006; **18**: 531–6

BACKGROUND. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Short Form-36 (SF-36) are the most commonly used measures to assess disability in OA. There is little consensus, however, about which measure to use across different types of OA. Although new measures have been developed to assess disability, it remains unclear whether or not these are an improvement over existing measures. The International Classification of Functioning, Disability, and Health is becoming an important consideration |2|. Although the World Health Organization (WHO) has traditionally focused on infection control and mortality reduction, WHO now increasingly recognizes the importance of reducing the burden associated with health conditions, and particularly the burden of musculoskeletal disease in the context of the Bone and Joint Decade. This review addresses the use and properties of existing measures and newly developed measures of activity limitation, before examining how conceptual advances have led to disability assessment or activity limitation |3|.

INTERPRETATION. There has been considerable research on the use of the WOMAC and SF-36 in OA studies, with good responsiveness of both these instruments. Nevertheless, in some areas, such as knee surgery, measures such as the WOMAC and SF-36 may fail to capture patients' sense of success, and several problems have been identified. New versions of existing measures, such as shortened versions of the WOMAC, produce similar information as the longer versions but are easier to complete. The International Classification of Functioning, Disability, and Health (ICF) is a consensus model that has created new approaches to measuring activity limitation. The ICF defines three main constructs of health – body functions and structures, activity and participation – and their opposites – impairment, activity limitation and participation restriction |**2**|. Within each construct are health and health-related domains (where a domain is defined as 'a practical and meaningful set of related physiological functions, anatomical structures, actions, tasks, or areas of life'). Within each domain (e.g. 'mobility') are categories (e.g. 'walking', 'lifting' and 'carrying objects'), which are units of classification. The ICF has developed core sets for OA. The core sets suggest which of the ICF categories should be included to guide multidisciplinary assessments. For OA, the core set identified 19 activity and participation categories from the mobility domain. The other domains were self-care and domestic care (three categories each), community, social and civil life (two categories), and interpersonal interactions and relationships and major life areas (one category each). It has been shown that existing measures do not map onto single ICF constructs so it is likely that new measures or adaptations to existing measures will be required. The ICF core sets define what to measure, not how to measure.

Comment

The ICF model is beginning to be reflected in new measures of activity limitation in OA and in one case has formed the basis of a culturally specific measure – the 25-item outcome measure for Japanese people with knee osteoarthritis (Japanese Knee Osteoarthritis Measure, JKOM) |**4**|. Because the ICF is the universal and standardized language to describe functioning and health, the concepts contained in existing measurement instruments can potentially be translated into ICF-compatible language, after which content comparisons among these instruments can be performed. This may facilitate the selection of specific measures that are most applicable to the core set comparisons. In clinical practice, the ICF has the potential to significantly increase the quality of rehabilitation care delivery |**5**|.

Glucosamine and chondroitin sulphate in knee osteoarthritis

Glucosamine, chondroitin sulphate, and the two in combination for painful knee osteoarthritis

Clegg D, Reda D, Harris C, *et al. N Engl J Med* 2006; **354**: 795–808

Background. Complementary or alternative therapies for osteoarthritis are commonly used, and the dietary supplements glucosamine and chondroitin sulphate have been advocated as safe effective options for OA, especially in the lay media. A meta-analysis of studies evaluating efficacy of these nutraceuticals suggested potential benefit |6| but raised questions on the scientific quality of the studies. The National Institutes of Health (NIH) funded a much awaited Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), the results of which were published in the *New England Journal of Medicine* |7|. The primary objective was to compare the efficacy of treatment with glucosamine, chondroitin sulphate or the two in combination in patients with knee OA.

Interpretation. This was a randomized, placebo- and celecoxib-controlled trial of 1500 mg of glucosamine hydrochloride daily, 1200 mg of chondroitin sulphate daily, or the two in combination. Patients who were diagnosed with knee OA, defined as pain for ≥6 months and radiographic evidence of tiobiofemoral osteophytes of ≥1 mm, were included in this 24-week study. In addition to their allocated treatment, patients were allowed to take acetaminophen (up to 4000 mg daily). The primary outcome, determined by expert consensus, was a 20% decrease in the summed score on the pain subscale of the WOMAC from baseline to week 24. A total of 1583 patients were included in this trial, with the majority female (64.1%), and a mean age of 58.6 years. Patients were randomly allocated to one of five treatment groups: glucosamine hydrochloride 500 mg three times daily; sodium chondroitin sulphate 400 mg three times daily; glucosamine 500 mg and chondroitin sulphate 400 mg three times daily; celecoxib 200 mg daily;

or placebo. The results showed that the patients in the placebo group had a rate of response to treatment of 60.1%. Comparatively, the rate of response to glucosamine was 3.9% higher ($P = 0.30$), the rate of response to chondroitin sulphate was 5.3% higher ($P = 0.17$), the rate of response to combination treatment was 6.5% higher ($P = 0.09$), and the rate of response to celecoxib was 10.0% higher ($P = 0.008$). Significantly higher rates of response were observed in a subgroup of patients with moderate to severe pain who received combination therapy: rate of response with combination treatment was 79.2%, compared with 54.3% in patients treated with placebo ($P = 0.002$).

Comment

This large NIH-funded multicentre trial is an important milestone for evidence-based therapeutics for knee OA. The authors concluded that glucosamine and chondroitin sulphate alone or in combination do not significantly reduce pain in patients with knee OA. Over 1500 patients participated in GAIT, and there was sufficient power to detect even small therapeutic effects. They also concluded that combination therapy with glucosamine and chondroitin sulphate might be beneficial in a subgroup of patients with moderate to severe knee pain. The editorial accompanying the study results raised concerns that the preparation of glucosamine used in GAIT, glucosamine hydrochloride, might be less efficacious than glucosamine sulphate. There is at present no evidence that sulphate increases the level of glucosamine in the blood. On the basis of the results from GAIT, it seems prudent to tell patients with symptomatic knee OA that neither glucosamine hydrochloride nor chondroitin sulphate alone has been shown to be more efficacious. The GAIT study confirmed previous trial data that both glucosamine and chondroitin are safe with a side-effect profile similar to that of placebo. Therefore, if patients who are using these nutraceuticals perceive benefit, I am reluctant to withdraw their use. An analysis of the structural effects of glucosamine and chondroitin will emerge from the GAIT study in a year.

Intra-articular *Botulinum* toxin A: a potential new therapeutic approach for painful osteoarthritis

Long term effects of intra-articular *Botulinum* toxin A for refractory joint pain

Mahowald M, Singh J, Dykstra D. *Neurotox Res* 2006; **9**: 179–88

Background. The major pharmacological treatment in OA is analgesics, with acetaminophen generally prescribed as first line because of its safety. Non-steroidal anti-inflammatory drugs (NSAIDs) and the selective cyclo-oxygenase type 2 inhibitors (COX-2) are also widely used but have unacceptable toxicity profiles.

Intra-articular steroid injections have generally shown excellent results and need not be reserved for those with an effusion. A potential new approach is intra-articular injection of Botulinum toxin A. In this case series, the authors review their 12-month clinical experience with intra-articular injections of *Botulinum* toxin type A (BoNT/A) for refractory joint pain |8|.

Interpretation. Eleven patients (two female and nine male patients aged 42–82 years) with chronic arthritis who had failed treatment with oral and/or intra-articular medications and were not candidates for joint surgery were studied. Five patients had OA, five had a diagnosis of rheumatoid arthritis (RA), and one patient had psoriatic arthritis (PsA). Fifteen joints were injected with BoNT/A: six lower extremity joints (three knees and three ankles) with 25–50 units, and nine shoulders with 50–100 units. Patients were followed for a minimum of 1 year or longer. Maximum pain relief was measured by comparing baseline pain on a numeric rating scale (0–10) to pain at the time of maximum pain relief (paired *t*-test). Maximum improvement in function was assessed using paired *t*-tests for improvement in active flexion and abduction for the shoulder joint, and the time to perform 'sit to stand' 10 times for the lower-extremity joints. A clinically and statistically significant improvement was noted after intra-articular BoNT/A injections, with mean maximum decrease in lower extremity joint pain of 55% ($P = 0.02$) and 36% ($P = 0.044$) improvement in the timed stands test noted at 4–10 weeks after injection. There was a 71% mean maximum reduction in shoulder pain ($P < 0.001$), and active range of motion increased 67% in flexion and 42% in abduction ($P = 0.01$). No immediate or delayed adverse effects related to BoNT/A were noted after the injection. Duration of pain relief was variable and ranged from 3 to 12 months. Five joints were re-injected with BoNT/A and experienced a similar decrease in joint pain that lasted 3–12 months.

Comment

This is the first report of the long-term effects of intra-articular BoNT/A injections to treat chronic joint pain and the efficacy of repeat injections. The use of BoNT/A, an agent that is widely used as a neurotherapeutic and cosmetic, to treat joint pain is a non-Food and Drug Administration (FDA)-approved 'off-label' treatment. Potential adverse effects such as muscle or joint paralysis were not observed. The effects are similar to those of steroid injection. This study was small and uncontrolled, and larger studies are needed; nevertheless, this paper addressed a difficult-to-treat group of patients that are only too frequently encountered in clinical practice: those with refractory joint pain who have failed the usual oral and injectable therapies. The same authors have also reported efficacy of BoNT/A intra-articular injections for painful total knee arthroplasty |**9**|. The mechanism of pain relief with *Botulinum* toxin injection remains speculative. There is emerging data from animal models of OA of the possible chondroprotective effect of *Botulinum* toxin |**10**|.

Biomarkers in osteoarthritis: will they measure up?

Molecular markers of cartilage breakdown and synovitis at baseline as predictors of structural progression of hip osteoarthritis. The ECHODIAH Cohort

Mazieres B, Garnero P, Gueguen A, *et al. Ann Rheum Dis* 2006; **65**: 345–9

Background. A rich literature exists on biomarkers of OA. One of the suggested roles of the biomarkers is to predict disease progression. Biomarkers that have been suggested to be associated with radiographic progression of OA include serum C-reactive protein (CRP), serum hyaluronic acid (HA), serum cartilage oligomatrix protein (COMP) and collagen type II fragments, as well as biochemical markers of bone and synovium. Many commercial kits are now available and measurement of biomarkers is relatively easy. On the other hand, biomarkers reflect changes in the metabolism of all bones and cartilages of the body and, as the changes of OA in the joint are local, it is unclear whether changes induced by degeneration of one or a small number of joints are sufficient to be detected in serum or urine. It is also unclear if measurement of several markers helps this goal. These investigators used several systemic markers of bone, cartilage, and synovium to determine if structural progression of hip OA could be predicted |11|.

Interpretation. This study investigated a panel of 10 biochemical markers in a homogeneous and well-characterized cohort of 333 patients with painful hip OA who were treated with diacerin and placebo in a multicentre, prospective, double-blind, 3-year follow-up trial. High functional impairment, a joint space width < 2 mm, and lateral migration of the femoral head increased the risk of progression. In addition, patients in whom baseline serum hyaluronan (sHA) and urinary C-terminal cross-linking telopeptide of collagen type II (uCTX-II) levels were in the upper tertile had a relative risk of progression of 3.73 (95% CI 2.48–5.61) compared with patients with markers in the two lower tertiles. Multivariate regression analysis gave concordant results and indicated that uCTX-II and sHA together with, but independently of, high functional impairment, joint space width (JSW) < 2 mm and treatment modalities, are the most important risk factors for joint space decrease or total hip arthroplasty requirement. uCTX-II is a marker of cartilage destruction and sHA is a marker of synovitis.

Comment

Ideally, biomarkers for use in clinical rheumatology must meet several criteria: first they must be able to diagnose the presence of OA, before radiographic evidence of joint damage; second, they should identify patients at increased risk of disease progression; and, third, they should be capable of monitoring the efficacy of anti-inflammatory and disease-modifying drugs for OA. To achieve these goals, biomarkers need to be tissue specific to allow for interpretation and decision-making. Biomarkers, when measured in blood or urine, provide information on

systemic skeletal tissue turnover and not necessarily on alterations in the signal osteoarthritic joint. The extent of degenerative disease present in the knees, hips, hands and lumbar discs contributes independently and additively to urinary CTX-II levels, which therefore represent the total body contribution to systemic levels. Also, the preanalytical factors that can influence the levels of these markers independently of OA have to be adequately controlled. For example, it has been demonstrated that even a moderate walking activity can significantly influence serum COMP concentration in a healthy population |**12**|, and therefore controlling physical activity prior to blood sampling for biomarker tests is critical. Although this study suggests higher baseline levels of uCTX-II and sHA are associated with greater progression of hip OA, molecular markers cannot predict the absolute rate of progression in a given patient. Also, time-integrated measures may be better predictors of progression than a single baseline measurement because disease activity is likely to vary over time.

Unloading joints to treat osteoarthritis

Footwear alterations and bracing as treatments for knee osteoarthritis

Krohn K. *Curr Opin Rheumatol* 2005; **17**: 653–6

Background. One of the most potent factors associated with joint space loss in longitudinal studies of knee osteoarthritis is limb malalignment. During normal gait, the medial compartment of the knee is loaded more than the lateral compartment. It is estimated that 60–80% of the load during midstance phase of gait is distributed to the medial compartment. This is due to the external varus moment (or adductor moment), which is the torque generated from the ground reaction force during stance phase as a result of the body's centre of gravity falling medial to the knee joint. This, in part, is why medial compartment disease is more prevalent than lateral compartment disease. Given the importance of the knee varus moment in the progression of medial compartment knee OA, the use of a knee brace or an in-shoe lateral wedge to reduce this torque constitutes a logical conservative treatment. This review examined the relevant literature of the biomechanical process of knee osteoarthritis and the use of foot orthoses and knee braces to change the biomechanical forces to reduce pain and improve function in patients with symptomatic knee OA |13|.

Interpretation. Key studies were reviewed. In one key article, Sharma *et al*., in an 18-month follow-up study on persons with symptomatic knee OA, reported that varus static alignment markedly increased the risk of medial joint space progression [adjusted odds ratio (OR) = 4.09], whereas valgus static alignment increased the risk of lateral progression (OR = 4.89) |**14**|. Dynamic malalignment may be a stronger risk factor for structural progression than static alignment. In a prospective study it was shown

that the baseline adduction moment, or dynamic load on the medial compartment, predicted radiographic OA progression at 6-year follow-up |**15**|. Specifically, 80% of progressors had a high adduction moment (≥5 weight×height), and, when both static and dynamic alignment were examined together, dynamic alignment was more predictive of progression. Lateral heel wedges have been shown to be effective in reducing the symptoms of medial compartment knee OA. The 5° wedge reduced the peak knee varus torque by 6% and the 10° wedge reduced peaks by 8%. The 10° wedge was associated with discomfort. Both the efficacy at the knee and the foot discomfort associated with orthoses seem to have dose effects as determined by the angle (or height) of the lateral wedge. Increasing valgus alignment with a knee brace can reduce the net varus moment and estimated medial compartment load. Additionally, knee braces can improve proprioception and provide mechanical support and may improve the feeling of instability that often accompanies knee OA.

Comment

The European League against Rheumatism (EULAR) guidelines for the management of knee OA |**16**| and new insights into treatment approaches for OA |**17**| recommend lateral wedging as a conservative treatment for medial compartment OA. A recent Cochrane review upholds the findings of the above review |**18**|. Wedge insoles are a very practical way of improving the short-term pain and improving function. In patients who are not candidates for surgery, consideration should be given to orthotics. Whether use of orthotics to unload joints has any major long-term beneficial effects in OA, such as slowing of radiographic progression or disease modification, is not known.

Obesity and osteoarthritis: the potential of adipokines in driving arthritis

Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production

Presle N, Pottie P, Dumond H, *et al. Osteoarthritis Cartilage* 2006; **14**: 690–5

Background. Well-known risk factors for knee OA include obesity, and this association is particularly strong in women. Analysis of twin data has shown that this association is not explained by shared genetic factors between obesity and knee OA phenotypes and that the association is explained by mechanical or environmental causes |19|. However, it appears that the relationship may be more complex. Adipose tissue behaves like an endocrine organ and produces a vast array of inflammatory proteins such as interleukin 1 (IL-1). These proinflammatory

proteins are linked to diabetes in obese subjects. It is now becoming appreciated that adipose tissue is a source of leptin or adipoleptin proteins, which are not only more prominent in the synovial fluid of a joint with OA, but also may promote progression by more than biomechanical means alone. The investigators sought to analyse the distribution of leptin, adiponectin and resistin between paired serum and synovial fluid (SF) samples of patients with OA and to determine the potential sources of these adipokines in the joint |20|. The active free form of leptin was also examined by evaluating the level of the soluble leptin receptor (sOb-R).

Interpretation. Levels of adipokines and sOb-R were measured in serum and synovial fluid collected from patients with OA. The levels of adipokines were also determined from cultured joint tissues (synovium, infrapatellar fat pad, meniscus, osteophyte, cartilage and bone). The adipokines exhibited different patterns of distribution between the joint and the circulating compartment. Serum levels of resistin and adiponectin exceeded those in the paired SF. Conversely, leptin SF concentrations were similar or higher than those measured in serum counterparts. Leptin and adiponectin in SF may derive from each joint tissue examined, whereas resistin was not detected in cultured explants. Synovium and infrapatellar fat pad were the major sources of adipokines, but osteophytes also released large amounts of leptin. The sOb-R deficiency found in SF further increased the difference in the bioactive leptin levels between serum and SF. A gender-specific difference was observed with women exhibiting the highest levels of free leptin in the joint. The data suggest that serum levels of adipokines are not predictive for SF determination. The joint cavity is a special place where each adipokine undergoes specific regulatory pathways, strengthening the hypothesis that adipokines may have local effects in the joint and may account for the high prevalence of OA in women.

Comment

Even if it is usually accepted that mechanical loading contributes to OA in obese patients, these recent advances in the physiology of adipose tissue add further insights in understanding the relationship between obesity and knee OA. Indeed, the positive association between obesity and OA is observed not only for knee joints but also for non-weight-bearing joints, such as the hands |**21**|. The adipokines leptin, resistin and adiponectin, and new ones that are yet to be discovered, exhibit pleiotropic functions including lipid and glucose metabolism, blood pressure regulation, insulin sensitivity, bone formation and angiogenesis |**22**|. A new hypothesis has been put forward that OA is a systemic disorder in which dysregulation of lipid homeostasis can be one of the pathophysiological mechanisms |**23**|. In addition to OA, obesity is associated with vascular disease, and an interesting hypothesis about the role of atherosclerosis in the progression of OA has been proposed |**24**|. All these recent advances add weight to the notion that OA is not just a disease of articular cartilage alone but also a systemic disorder in which circulating factors linked to altered lipid and glucose metabolism may explain the diversity of pathophysiological changes found.

Proteomics: applications to the study of osteoarthritis

Proteomic characterization of human normal articular chondrocytes: a novel tool for the study of osteoarthritis and other rheumatic diseases

Ruiz-Romero C, Lopez-Armada M, Blanco F. *Proteomics* 2005; **5**: 3048–59

Background. With the completion of the genome project in 2003, a novel investigation line emerged in chronic disease – that of proteomics. Proteomics, the large-scale analysis of proteins, is complementary to genomics because of its focus on the identification and characterization of gene products (i.e. proteins). Proteomics is the necessary next step for biomedical research because proteins, not DNA, are the actual mediators of biological functions within cells, as well as of pathophysiology in disease states. Proteomics encompasses many technical disciplines and of the various disciplines, mass spectrometry (MS)-based proteomics allows high-throughput analysis of complex protein samples for clinical applications |25,26|. The chondrocyte is the major cell type in mature cartilage and it is important in the control of cartilage integrity. In order to identify the pathological processes involved in the destruction of articular cartilage, it is first necessary to characterize the normal protein homeostasis of chondrocytes in healthy tissue. There is currently a lack of knowledge about the chondrocyte proteome. To address this deficiency, the investigators have obtained the first reference map of the human normal articular chondrocyte |27|.

Interpretation. Cultured cells were used to obtain protein extracts. Almost 200 spots were excised and analysed using MS. The analysis led to the identification of 136 spots that represent 93 different proteins. A significant proportion of proteins are involved in cell organization (26%), energy (16%), protein fate (14%), metabolism (12%) and cell stress (12%). From all the identified proteins, cytoskeleton-related proteins (vimentin, transgelin and destrin), cathepsin D, heat-shock protein 47, mitochondrial superoxide dismutase and members of the annexin family were more abundant in chondrocytes than in other types of mesenchymal cells. These differences between chondrocyte and mesenchymal (Jurkat-T-cell) cell types were confirmed by consulting reference maps available. The investigators found a high abundance of proteins that belong to the annexin family, which mediate calcium influx into the growth plate chondrocytes and positively regulate terminal differentiation, mineralization and apoptosis events in these cells. The other group of chondrocyte proteins whose abundance was significant is one related with the cytoskeleton. The actin cytoskeleton modulates not only cell phenotype, but also apoptosis. Nuclear actin accumulation is considered as a new marker of cellular senescence. Transgelin has also been described as a senescence marker. Considering the well-known association between OA and ageing, the study of these senescence proteins may open new research lines.

Comment

Protein microarray technology is still in its relative infancy because of the complexity of proteins relative to DNA analysis. One of the key limiting factors for generating protein microarrays with utility for studying the degenerative state is the lack of known protein targets. Nevertheless, the study of the intracellular proteomic profile of the chondrocyte is a good approach to gain insight into proteins involved in cellular metabolism and organization, as well as proteins participating in extracellular matrix synthesis and turnover of articular cartilage. This technique can also be used to understand the pathogenesis of OA, which is related to ageing. The protein microarray may become the high-throughput assay that is most efficacious as a diagnostic tool for chronic diseases like OA.

Reactive oxygen species in cartilage degradation

Cellular events leading to chondrocyte death after cartilage impact injury

Green DM, Noble PC, Ahuero JS, Birdsall HH. *Arthritis Rheum* 2006; **54**: 1509–17

Background. Human cartilage is subjected repeatedly to peak stresses of up to 15–20 MPa. It is well appreciated that acute impact loading causes degeneration of articular cartilage, with chondrocyte apoptosis and proteoglycan degradation in the zone of injury. The role of the inflammatory system in the response of articular cartilage to mechanical trauma has yet to be fully elucidated. Using *in vivo* and *in vitro* models, this study examined the mechanisms of chondrocyte death after impact injury and the role of leucocytes in extending the zone of injury to chondrocytes still resident in the articular matrix |28|.

Interpretation. The investigators used a blunt trauma model to acutely injure the cartilage and determined that the observed cell death could be inhibited by blocking nitric oxide (NO) synthase. NO by itself is unlikely to cause chondrocyte death, and therefore these findings suggest that excess NO had combined with other reactive oxygen species (ROS) to form highly toxic compounds. In addition, the injured cartilage was more susceptible to further injury mediated by leucocytes. The injured chondrocytes increased expression of intercellular adhesion molecule-1 (ICAM-1), an adhesion receptor for leucocytes. Adhesion of leucocytes to the injured chondrocytes resulted in death of additional cells due either to stimulation of further production of toxic ROS by the chondrocytes or to release of ROS from leucocytes.

Comment

This paper adds to the growing body of evidence that oxidative damage contributes to cartilage degeneration. Abnormal mechanical forces appear to induce the chondrocyte from a level of low metabolic activity and stimulate the cell to produce a host of inflammatory mediators that serve to increase the catabolic activity. On the other hand, chondrocytes also produce a host of growth factors that serve to stimulate matrix production and inhibit production of proteolytic enzymes. It appears that a defect in the anabolic activity would promote degeneration. Ageing is strongly associated with OA. The age-related changes in the chondrocyte result in a cell that is less responsive to growth factor stimulation, and, therefore, injury-induced matrix remodelling does not take place and there is continued catabolic activity and continued damage to the matrix. If the abnormal mechanical loading that is observed in OA is found to be sufficient to stimulate a chronic excess of ROS, this could be an important mechanism that ties mechanical stress and ageing changes in cartilage to the development of a proinflammatory state and an imbalance of the anabolic and catabolic activity. If correcting abnormal mechanics is not possible in some patients, then targeting the molecular mechanism by which abnormal mechanics results in degeneration could have therapeutic value. Several compounds that inhibit NO synthase are under investigation as potential disease-modifying therapy in OA.

Enzymes: 'weapons' of destruction for articular cartilage. Clinical implications of basic research

Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis

Glasson SS, Askew R, Sheppard B, *et al. Nature* 2005; **434**: 644–8

ADAMTS5 is the major aggrecanase in mouse cartilage in vivo and in vitro

Stanton H, Rogerson FM, East CJ, *et al. Nature* 2005; **434**: 648–52

Background. A necessary and plentiful component of articular cartilage extracellular matrix is aggrecan, a large proteoglycan consisting of a protein core backbone substituted with many highly sulphated glycosaminoglycans. Aggrecan provides cartilage with the ability to resist compressive forces. Accelerated proteolysis of aggrecan and the consequent loss of the glycosaminoglycan

(GAG)-bearing region of the molecule during arthritis is an early event in disease pathogenesis |29|. Since the discovery a few years ago that several members of the ADAMTS (a disintegrin and metalloprotease with thrombospondin-like repeat) family of enzymes were able to cleave aggrecan at its known site of degradation in human joint diseases, the race was on to find which ADAMTS(s) was/were involved in cartilage destruction. To date, three enzymes capable of degrading aggrecan have been identified: ADAMTS-1, ADAMTS-4 and ADAMTS-5. The inactivation of ADAMTS-1 had been shown not to protect mice from experimental arthritis |29|, but the importance of ADAMTS-4 and ADAMTS-5 was not known. To address this issue both Glasson *et al.* and Stanton *et al.* created mice lacking either ADAMTS-4 or ADAMTS-5 |30,31|.

Interpretation. The groups published their findings simultaneously in the journal *Nature*. They found that the inactivation of either enzyme did not negatively affect normal development, growth or the integrity of articular cartilage in unchallenged mice. Both groups then challenged the mutant mice. Glasson *et al.* examined the effect of surgically induced joint instability and cartilage destruction. Severity of joint pathology revealed a significant reduction ($P < 0.05$) in the scores of the ADAMTS-5 +/– and ADAMTS-5 –/– mice compared with wild-type mice. This inability to cleave aggrecan at the aggrecanase site was further substantiated by lack of appearance of these fragments after *in vivo* cytokine stimulation of articular cartilage from ADAMTS-5 –/– mice. Stanton *et al.*, using a model of inflammatory arthritis, demonstrated that deficiency in ADAMTS-5 completely prevented the IL-1-induced release of aggrecan from murine articular cartilage. In contrast, deletion of ADAMTS-4 had no protective effect.

Comment

There are many animal models of OA, and research on these models remains highly dynamic due to difficulties in studying OA in humans. Genetically modified mice constitute the best tools for mechanistic studies aiming at understanding the functional role of specific molecules in cartilage homeostasis and OA pathology. In these two papers it has been shown that, compared with wild-type mice, ADAMTS-5-deficient mice were more resistant to aggrecan loss and articular cartilage destruction induced by joint instability or inflammatory challenge. These are the first reports to indicate that a single gene deletion can significantly slow down articular cartilage destruction in an animal model of OA and illustrate the molecular basis of a complex degenerative disease. The physiological relevance of these findings to human disease remains questionable; both increases |**32**| and decreases |**33**| in ADAMTS-5 have been reported for OA cartilage, compared with normal cartilage, in humans. Nevertheless, potentially, they identify ADAMTS-5 as a key target for the development of novel, adapted therapies for OA. Corroboration of these findings in human osteoarthritis will require examination of human osteoarthritic cartilage and demonstration of therapeutic efficacy of targeted inhibitors in the clinic. If ADAMTS-5 has an identical function in humans, treatment with an inhibitor may prevent cartilage destruction or quickly stop its progression.

Conclusion

Much has been learned of the biology of OA. Three major components are affected in OA – bone, synovium, and cartilage – which produce cytokines, growth factors and proteases that have been implicated in disease progression. As the understanding of the molecular basis of disease progression increases, opportunities will emerge to test agents that block specific pathogenic processes. Challenges include the ability to improve identification of patients at risk of progression, using knowledge of the epidemiological and biochemical markers, genetics, and now proteomics, which will predict clinically meaningful progression. In the meantime, we should be looking at simple ways to achieve benefits that accompany interventions such as mechanical unloading and encouraging optimal body weight in our patients. Use of glucosamine and chondroitin sulphate is extremely popular. These are safe supplements; however, the preliminary results of the NIH-funded trial may dampen the enthusiasm for these nutraceuticals. The most attractive therapeutic targets for the future appear to be the inflammatory process by reducing NO and ROS, and cartilage degradation by inhibiting aggrecanases.

The field in OA continues to open up and a new era in which therapeutics that specifically block key mechanisms for structural changes can be brought into development and eventually into clinical trials.

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8

Magnetic resonance imaging for osteoarthritis

KIMBERLY AMRAMI

Until recently, the imaging of osteoarthritis (OA) has primarily been limited to radiography. Many single-point and longitudinal studies have used either standard or specially positioned radiographs as their sole imaging modality for the assessment of the severity of disease and to evaluate progression over time. The classic radiographic grading system for osteoarthritis, that of Kellgren and Lawrence, is based on standard frontal and lateral radiographs and uses gross findings such as osteophytes, visible joint space narrowing and subchondral cysts to determine how individual patients fit into a simple five-point grading scale. This is known to be most accurate in late-stage disease and insensitive to early structural changes in cartilage. As the approach to the management and treatment of OA has evolved to earlier diagnosis and intervention, the demands on imaging and other diagnostic tools have increased. When the endpoint of all OA was ultimately joint replacement, a test such as plain radiography was adequate; in today's medical environment, where early disease-modifying therapies are an option, a test that is sensitive for early changes is required. It has become clear in recent years that the imaging test of choice for this purpose is magnetic resonance imaging (MRI).

MRI uniquely can assess both the qualitative and quantitative degeneration of articular cartilage seen in OA. Normal healthy hyaline articular cartilage is composed of sparse chondrocytes within a matrix of long-chain proteoglycans and collagen, which is ordered in a specific way into the familiar laminar orientation reflecting the difference in function of articular cartilage compared with undifferentiated hyaline cartilage. The largest constituent of cartilage is water, but this water is tightly bound within the overall negatively charged proteoglycan matrix. The relative concentration of proteoglycans is different depending on the layer of cartilage examined, and the orientation of collagen fibrils is also different at each level on histological review. The deep calcified zone of cartilage anchoring the structure to bone is also unique. All of these structures and differences have MRI correlates that can be exploited by using both standard and advanced imaging techniques.

Qualitative MRI for OA primarily looks at visually perceptible changes in free water content within articular cartilage. Image contrast in MR is generated by a variety of methods, but can be characterized as either T1-weighted (where fluid is dark and fat is very bright) or T2-weighted (where fluid is very bright). The qualitative assessment of articular cartilage primarily relies on imaging

sequences that use T2-weighting in some form, usually with a fast spin echo (FSE) sequence. By choosing appropriate parameters for the imaging sequence [usually a combination of a long repetition time (TR > 2000 ms) and an intermediate echo time (TE = 40–60 ms)] cartilage may be distinguished from joint fluid. In the case of normal hyaline articular cartilage, the overall appearance of the cartilage is grey in contrast with the white joint fluid; on high resolution imaging the perpendicularly oriented collagen fibrils will cause some low signal within the cartilage. This effect is accentuated by chemically selective fat saturation, which decreases background signal and increases the perceptible dynamic range of contrast within the cartilage, making it possible to see alterations in the expected laminar appearance of cartilage. If FSE imaging is used there is some additional boost from the effects of magnetization transfer, a phenomenon that decreases background signal and makes T2 changes more conspicuous. As articular cartilage degenerates, the earliest changes seen on MRI involve subtle increases in T2 signal representing an increase in free water within the cartilage. As the degeneration progresses, fissuring and focal defects and flaps can be seen on high-resolution MRI. A classification system, the modified Outerbridge classification, has been used to grade changes of OA on MRI. The original Outerbridge classification is an arthroscopic grading system; the accuracy of its MRI correlate depends to some degree on the quality of MRI used in that higher-resolution imaging can better show subtle regional changes within cartilage. As with radiography, the modified Outerbridge classification has been shown to correlate better with higher grades of OA, probably due to prior studies that correlated arthroscopic findings with less technically advanced MRI. The modified Outerbridge classification is a relatively simple five-point scale that roughly corresponds to the degrees of severity described by the classic Kellgren–Lawrence scale. However, because of the relatively poor correlation with the earliest disease, multiple newer grading systems have been proposed that take into account factors such as T2 signal and structural changes in cartilage, synovitis and joint effusions, osteophytes and even subchondral bone marrow oedema and remodelling of bone in response to the loss of cartilage. The most comprehensive of these is the WORMS (whole-organ magnetic resonance imaging score) for knee OA proposed by Peterfy and colleagues |**1**|, which was developed for use in epidemiological studies – highly detailed, it is probably too complicated and time-consuming for application in clinical practice. Currently most practitioners are using some combination of description and the 0–4 grading system of the modified Outerbridge classification until such time that a more sophisticated and easy-to-use grading system is validated. Felson and colleagues |**2**| have shown that the finding that correlates best on MRI with symptoms of OA is the presence of joint effusions and bone marrow oedema (both relatively late findings indicating advanced cartilage loss), but most practitioners advocating the use of MRI for OA aim to identify disease in the preclinical or very earliest clinical stages, relying on subtle signal changes within the cartilage to show the earliest degradation of cartilage.

Another technique for qualitative MRI for OA involves the use of T1-weighted imaging with chemical fat suppression, typically using a gradient recalled echo technique. Hyaline articular cartilage appears very bright against an overall dark background. While this type of imaging is often used for volumetric measurements or for segmentation of cartilage due to the extreme difference in contrast between cartilage and other tissues, it can only demonstrate focal defects or surface irregularities; unlike the T2-based methods described above, it cannot show any signal changes within the cartilage that would be indicative of the earliest types of changes, where the cartilage thickness and surface appearance may be maintained but where there is loss of the biomechanical integrity of the cartilage within the proteoglycan matrix and collagen structure, giving it limited value on its own.

Other types of T2-weighted or fluid-sensitive sequences including steady-state free precession sequences, such as FIESTA (fast imaging employing steady-state acquisition) and true FISP (fast imaging with steady-state precession), fast recovery FSE and others, have been used for cartilage imaging but at this time a high-resolution, intermediate-weighted (proton density) T2 sequence with chemically selective fat suppression remains the most robust and easily applied technique for the qualitative assessment of articular cartilage with MRI.

Some of the most exciting recent advances in MRI for OA have occurred with the development of new techniques for the quantitative evaluation of OA. These range from relatively simple techniques, such as volumetric measurements of cartilage using high-resolution, 3-D T1-weighted acquisitions as described above, to very sophisticated tests that use highly specialized techniques to assess the charge density of cartilage *in vivo* as a surrogate for proteoglycan concentration. Several of these techniques are now available for use outside the research setting while some remain investigational. All of these newer techniques are correlated with either proteoglycan concentration or integrity of the collagen network; the only exceptions to this are the standard techniques that look at cartilage thickness and volume without assessing the ultrastructure of the cartilage under evaluation.

T2 mapping, which is the quantitative measure of T2 signal values within cartilage, has recently become available on many commercial MRI systems. This technique requires a multi-echo acquisition that generates a curve looking at T2 values at different echo times. A decay curve is generated and T2 values, both regional and more global, can be calculated. This is usually displayed as a colour map that shows sites where T2 values are elevated and cartilage is degenerated. Very high-resolution or high-field imaging may even show the laminar orientation of normal cartilage. Using newer pulse sequences this can be accomplished in 5 min or less, with vendor software providing analysis and images that may be archived. This technique is currently best used for post-operative situations such as grafting for osteochondral lesions, in which it can help to differentiate the presence of hyaline versus fibrocartilage within the graft. Current multisite trials are under way to assess the reproducibility of T2 mapping across time and using different types of equipment. T2 mapping has great promise as a relatively simple tool that could be

widely available, but questions regarding reproducibility across time and between different types of MRI systems remained to be answered before it can be considered a robust clinical tool for assessing and following patients with early OA, especially as it appears to correlate better with collagen degradation, which is a later finding in early OA than proteoglycan loss.

The proteoglycan loss seen in very early OA can be assessed *in vivo*, but the techniques are more complicated and not commonly seen outside of the research setting. The first of these was developed by Deborah Burstein and colleagues |**3**| at Harvard and relies on the charge difference between healthy and degenerated articular cartilage. It has been known for some time that the overall charge of normal cartilage is slightly negative due to the negatively charged long-chain proteoglycans; this is felt to be important for the hydrostatic properties of intact cartilage. As cartilage degenerates and proteoglycan concentration decreases, cartilage becomes relatively less negatively charged. As with T2 mapping, these changes may be regional or global. Burstein's method, delayed gadolinium-enhanced MRI of cartilage, or dGEMRIC, involves the injection of gadolinium-DTPA 2 intravenously. After a delay of about 1–1.5 h, the patient undergoes MRI including T1 mapping, which looks at the distribution of the negatively charged contrast material into the cartilage from joint fluid by diffusion. Because of its negative charge the contrast will preferentially bind to more positively charged degenerated cartilage and a map of the contrast distribution within the cartilage can be created. This can be assessed quantitatively, but like T2 mapping is usually presented in the form of a colour map. It is very time-consuming and requires the injection of contrast making it somewhat more invasive than T2 mapping. It is very sensitive for early changes of OA and has been shown to identify preclinical disease in patients with hip dysplasia. It has also shown utility in following patients after cartilage grafting or repair but remains primarily a research tool due to its complexity and long imaging times. As the technique is simplified and the imaging shortened it may have broader application in the clinical setting.

Another method that has been shown to correlate with proteoglycan content in normal and degenerated cartilage is T1-rho imaging. The T1-rho value is the time constant of the exponential decay of magnetization during a spin-lock pulse. The rate of relaxation, which is the inverse of T1-rho, is sensitive to molecular interactions between bulk water and macromolecules such as proteoglycans, and changes in this constant have been shown to correlate with proteoglycan concentration *in vitro*. While very promising as a technique because, unlike dGEMRIC, it does not require contrast administration and potentially indicates earlier changes in cartilage than T2 mapping, it is challenging to perform *in vivo*, very time-consuming and is energy-intensive, which limits the amount of cartilage that can be assessed in one imaging session. Further refinements in the pulse sequence may diminish some of these problems and make it more widely available for clinical use. As with T2 mapping and dGEMRIC, T1-rho values can be displayed numerically or as a colour map.

Beyond these specialized tools, many more widely available advances in MRI overall have improved the quality and clinical relevance of MRI for assessing OA.

Imaging at the highest spatial resolution possible requires the highest possible signal-to-noise ratio (SNR). One of the simplest ways to achieve this is to image at a field strength of 1.5 T or higher as SNR is linearly correlated with field strength; this means that a 3-T imager has 20 times the SNR of a low-field 0.15-T dedicated extremity magnet. Another way to ensure the highest image quality is to use an optimized receiver coil for the anatomy under investigation. The improvement in image quality achieved in these ways will result in better identification of early changes of OA, which will hopefully lead to earlier, less invasive, interventions and treatments for patients. While the cost of MRI is high compared with traditional radiography, its ability to detect early disease and non-invasively monitor treatment with less invasive therapies will justify its price in the long run.

The current literature on MRI for OA is largely concentrated on moving away from visual, qualitative evaluations to quantitative assessments that can be standardized and help direct and follow treatment strategies. The papers below represent this trend and include both human and animal studies *in vivo* and *in vitro*.

Osteoarthritis of the knee: comparison of MR imaging findings with radiographic severity measurements and pain in middle-aged women

Hayes CW, Jamadar DA, Welch GW, *et al. Radiology* 2005; **237**: 998–1007

Background. This study comparing MRI with radiographic findings looked retrospectively at a group of middle-aged women (*n* = 117, aged 32–56) who were studied as part of a larger community-based arthritis study. The women were categorized as having no pain and no OA, no pain and OA, pain and no OA, or pain and OA. Weight-bearing radiographs and MRI with cartilage-specific sequences were obtained in all subjects. The radiographs were rated using the Kellgren and Lawrence system and the MRIs were graded using a number of parameters including cartilage defects, bone marrow oedema, subchondral cysts, ligamentous and meniscal pathology, joint effusion and synovitis. The knees were assessed globally and by region.

Interpretation. Nearly half of the patients were rated Kellgren and Lawrence grade 0 on their radiographs; over 90% were grade 2 or less. The authors found that pain was positively correlated with increasing Kellgren and Lawrence grade as well as MRI findings including cartilage defects, osteophytes, joint effusion or synovitis and meniscal or ligamentous abnormalities and bone marrow oedema. There were relatively more findings identified in the patellofemoral compartment with MR than with radiography, which was more associated with medial and lateral compartment pathology. Patients with pain and radiographic evidence of OA had more findings on MRI. Patients with radiographic evidence of OA but no pain had more MR findings than patients without OA and pain or with pain but no radiographic evidence of OA.

Comment

The value of this study is not that it validates the correlation of an increased number of MR findings with rising grades of radiographic OA but rather that it looked at imaging findings in two very interesting groups that we would imagine would benefit from more advanced imaging: those with radiographic evidence of OA but no pain and those with knee pain but no radiographic evidence of OA. Patients with radiographic evidence of OA but no pain had more MRI findings than did patients without radiographic evidence of OA, with bone marrow oedema a frequent finding in this group, which cannot, of course, be assessed on radiography and was highly statistically significantly correlated with pain. In this study, limited as it was to women and patients overall younger than in most OA studies, there was an increased incidence of patellofemoral arthritis that was better seen on MRI than on the radiographs. While the overall conclusion of the paper is that there was strong correlation between the radiographs and MRI with increasing disease severity, it is clear that MRI adds unique information in this group of younger women with less severe OA. The authors caution that this information cannot be extrapolated to men, who typically have different patterns of OA, or to older patients with more established disease.

Magnetic resonance imaging findings in the follow-up of patients with different stages of osteoarthritis and the correlation with clinical symptoms

Phan CM, Link TM, Blumenkrantz G, *et al. Eur Radiol* 2006; **16**: 608–18

Background. This prospective study examined a small cohort of normal subjects and patients (40 total) at baseline and then with two follow-up visits at approximately 1.4 and 2.4 years. The study subjects underwent radiography at baseline to establish the Kellgren and Lawrence grade. While all subjects completed both the baseline and first follow-up MRI, only 26 completed the second follow-up MR examination. The study subjects were also assessed clinically and completed Western Ontario and McMaster Universities (WOMAC) questionnaires.

Interpretation. The authors found progression of findings on MRI over the course of the study but no statistically significant correlation with clinical symptoms as rated by the WOMAC questionnaire. They conclude that MRI is well suited to longitudinal follow-up of OA and effective at identifying progression not identifiable on radiographs, such as cartilage defects, bone marrow oedema and internal derangement of the knee.

Comment

This study has several limitations. It did not look at progression on radiographs to determine whether or not they showed similar progression as radiographs were obtained only at baseline. The small number of patients completing the second

follow-up probably also contributed to the lack of statistical correlation with the clinical questionnaire. The authors postulate that the lack of correlation between the observed increasing severity of disease on MRI and clinical findings may be due to the adjustments patients make as their symptoms worsen, but this is doubtful given that the WOMAC has been validated for both single-point and longitudinal studies of OA. A larger study of both radiographic and MRI correlation with clinical measures and WOMAC may help to better establish the relationship between progression of findings on MRI and measurable changes in pain and function measured clinically.

The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis

Amin S, LaValley MP, Guermazi A, *et al. Arthritis Rheum* 2005; **52**: 3152–9

Background. This is a larger study of an older, mixed gender cohort compared with the two studies discussed above. In this study 224 patients with a mean age of 66 were evaluated at baseline and then at 15 and 30 months with radiographs and MRI (Fig. 8.1). The original cohort consisted of 324 subjects, but only 224 underwent all study tests. The study used a semiquantitative method for evaluating changes on MRI (namely, the WORMS grading system described by Peterfy *et al.* |1|) rather than strictly quantitative measures of cartilage thickness of volume to assess cartilage loss. The degree of joint space loss on radiography was also graded qualitatively rather than measured.

Interpretation. The authors noted that radiographic changes were specific but not sensitive to cartilage loss and that cartilage loss in regions such as the posterior femur and central areas of the tibia and femur was less likely to be appreciated on radiography compared with MRI. They also had a subgroup of patients (42%) who had cartilage loss on MRI without associated radiographic changes. The authors conclude that radiography is insensitive and will miss a substantial number of cases where there is cartilage loss if used alone. They also note that progression of joint space narrowing on radiography does correlate with cartilage loss on MRI.

Comment

This study is of a relatively large cohort of men and women with symptomatic OA gleaned from a community-based OA study (Boston Osteoarthritis of the Knee Study), making it one of the larger studies of its type to include both radiography and MRI in longitudinal follow-up. The primary weakness of this study is the lack of truly quantitative measurement used. The radiographs were rated by a single reader for progression of joint space narrowing and the MR images were evaluated by three readers working in two teams with all readers trained by the same musculoskeletal radiologist. There were no comments regarding inter-observer reliability for the WORMS scoring, which is important as it is a very detailed and complicated system. There was also no attempt to correlate imaging findings with clinical symptoms.

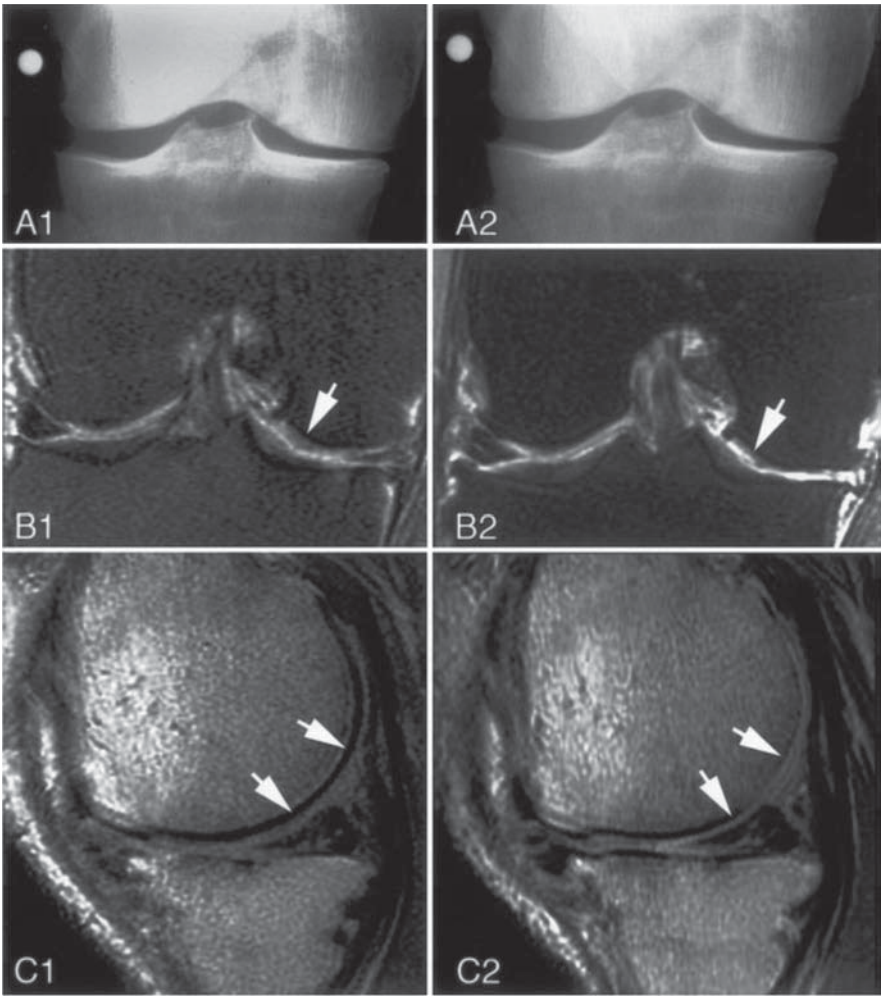

Fig. 8.1 Example of medial compartment cartilage loss without radiographic progression. (A) Baseline (A1) and 30-month follow-up (A2) semiflexed, weight-bearing knee radiographs. (B) Corresponding magnetic resonance image of the same knee with spin-echo, fat-suppressed and T2-weighted coronal views at baseline (B1) and follow-up (B2). (C) Spin-echo, proton-density and T2-weighted sagittal views at baseline (C1) and 30-month follow-up (C2). Arrows indicate areas of cartilage loss. Source: Amin *et al.* (2005).

Probably the most important finding that is relevant to the suitability of MRI for the assessment of OA is that in 42% of the subjects cartilage abnormalities were observed with MRI but not on radiographs, suggesting that radiography is too insensitive to use as a tool for longitudinal follow-up of OA. However, the lack of discussion of the relationship of these MR findings to either symptoms or treatment limits the value of this study.

The validation of simple scoring methods for evaluating compartment-specific synovitis detected by MRI in knee osteoarthritis

Rhodes LA, Grainger AJ, Keenan AM, *et al. Rheumatology* 2005; **44**: 1569–73

Background. This paper looked at creating a simple, semiquantitative scoring system for the assessment of synovitis on MRI for patients with clinical evidence of knee OA. Thirty-five subjects with symptomatic OA were evaluated using contrast-enhanced MRI to assess the burden of knee synovitis. Four sites in the knee were rated and were graded on a severity scale from 0 to 3. Volume measurements of the enhancing tissue representing synovitis were also performed. The volume measurements were performed by one reader and the semiquantitative scoring by a second reader. Both were blinded to the results of the other method. A total of 140 sites were included in the statistical analysis. No correlation was made with the severity of clinical symptoms. Statistical analysis was aimed at correlating the simple semiquantitative scoring with the burden of synovitis, which required more time-consuming volumetric analysis.

Interpretation. There was good correlation between the two methods, with correlation coefficients (*r*) ranging from 0.86 for the medial parapatellar recess to 0.71 for the lateral region. There was some minor overlap in confidence intervals when comparing the two methods but, in general, the simpler scoring method predicted the volume measurements in a majority of cases when using regression analysis. The authors conclude that the simpler method, which describes the enhancing synovium as normal (0), diffusely but uniformly thickened (1) or having nodular thickening (2) or gross nodular thickening (3), is a valid measure of the degree of synovitis when compared with more complex volume measurements.

Comment

Many of the scoring systems for MRI of OA currently being assessed in the literature are extremely detailed, very complicated and too cumbersome to consider using outside of the realm of research. The value of a simple and validated scoring system that correlates with more complex assessments and has clinical relevance cannot be overstated. In this case the simpler four-point scoring system had high correlation with volume measurements, which is heartening. Unfortunately, the value of this study is limited due to the lack of correlation with clinical symptoms or severity of OA as ranked on other validated measures such as the WOMAC or even radiography. In addition, it requires the use of contrast enhancement, a less than common approach to knee MRI. In most cases when appropriate MRI parameters are employed, synovitis can be distinguished from simple joint fluid. It would add value to the scoring system proposed if it could be applied to non-contrast imaging of the knee.

Computer-aided quantification of focal cartilage lesions using MRI: accuracy and initial arthroscopic comparison

Lee KY, Masi JN, Sell CA, *et al. Osteoarthritis and Cartilage* 2005; **13**: 728–37

Background. This paper describes the application of a previously developed computer algorithm called the gradient peak method (GPM) to quantify cartilage lesions that were created in procine knees (37 lesions) and measured manually. A subset of lesions ($n = 15$) had images at both 1.5 and 3T. Three patients with known chondral lesions were also scanned at 1.5T and analysed using this method with comparison with arthroscopic correlation. The GPM is a method that analyses boundaries based on gradients and curvature thickness rather than some techniques that look at thickness alone to create maps. Because of this it is applicable to curved surfaces such as the knee, which may otherwise be challenging for more traditional, non-topographic methods. The sequence used to obtain images for analysis was a 2-D spoiled gradient recalled echo (SPGR) sequence with a small field of view and high spatial resolution, which required over 9 min to acquire for 2 mm slice thickness and 19 min for 1 mm slice thickness. No contrast was necessary.

Interpretation. When compared with manual measurements on either the specimens or at arthroscopy, the estimates of lesion size using GPM were reasonably accurate, with the error within the expected range given the limitation of the imaging (i.e. depth and diameter error was within two times the in-plane resolution and within the measurement of slice thickness) and were accurate for the patients when compared with arthroscopy. The authors conclude that this method is feasible and accurate both *in vitro* and *in vivo* and that it may be a useful adjunct to image analysis for radiologists for the diagnosis and monitoring of OA. There were no statistically significant differences between the accuracy at 1.5 and 3T, but this comes as no surprise because the spatial resolution on the comparative examinations was the same.

Comment

This study shows that a computer-aided tool can be accurate in the assessment of focal cartilage defects, which may lend itself to following these lesions with disease-modifying therapies in a non-invasive way. This work is largely still in the feasibility stage and the amount of user input required to attain the results reported here is considerable. In addition to that limitation, the time required for image acquisition in order to achieve the appropriate spatial resolution needed for analysis is far in excess of what would be tolerated by most patients. Having said that, this work has tremendous potential to improve the radiological assessment of focal cartilage defects. Readers of these studies, including experienced radiologists, are notoriously inaccurate when making volumetric measurements from 2-D images. If the user input can be decreased and the imaging time decreased, perhaps through the use

of techniques such as parallel imaging, this would be a tremendously helpful tool for assessing patients, especially young patients with limited focal chondral defects related to trauma, for progression and repair.

Quantitative cartilage volume measurement using MRI: comparison of different evaluation techniques

Maataoui A, Graichen H, Abolmaali ND, *et al. Eur Radiol* 2005; **15**: 1550–4

Background. This interesting paper compares two methods of cartilage volume measurement in 12 knees of patients with known OA. The patients were imaged with a typical volumetric gradient echo sequence using selective water excitation rather than chemical fat suppression, which is typical for the scanner type used for this study. Cartilage volume in the tibial and patellar compartments was then analysed using two methods: one a validated multiprocessing computer system requiring a lengthy, off-line analysis and the second using a workstation programme provided by the vendor and which was originally designed to analyse cardiac images.

Interpretation. Although measurements varied slightly between the two systems they were not statistically significantly different, suggesting that the less time-consuming and more easily accessed workstation programme could be used with confidence for assessing cartilage volume at the knee.

Comment

Most validated semiautomated and automated analysis of cartilage thickness and volume requires laborious user input to segment images and determine boundaries for the purpose of analysis as well as often using lengthy, off-line analysis, which limits the use of this information outside of the realm of research – it simply takes too long to have clinical relevance in most cases. In this study user input was required for both systems but the vendor software was appreciably easier to use with better delineation of the cartilage surfaces, which made segmentation and boundary setting far easier. The vendor system has some limitations that the more powerful computer system does not, specifically regarding measurements of cartilage thickness, which were not possible with the simpler technique, and which may have more value for prognostication and longitudinal follow-up than total or compartmental cartilage volume measurements. The patients in this study all had relatively severe knee OA so it is likely that some error was introduced by the difficulty in assessing tibial cartilage in the face of significant cartilage loss there. Nevertheless, this is an important advance in making quantitative tools for OA more accessible and of more added value to clinicians and radiologists in their daily work assessing these patients.

Bone marrow abnormalities on magnetic resonance imaging are associated with type II collagen degradation in knee osteoarthritis. A 3-month longitudinal study

Garnero P, Peterfy C, Zaim S, Schoenharting M. *Arthritis Rheum* 2005; **52**: 2822–9

Background. This study compared findings on knee MRI in 377 patients with painful knee OA at baseline and again at 3 months. Seventy-six per cent of the subjects were women and most were older with well-established disease. Specific imaging was performed to assess subchondral bone marrow oedema (either a short TI inversion recovery (STIR) sequence or a T2 sequence with frequency selective fat suppression). The imaging was reviewed by a single trained radiologist using a four-point scale for severity of the oedema. The patients also underwent testing of urine for C-terminal cross-linking telopeptide of collage type II (CTX-II) at baseline, months 1 and 3. Serum levels of CTX-I, a marker of bone resorption, were also measured at these time intervals.

Interpretation. Eighty-two per cent of patients had bone marrow oedema on MRI. The severity scores for bone marrow oedema had a highly statistically significant correlation with CTX-II levels. Patients with the highest levels of CTX-II at baseline had a relative risk of worsened bone marrow abnormalities at 3 months compared with patients with the levels in the lowest third. In patients in whom bone marrow oedema decreased at 3 months, measurements of urinary CTX-II also fell. Approximately 30% of patients had changes in bone marrow oedema after 3 months. No correlation was found between bone marrow oedema on MRI and serum CTX-I measurements.

Comment

This is an innovative paper comparing a biochemical marker of cartilage degeneration that is excreted in urine (CTX-II) with a finding on MRI (bone marrow oedema) known to have high correlation with clinical symptoms. In this cohort of older patients (average age = 63) with long duration of disease (greater than 6 years on average), the changes over a period as short as 3 months are dramatic and unexpected. Almost 10% of patients had decreased in bone marrow oedema and nearly 20% had an increase with associated changes in CTX-II, a marker of active cartilage degradation, suggesting that even with established and moderately advanced disease short-term change for better or worse can be seen. Unfortunately, this study was of very short duration and did not correlate either the CTX-II levels or MRI findings with symptoms, but it does suggest that bone marrow oedema, long known to have a significant correlation with clinical symptoms in OA, can be a marker of disease activity as well as of severity. This is an especially important concept for following patients with disease-modifying drug regimens, in whom it could be used to assess treatment success in as little as 3 months.

Double echo steady-state magnetic resonance imaging of knee articular cartilage at 3 teslas: a pilot study for the Osteoarthritis Initiative

Eckstein F, Hudelmaier M, Wirth W, *et al. Ann Rheum Dis* 2006; **65**: 433–41. Published online 26 August 2005

BACKGROUND. This paper compares two types of MR image acquisition for the purpose of measuring cartilage morphology (thickness and volume) at 3T. In this case, the 'gold standard' method using a high-resolution 3-D fast low-angle shot (FLASHwe) is compared with a newer sequence using steady-state imaging called double echo steady-state (DESSwe). Both were performed using selective water excitation rather than frequency selective fat suppression, which is typical for this manufacturer. The primary motivation for comparing these two methods is that the 3-D FLASHwe is limited to a 1.5 mm slice thickness, whereas DESSwe can achieve a slice thickness of 0.7 mm, making it a likely technique for performing nearly isotropic imaging, which minimizes volume averaging and facilitates multiplanar and volumetric reconstructions. The thinner sections and improved spatial resolution should result in more accurate measurements. 3T is an important tool for potentially using this technique as this kind of resolution would result in a significantly signal-starved image at 1.5T, where noise could become a very significant limitation in obtaining accurate measurements.

INTERPRETATION. Overall the error was slightly greater with the DESSwe, particularly using the sagittal reformatted images where the error ranged from 2.3% to 8.2%. Nonetheless, the correlation coefficients for DESSwe with the traditional 3-D FLASHwe images ranged from 0.88 to 1.0, suggesting that the higher-resolution DESSwe is at least as accurate as the traditional imaging.

Comment

Segmentation was deemed more difficult with the traditional FLASHwe images due to less image contrast between cartilage and fluid, and because of the slight uncertainty in determining boundaries in some cases due to partial volume effects of the larger imaging voxel. Further study is warranted, but DESSwe appears to have potential value as a very high-resolution imaging sequence for quantitative measurements in OA. Its reproducibility and value for longitudinal studies will need to be validated with further study.

Fat-suppressed 3-D spoiled gradient echo MRI and MDCT arthrography of articular cartilage in patients with hip dysplasia

Nishii T, Tanaka H, Nakanishi K, *et al. AJR* 2005; **185**: 379–85

Background. This work assesses the accuracy of multidetector computed tomography (MDCT) arthrography of the hip compared with 3-D spoiled gradient recalled echo (SPGR) MRI against a reference standard of arthroscopy in patients with developmental dysplasia of the hip. This group of patients is known to develop early OA of the hip and is typically younger than most patients with hip OA. Radiography has been the traditional imaging method for these patients, but recent work has shown that degeneration of articular cartilage can be present even when joint space is maintained on radiographs. MRI has traditionally been the next line of imaging for hip OA with its improved tissue contrast and ability to detect findings such as bone marrow oedema and large joint effusions, which have been occult on radiography and, to a lesser degree, CT. This study compares two imaging methods that look at the surface and not the ultrastructure of cartilage, namely fat-suppressed T1-weighted 3-D SPGR, which shows articular cartilage as bright against a dark Background, and CT arthrography, where the positive contrast outlines the low dense articular cartilage at the hip, essentially highlighting it between bright subchondral bone and contrast.

Interpretation. The results are not surprising: CT provided higher sensitivity for cartilage lesions grade 2 or higher when compared with MRI for both observers, and inter-observer reliability for lesions grade 2 or higher was substantially better with CT than MRI (Fig. 8.2). This is due for the most part to the much higher inherent spatial resolution of CT compared with MRI. Both have signal-to-noise ratio (SNR) limitations but the higher contrast resolution of CT arthrography contributes to improved visualization of defects as does the higher spatial resolution – in this case the CT images were acquired at 0.5 mm slice thickness with a 0.5×0.5 mm in-plane resolution compared with the MRI ,which had a slice thickness of 1.5 mm and in-plane resolution of 0.63 mm acquired during a 10-min acquisition. The MRI was performed without contrast whereas the CT required the installation of intra-articular contrast under fluoroscopic guidance. The authors conclude that CT arthrography is a sensitive and reproducible method for assessing cartilage loss in patients with hip dysplasia.

Comment

The results of this study suggest that CT is more accurate than MRI for the detection of cartilage lesions in this population but overlooks some important issues – namely that the technique is best suited to moderate- or high-grade osteoarthritis and that it is limited to the detection of focal defects or surface abnormalities. MRI has the ability to detect earlier changes in the deep structures of cartilage even when the surface is unaltered. The most meaningful work in the assessment of preclinical OA in hip dysplasia has been done by Burstein's group using dGEMRIC. They have shown very early changes in the charge density of cartilage in these patients indicating proteoglycan loss even when the cartilage is grossly morphologically normal. MRI of the hip does suffer from limitation in spatial resolution – this can be resolved to some degree by the use of improved receiver coils and moving the 3 T or higher – but it remains the imaging study of choice for preoperative assessment

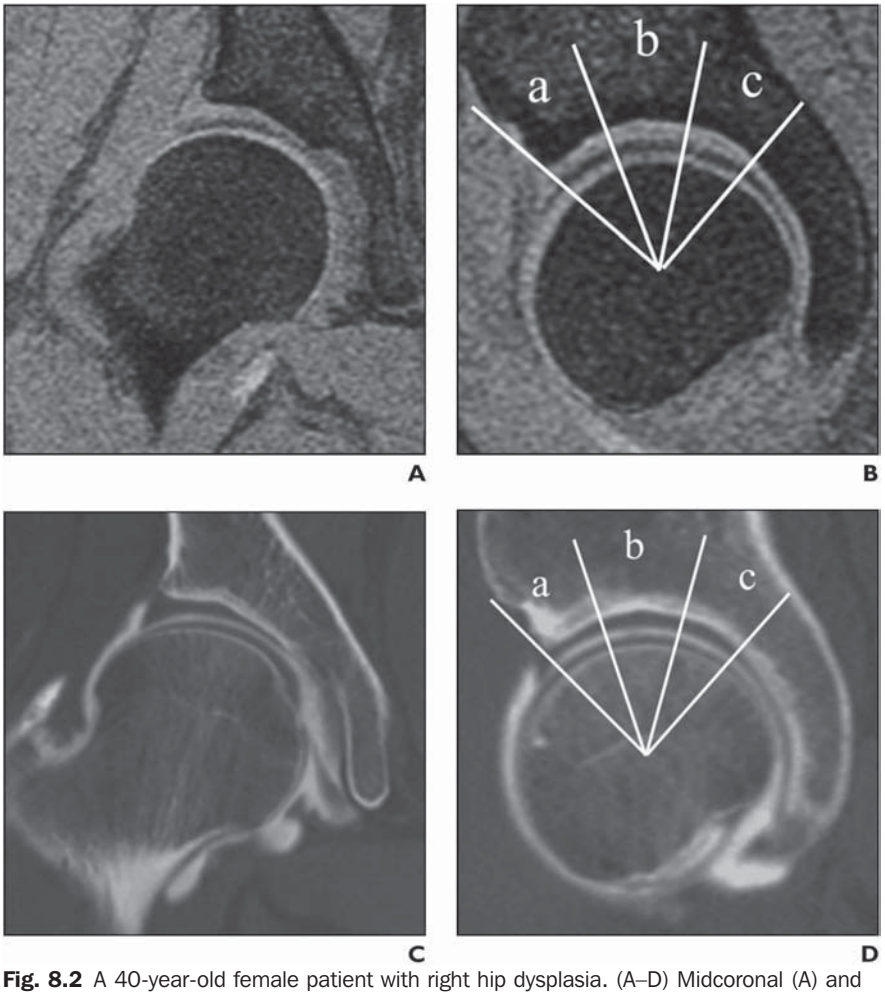

Fig. 8.2 A 40-year-old female patient with right hip dysplasia. (A–D) Midcoronal (A) and midsagittal (B) views of 3-D MR images and midcoronal (C) and mid-sagittal (D) views of CT arthrography images show hip joint. Acetabular and femoral cartilages were evaluated using zone classification shown in midsagittal images (B and D). Weight-bearing area was divided into three 30° ranges: superoanterior (a), superior (b) and superoposterior (c) zones. Source: Nishi *et al.* (2005).

of hip dysplasia. Computed tomography arthrography is an important tool but requires an invasive procedure and exposure to ionizing radiation for what are often young patients. As such, it is best reserved for those patients unable to undergo MRI.

Quantification of cartilage biomechanical and biochemical properties via T1-rho magnetic resonance imaging

Wheaton AJ, Dodge GR, Elliott DM, *et al. Magnetic Resonance Med* 2005; **54**: 1087–93

Background. There have been many papers in the last few years from this group, led by Ravinder Reddy. T1-rho is an MRI technique that uses a highly specialized MR radiofrequency pulse called a spin-lock radiofrequency pulse. The T1-rho parameter is actually the time constant of the exponential decay of signal after the application of the pulse. The rate of relaxation (the inverse of T1-rho) is sensitive to the interactions between bulk water molecules and their macromolecular environment at a specific resonant frequency. In the case of cartilage, the interaction that is measured is between water and the long-chain proteoglycans that make up the extracellular matrix of hyaline articular cartilage. T1-rho measurements have been shown to correlate with proteoglycan concentrations in tissue and, as such, are potentially a sensitive measure of early cartilage degeneration. This study used T1-rho methodology to look at explanted bovine patellae with cores obtained from the centre of each sample. The samples were divided into control and treatment with human interleukin 1B to mimic the inflammatory process associated with the development of OA, and were incubated in groups for 3, 6 and 10 days. The samples were imaged in a 4.7-T imager using a 2-cm receiver coil for optimum SNR. T1-rho maps were created for each sample (Fig. 8.3) and all underwent detailed histological evaluation, including assessing for proteoglycan concentration and type II collagen.

Interpretation. In this study proteoglycan concentration was strongly correlated with the T1-rho relaxation rate in both normal and degraded specimens, with statistically significant differences between the normal and degraded tissue.

Comment

T1-rho is a potentially very promising non-invasive technique for the assessment of proteoglycan concentration *in vivo*. Currently the only available method for assessing proteoglycan concentration *in vivo* is dGEMRIC, which uses charge density in cartilage as a surrogate for proteoglycan content in cartilage. Also, dGEMRIC requires the injection of contrast as well as extended imaging times, making it relatively unattractive as a clinical tool. Early human studies have shown the feasibility of using T1-rho *in vivo* but, unfortunately, T1-rho has some serious limitations that at the present time impede its translation to use in humans other than in a very specialized research environment. T1-rho is very radiofrequency intensive, which may lead to unacceptable tissue heating; in the best case scenario it allows very limited imaging (one or two slices) with a given safety limit. Further, its overall SNR is quite low at conventional field strengths, suggesting that imaging at high field may be required to achieve adequate image quality in a clinically

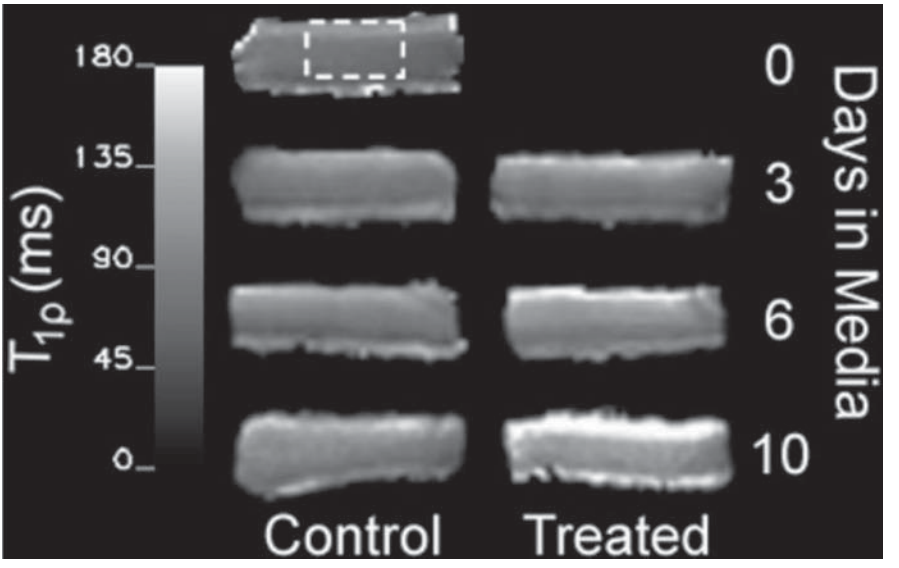

Fig. 8.3 T1p maps of representative specimens from each group and time point. Also shown on the T1p map of the 0-day specimen is the region of interest from which the bulk T1p data were calculated. Source: Wheaton *et al.* (2005).

relevant acquisition time; however, the effects of heating are dramatically increased at higher field strengths, making this technically challenging. Work is under way by Reddy and his colleagues |**4**| to modify this pulse sequence so that it would have broader applicability but, until those modifications can make this a more usable tool for human studies, it will primarily remain a method for the non-destructive assessment of articular cartilage *in vitro*.

Long-term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes

Raynauld JP, Martel-Pelletier J, Bethiaume MJ, *et al. Arthritis Res Ther* 2006; **8**: R21. First published online 30 Dec 2005

Background. In this study a semiautomated quantitative MR technique, volume measurement, was compared over time with other MR features such as the status of the menisci, clinical and demographic data including the WOMAC and SF-36 questionnaires and urinary CTX-II, a biomarker of cartilage degeneration, as well as weight-bearing radiographs. Patients (107) who were part of a larger study cohort for a bisphosphonate drug trial were included and had all study interventions at baseline, 12 and 24 months. The patients were selected from the larger cohort due to their symptomatic OA requiring medical intervention such

as pain relievers. All had radiographic changes of OA on X-ray but had to have a measurable joint space width medially on radiographs (2–4 mm) to assure that disease was not severe. Both the MRI images and digitized radiographs were analysed in a semiautomated fashion with user input for boundary assessment and segmentation. There was high inter-observer reliability for the scoring system used by the readers for the MR examinations.

Interpretation. The results showed progressive loss of cartilage volume globally of 3.7% and 5.5% in the medial compartment with large standard deviations, which make these data overall less meaningful; however, the authors were able to stratify the patients into three groups, fast, intermediate and slow progressors, based on the rate of change in their knee cartilage volumes. The predictors of fast progression included meniscal pathology, bone marrow oedema, high body mass index/weight and age. Interestingly, the loss of cartilage was associated (not statistically significantly so) with *less* knee pain. There was no correlation with joint space width, urine biomarkers or the WOMAC scores of the subjects. The authors conclude that this study shows the advantage of quantitative MRI for reliably measuring structural changes in knee cartilage and that differences can be appreciated over as little as 1 year. They further state that their study has value in identifying risk factors for OA progression.

Comment

This study is an example of the use of an advanced technology (quantitative MRI) to assess the progression of a physical property (in this case cartilage volume) over time in a group of patients with proven clinical disease and symptoms. Measurable changes in cartilage volume can be appreciated, but their clinical relevance is questionable in light of the complete absence of correlation with clinical and other radiographic measures and the slight inverse relationship with pain. It is well known that structural changes in the knee, including joint space narrowing appreciated on radiography, are associated with increasing symptoms in the affected compartments, but that is typically an indirect measurement of cartilage thickness rather than cartilage volume. Cartilage volume may decrease over time for a number of reasons, including simple senescence, making it perhaps a less helpful parameter for measurement over time. The correlation of cartilage loss with specific risk factors for OA such as body mass index, age and internal joint derangement is interesting and potentially has value for prognostication and future treatment of patients who may have these risk factors but do not currently have symptomatic OA, but the lack of correlation with clinical symptoms and functions makes this study overall less useful than it appears at first glance. The treatment of patients, not imaging studies, is the goal. Beautiful and reproducible imaging without clinical relevance in and of itself does not add value in the care of these patients.

Conclusion

MRI has become an important modality in the assessment of OA in both the clinical and research settings. While useful for the qualitative visual assessment of

OA changes, MRI is making significant advances in specialized imaging that allows quantitative assessment of changes and correlation with histological and biochemical markers of OA. Studies using these techniques for volume measurements have had mixed results, with only a few showing good correlation with clinical measures and symptoms, suggesting that further study and validation is warranted before these tools are made available for standard clinical imaging. Other MR markers with high correlation with clinical symptoms and disease severity, such as cartilage thickness, bone marrow oedema and synovitis, may on their own be as valid as, or even more valid than, the more complex volumetric measurements for clinical assessment of OA.

In spite of this, it is clear that the role of MRI for OA is rapidly increasing as patients are shown to benefit from less invasive treatments at earlier stages of disease than previously possible. As early intervention and sophisticated disease-modifying regimens become widely available for the treatment of early OA, the role of MRI for this ubiquitous clinical problem will increase in importance as a powerful tool for diagnosing early disease and monitoring treatment.

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9

Gout

JASVINDER SINGH

Gout is among the most common type of chronic inflammatory polyarthritis in adults and is the commonest type in men. There has been a renewed interest in this disease due to the possibility of newer therapeutic agents becoming available for treatment. Well-designed epidemiological studies that have been published recently have examined the incidence, prevalence and time trends and the association of dietary factors, comorbidity and medication use with gout |**1–6**|. The relationship of gout with the cardiovascular diseases and the metabolic syndrome has been explored in more detail. A phase I trial of PEG-uricase and a phase III randomized controlled trial of febuxostat, a new selective xanthine oxidase inhibitor |**7**|, indicate that these agents are promising. In addition, randomized studies of colchicine prophylaxis, intermittent allopurinol use and withdrawal of allopurinol have provided important clinical data |**8–10**|. Studies using the animal models have helped us understand the role of various cytokines, and cell receptors in crystal-induced inflammation |**11–13**|. Evidence-based quality standards have been published for treatment of gout, and have been assessed by various studies using managed care organizations and national healthcare system databases. Finally, well-designed epidemiological studies have examined gout in women, in post-transplant and other specific populations |**14–16**|. In conclusion, this is an exciting era of active research in the field of gout and crystal diseases. New findings from the ongoing research will provide the physicians with more knowledge and tools to provide better care to their patients with gout.

Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey

Choi HK, Ford ES, Li C, Curhan G. *Arthritis Rheum* 2007; **57**: 109–15

BACKGROUND. To determine the prevalence of metabolic syndrome among patients with gout and to examine the association between the two conditions in a nationally representative sample of US adults. Using data from 8807 participants age ≥20 years in the Third National Health and Nutrition Examination Survey (1988–1994), we determined the prevalence of metabolic syndrome among individuals with gout and quantified the magnitude of association between the two conditions. We used both the revised and original National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria to define metabolic syndrome.

Interpretation. The prevalence [95% confidence interval (CI)] of metabolic syndrome according to revised NCEP/ATP III criteria was 62.8% (51.9–73.6%) among individuals with gout and 25.4% (23.5–27.3%) among individuals without gout. Using 2002 census data, approximately 3.5 million US adults with a history of gout have metabolic syndrome. The unadjusted and age- and sex-adjusted odds ratios (95% CI) of metabolic syndrome for individuals with gout were 4.96 (3.17–7.75) and 3.05 (2.01–4.61) respectively. With the original NCEP/ATP criteria, the corresponding prevalences were slightly lower, whereas the corresponding odds ratios were slightly higher. The stratified prevalences of metabolic syndrome by major associated factors of gout (i.e. body mass index, hypertension and diabetes) remained substantially and significantly higher among those with gout than those without gout (all P-values < 0.05). These findings indicate that the prevalence of metabolic syndrome is remarkably high among individuals with gout. Given the serious complications associated with metabolic syndrome, this frequent comorbidity should be recognized and taken into account in long-term treatment and overall health of individuals with gout.

Comment

This epidemiological study used data from the Third National Health and Nutrition Examination Survey to examine the association of gout and the metabolic syndrome. The authors found that the prevalence of metabolic syndrome was 63% among the patients with gout, almost twice that of patients without gout. Age- and sex-adjusted odds ratios for metabolic syndrome were three times higher in patients with than in those without gout. The adjusted odds ratio of the prevalence of individual components of the metabolic syndrome ranged from 1.26 to 2.63 in gout vs. non-gout subjects. This study highlights the fact that, although gout itself does not increase the risk of mortality, it is associated with a high prevalence of comorbid conditions that may increase mortality and organ-failure. Since two-thirds of gout patients have metabolic syndrome, screening gout patients for these conditions is likely to allow early diagnosis and treatment of these conditions.

Gout and the risk of acute myocardial infarction

Krishnan E, Baker JF, Furst DE, Schumacher HR. *Arthritis Rheum* 2006; **54**: 2688–96

Background. To determine if hyperuricaemia and gouty arthritis are independent risk factors for acute myocardial infarction (MI) and, if so, whether they are independent of renal function, diuretic use, metabolic syndrome, and other established risk factors. Multivariable logistic and instrumental variable probit regressions were performed on data from the Multiple Risk Factor Intervention Trial (MRFIT).

Interpretation. Overall, there were 12 866 men in the MRFIT who were followed up for a mean of 6.5 years. There were 118 events of acute MI in the group with gout (10.5%) and 990 events in the group without gout (8.43%; $P = 0.018$). Hyperuricaemia

was an independent risk factor for acute MI in the multivariable regression models, with an odds ratio (OR) of 1.11 (95% CI 1.08–1.15, $P < 0.001$). In multivariable regressions in which the above risk factors were used as covariates, gout was found to be associated with a higher risk of acute MI (OR 1.26, 95% CI 1.14–1.40, $P < 0.001$). Subgroup analyses showed that a relationship between gout and the risk of acute MI was present among non-users of alcohol, diuretics, or aspirin and among those who did not have metabolic syndrome, diabetes mellitus, or obesity. In separate analyses, a relationship between gout and the risk of acute MI was evident among those with and without hyperuricaemia. The independent risk relationship between hyperuricaemia and acute MI is confirmed. Gouty arthritis is associated with an excess risk of acute MI, and this is not explained by its well-known links with renal function, metabolic syndrome, diuretic use and traditional cardiovascular risk factors.

Comment

This epidemiological study used the data from the MRFIT study to examine whether gouty arthritis and hyperuricaemia are independent risk factors for acute MI. Hyperuricaemia and gout were found to significantly increase the odds of acute MI by 11% and 26%, respectively, after adjusting for multiple risk factors including age, blood pressure, serum cholesterol, smoking, serum creatinine, fasting glucose, diuretic use, aspirin use, alcohol use, diabetes mellitus and family history of acute MI. An important finding of this study was that gout was an independent risk factor for incident MI. The mechanism by which gout increases the risk of MI is unclear. One possible mechanism may be the presence of chronic systemic inflammation, and it would be interesting to assess if non-traditional risk factors including C-reactive protein and others can explain this increase in risk. The finding of association of hyperuricaemia and MI is similar to previous studies.

Severity of gouty arthritis is associated with Q-wave myocardial infarction: a large-scale, cross-sectional study

Chen SY, Chen CL, Shen ML. *Clin Rheumatol* 2007; **26**: 308–13 (epub 11 May 2006)

Background. To examine whether serum urate level and other aspects of gouty arthritis are independently associated with Q-wave myocardial infarction (QWMI) in gouty population, we performed a cross-sectional study. A total of 22 572 gout patients were enrolled. Q-wave myocardial infarction was defined as a positive finding by resting electrocardiographic criteria excluding the conditions producing pseudoinfarction. The variables of gout were tested univariately and multivariately, controlling for the covariates by logistic regression analysis. The above analysis was then repeated in subgroups of young-aged (< 50 years), old-aged (≥ 50 years), male, and female patients.

Interpretation. Increased serum urate level was significantly associated with QWMI in all subjects and male subgroup (OR 1.120, 95% CI 1.020–1.229; OR 1.106, 95% CI 1.001–1.223, respectively, for each mg/dl increment). After controlling for serum urate level and the covariates, increased affected joint count was also independently associated with QWMI finding in all subjects, male and old subgroups (OR 1.098, 95% CI 1.014–1.189; OR 1.094, 95% CI 1.005–1.192; OR 1.095, 95% CI 1.001–1.199 respectively). Tophi formation was independently associated with QWMI in the young subgroup (OR 2.494, 95% CI 1.159–5.366). None of the variables of gout, including hyperuricaemia, was significantly associated with QWMI in the female subgroup after controlling for covariates. This study first demonstrates that both the severity of gouty arthritis and serum urate level are associated with QWMI, while the association of urate to QWMI could be different between age groups and genders.

Comment

This is a cross-sectional study that found that the severity of gouty arthritis as assessed by higher joint count and increased serum urate level was associated with higher prevalence of QWMI. These analyses controlled for the traditional cardiovascular risk factors including age, gender, body mass index, smoking, alcohol use, diuretic use, total cholesterol, triglyceride, hypertension and diabetes. This is perhaps the only large epidemiological study that assessed association of disease severity characteristics with risk of MI. As the study was cross-sectional, interpretation of the cause–effect relationship is not possible. A large prospective cohort or case–control study is needed to confirm the findings of this study.

Control of hyperuricaemia in subjects with refractory gout, and induction of antibody against poly(ethylene glycol) (PEG), in a phase I trial of subcutaneous PEGylated urate oxidase

Ganson NJ, Kelly SJ, Scarlett E, *et al. Arthritis Res Ther* 2006; **8**: R12

Background. PEG-modified recombinant mammalian urate oxidase (PEG-uricase) is being developed as a treatment for patients with chronic gout who are intolerant of, or refractory to, available therapy for controlling hyperuricaemia. In an open-label phase I trial, single subcutaneous injections of PEG-uricase (4–24 mg) were administered to 13 such subjects (11 had tophaceous gout), whose plasma uric acid concentration (pUAc) was 11.3 ± 2.1 mg/dl (mean ± SD).

Interpretation. By day 7 after injection of PEG-uricase, pUAc had declined by an average of 7.9 mg/dl and had normalized in 11 subjects, whose mean pUAc decreased to 2.8 ± 2.2 mg/dl. At doses of 8, 12 and 24 mg, the mean pUAc at 21 days after injection remained no more than 6 mg/dl. In eight subjects, plasma uricase activity was still measurable at 21 days after injection (half-life 10.5–19.9 days). In the other five subjects, plasma uricase activity could not be detected beyond 10 days after injection; this was associated with the appearance of relatively low-titre IgM and IgG antibodies

against PEG-uricase. Unexpectedly, these antibodies were directed against PEG itself rather than the uricase protein. Three PEG antibody-positive subjects had injection site reactions at 8–9 days after injection. Gout flares in six subjects were the only other significant adverse reactions, and PEG-uricase was otherwise well tolerated. A prolonged circulating life and the ability to normalize plasma uric acid in markedly hyperuricaemic subjects suggest that PEG-uricase could be effective in depleting expanded tissue stores of uric acid in subjects with chronic or tophaceous gout. The development of anti-PEG antibodies, which may limit efficacy in some patients, is contrary to the general assumption that PEG is non-immunogenic. PEG immunogenicity deserves further investigation, because it has potential implications for other PEGylated therapeutic agents in clinical use.

Comment

This is a phase I trial of PEG-uricase at 4–24 mg single subcutaneous injection dose in 13 patients with gout, 11 of whom had tophaceous gout. PEG-uricase injection was associated with a significant reduction in plasma urate levels by 8 mg/dl (11 mg/dl pre-treatment to 2.8 mg/dl post treatment). Injection site reactions were seen in several patients: six subjects with mild to moderate pain that resolved in 24–48 h and three patients with late reaction with local swelling and erythema and urticaria. Phase II and phase III trial results are awaited to assess the safety and efficacy of this novel agent in treatment of tophaceous gout and refractory chronic gout.

Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study

Perez-Ruiz F, Atxotegi J, Hernando I, *et al. Arthritis Rheum* 2006; **55**: 786–90

Background. Withdrawal of urate-lowering therapy (ULT) is associated with recurrence of acute gouty arthritis and tophi, but no data are available about factors associated with recurrence of gouty symptoms. Therefore, life-long therapy prescription is usually advised, but the prospect of life-long therapy may contribute to very low compliance rates. The objective was to ascertain the outcome of ULT withdrawal after long-term, documented control of serum urate levels. A prospective, long-term, follow-up study of patients treated with ULT during a 5-year period was conducted. Both diagnosis and recurrence of gout were determined based on monosodium urate crystal identification in synovial fluid or material aspirated from tophi.

Interpretation. Low average serum urate levels while receiving ULT and during the follow-up period after ULT withdrawal were statistically associated with the longest period in which patients were free of gouty symptoms, suggesting that depletion and formation of the body's urate pool is dependent on both time and serum urate levels. Patients whose average serum urate levels were < 5.05 mg/dl while receiving ULT and

< 8.75 mg/dl after ULT withdrawal had the longest (> 4 years) time to recurrence. Proper and long-term reduction in serum urate level is associated with long-term periods in which patients are free of gouty symptoms, probably due to the reduction of the urate pool. These results suggest that 5-year intermittent, instead of life-long, ULT could be offered to patients with good serum urate control during ULT.

Comment

This prospective study assessed the effect of withdrawing ULT on the recurrence of acute gouty arthritis in patients with non-tophaceous crystal-proven gout with a serum urate ≤ 7 mg/dl. This study found that both lower urate levels during the therapy as well as during the withdrawal phase were associated with the longest symptom-free period, i.e. absence of acute gouty arthritis. This study raises a very interesting concept of 'remission', i.e. once the serum urate levels have been lowered, the risk of acute attacks is low in patients who maintain low serum urate levels, and some patients may be attack free for years. An earlier study found that intermittent ULT of 2 months/year is less effective in preventing acute attacks than continuous therapy. The current study suggests that some gout patients may stay in remission after lowering their serum urate with therapy. This means that some patients whose serum urate has been reduced in the target range for some duration may stay in remission even after short discontinuation of ULT, i.e. achieve 'remission'. Prospective randomized studies should test if planned withdrawal of ULT after achieving low serum urate is as effective as continuous ULT in patients with gout. The outcomes of these studies should include frequency of acute attacks, pain level and quality of life.

Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels: another insight to allopurinol-related toxicity

Perez-Ruiz F, Hernando I, Villar I, Nolla JM. *J Clin Rheumatol* 2005; **11**: 129–33

Background. Dosing of allopurinol should be corrected depending on renal function, but corrections based on either plasma creatinine (PCr) or creatinine clearance (CrCl) have been suggested to be minimal standards of care. Data from a cohort database of 484 gouty patients were used to calculate estimated allopurinol doses using CrCl and estimation of the clearance of creatinine using the equation of Cockroft and Gault (CrCl-CG) if, as a hypothesis, a dosage of 300 mg/day would be prescribed in any patient with PCr < 2.0 mg/dl. Also, allopurinol-related toxicity previous to rheumatological consultation, during previous allopurinol therapy, and the relationship between both and estimated allopurinol doses were reviewed.

Interpretation. The cut-off point of plasma creatinine < 2 showed 13% sensitivity and 100% specificity to detect CrCl < 50 ml/min. Correlation and agreement between

CrCl and CrCl-CG were good, as was the correlation between corrected doses using CrCl and CrCl-CG. One-third of patients with Pcr 1.0–1.5 mg/dl and 90% of those with PCr 1.5–2.0 mg/dl would receive estimated doses over 400 mg/dl/day CrCl. Also, 10% and 34% would receive estimated doses over 600 mg/dl/day CrCl respectively. Allopurinol-related toxicity previous to consultation (11%) was associated with estimated doses over 400 mg/dl/day CrCl and severe toxicity with estimated doses over 600 mg/dl/day CrCl. When patients were given doses corrected on CrCl, few side-effects were observed during follow-up (6.7%), and the only severe one was associated with corrected dose over 600 mg/day. Dosage adjustment of allopurinol should be based on clearance of creatinine or estimation of glomerular filtration using the Cockcroft–Gault equation. Plasma creatinine is insensitive enough to detect renal function impairment so that patients may be placed at risk for overdosing side-effects. Corrected doses over 600 mg/dl/day CrCl may be associated with increased risk of severe toxicity.

Comment

This study of renal function in 484 gout patients compared plasma creatinine with the calculated and the measured creatinine clearance. The dose of allopurinol was frequently incorrect if plasma creatinine levels were used for dosing. The cut-off point of creatinine < 2 showed 13% sensitivity and 100% specificity to detect creatinine clearance < 50 ml/min, implying that 87% of patients with creatinine clearance < 50 ml/min were missed using this plasma creatine cut-off. This study provides evidence that allopurinol dosing should be based on creatinine clearance on plasma creatinine levels.

Molecular analysis of the SLC22A12 (URAT1) gene in patients with primary gout

Vazquez-Mellado J, Jimenez-Vaca AL, Cuevas-Covarrubias S, *et al. Rheumatology (Oxford)* 2007; **46**: 215–19 (epub 11 July 2006)

Background. To analyse the *SLC22A12* (*URAT1*) gene in primary gout patients, first-grade relatives and healthy control subjects and the possible association with demographic and clinical data. Sixty-nine consecutive patients with diagnosis of primary gout, as well as 29 first-degree relatives and 120 healthy volunteers were included. Demographic and clinical data were obtained from the patients and relatives. DNA was purified from peripheral blood and all 10 exons of the *SLC22A12* (*URAT1*) gene were sequenced.

Interpretation. Six different mutations in the *SLC22A12* gene were found in 16 out of 69 (23%) patients with primary gout. Five mutations were in exon 5 and one in exon 4; five out of six mutations were heterozygous (one compound heterozygous) and one homozygous. The C850G mutation (exon 5) was found in 11 gout patients, these patients had lower levels of triglycerides than the rest of the group: 160 ± 56 vs. 292 ± 203 mg/dl ($P = 0.038$). In one family, *SLC22A12* mutations were found in three relatives within exon 5. There were no mutations in the other exons studied (1–3 and 6–10), nor in any

of the 10 exons of the 120 healthy volunteers. Several mutations in the *SLC22A12* gene associated with primary gout were found, the definite role of these mutations in URAT1 activity needs to be further studied.

Comment

This is an interesting study of mutations in the *URAT1* gene in patients with primary gout, compared with healthy control subjects. The study identified several gene mutations in patients with primary gout. Studies in larger and different population are needed to confirm these findings. Recognition of common gene polymorphisms and mutations in patients with primary gout will help us understand the pathophysiology of gout and design new treatments.

Gout-associated uric acid crystals activate the NALP3 inflammasome

Martinon F, Petrilli V, Mayor A, *et al. Nature* 2006; **440** (7081): 237–41 (epub 11 January 2006)

Background. Development of the acute and chronic inflammatory responses known as gout and pseudogout are associated with the deposition of monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals, respectively, in joints and periarticular tissues. Although MSU crystals were first identified as the aetiological agent of gout in the eighteenth century and more recently as a 'danger signal' released from dying cells, little is known about the molecular mechanisms underlying MSU- or CPPD-induced inflammation.

Interpretation. Here, it is shown that MSU and CPPD engage the caspase-1-activating NALP3 (also called cryopyrin) inflammasome, resulting in the production of active interleukin 1 β (IL-1 β) and IL-18. Macrophages from mice deficient in various components of the inflammasome such as caspase-1, ASC and NALP3 are defective in crystal-induced IL-1β activation. Moreover, an impaired neutrophil influx is found in an *in vivo* model of crystal-induced peritonitis in inflammasome-deficient mice or mice deficient in the IL-1β receptor (IL-1R). These findings provide insight into the molecular processes underlying the inflammatory conditions of gout and pseudogout, and further support a pivotal role of the inflammasome in several autoinflammatory diseases.

Comment

This study provides insight into mechanism of inflammatory response to urate crystals by using mouse knock-out models. The authors found that urate and CPPD crystals engage caspase-1-activating NALP inflammasome, leading to production of interleukins 1 and 18; these responses are absent in the inflammasome or the interleukin-1 receptor knock-out mice.

Melanocortin 3 receptors control crystal-induced inflammation

Getting SJ, Lam CW, Chen AS, *et al. FASEB J* 2006; **20**: 2234–41

Background. In this study, the anti-inflammatory profile of a selective melanocortin type 3 receptor (MC3-R) ligand [D-Trp8]-gamma-MSH was characterized, validating *in vitro* results with analyses in mice deficient for this receptor subtype. In wild-type (WT) macrophages, [D-Trp8]-gamma-MSH activated MC3-R (as tested by accumulation of cyclic AMP) and inhibited (by approximately 50%) the release of interleukin 1 (IL-1) and the chemokine KC (CXCL1), but was ineffective in cells taken from MC3-R null mice. *In vivo*, administration of 3–30 μg [D-Trp8]-gamma-MSH significantly inhibited leucocyte influx and cytokine production in a model of crystal-induced peritonitis, and these effects were absent in MC3-R null mice or blocked by co-administration of an MC3-R antagonist. Finally, in a model of gouty arthritis, direct injection of urate crystals into the rat joint provoked a marked inflammatory reaction that was significantly inhibited (by approximately 70%) by systemic or local administration of [D-Trp8]-gamma-MSH. In conclusion, using an integrated transgenic and pharmacological approach, strong proof of concept for the development of selective MC3-R agonists as novel anti-inflammatory therapeutics is provided.

Interpretation. This study investigated the role for MC3-Rs in urate crystal-induced inflammation. The effect of MSH-induced inhibition of interleukin 1 and chemokine KC, was absent in knock-out mice and was blocked by administration of receptor antagonist. In addition, systemic or local administration of MSH inhibited the inflammatory reaction induced by injection of urate crystals in rat joints. This study suggests that an MC3-R antagonist may be a potential therapeutic agent for suppressing crystal-induced inflammation.

Comment

This study establishes the anti-inflammatory role of an MC3-R antagonist in mouse models of crystal-induced inflammation. Therapeutic agents with this property may have a role in preventing or treating the inflammation associated with acute gouty arthritis.

MyD88-dependent IL-1 receptor signalling is essential for gouty inflammation stimulated by monosodium urate crystals

Chen CJ, Shi Y, Hearn A, *et al. J Clin Invest* 2006; **116**: 2262–71

Background. While it is known that MSU crystals cause the disease gout, the mechanism by which these crystals stimulate this inflammatory condition has not been identified. Here we find that the Toll/IL-1R (TIR) signal transduction adaptor myeloid differentiation primary response protein 88 (MyD88) is required for acute gouty inflammation. In contrast, other TIR adaptor molecules, TIRAP/Mal, TRIF and TRAM, are not required for this process.

Interpretation. The MyD88-dependent TLR1, -2, -4, -6, -7, -9, and -11 and IL-18 receptor (IL-18R) are not essential for MSU-induced inflammation. Moreover, MSU does not stimulate HEK cells expressing TLR1–11 to activate NF-κB. In contrast, mice deficient in the MyD88-dependent IL-1R showed reduced inflammatory responses, similar to those observed in MyD88-deficient mice. Similarly, mice treated with IL-1 neutralizing antibodies also showed reduced MSU-induced inflammation, demonstrating that IL-1 production and IL-1R activation play essential roles in MSU-triggered inflammation. Interleukin-1receptor deficiency in bone marrow-derived cells did not affect the inflammatory response; however, it was required in non-bone marrow-derived cells. These results indicate that IL-1 is essential for the MSU-induced inflammatory response and that the requirement of MyD88 in this process is primarily through its function as an adaptor molecule in the IL-1R signalling pathway.

Comment

This elegant study provides evidence for the role of IL-1 in urate crystal-induced inflammation, using a variety of approaches. Medications that block IL-1 may be candidates for treatment of crystal-induced inflammation. Currently, colchicine, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of this therapeutic approach, but they may be contra-indicated in many patients. A new therapeutic agent that targets IL-1 may offer an important option for these patients.

Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD)

Mikuls TR, Farrar JT, Bilker WB, *et al. Rheumatology (Oxford)* 2005; **44**: 1038–42 (epub 3 May 2005)

Background. To examine adherence to validated quality indicators assessing the quality of allopurinol use in the treatment of gout and asymptomatic hyperuricaemia. Physician adherence in the UK General Practice Research Database (GPRD) was determined to three validated quality indicators (QIs) developed to assess the quality of allopurinol prescribing practices. These indicators were developed to assess: (i) dosing in renal impairment; (ii) concomitant use with azathioprine or 6-mercaptopurine; and (iii) use in the treatment of asymptomatic hyperuricaemia. The association of patient-level

factors (sociodemographics, comorbidity, follow-up duration and concomitant medicine use) with the treatment of asymptomatic hyperuricaemia was also examined using multivariable logistic regression.

Interpretation. Of the 63 105 gout patients, 185 (0.3%) were eligible for QI 1 and 52 (0.1%) were eligible for QI 2. There were an additional 471 patients with asymptomatic hyperuricaemia eligible for QI 3. Rates of practice deviation for the three individual QIs ranged from 25% to 57%. Male sex, older age, a history of chronic renal failure, and a greater number of concomitant medications were significantly associated with increased odds of inappropriate treatment for asymptomatic hyperuricaemia. Hypertension and diuretic use were associated with lower odds of this practice. One-quarter to one-half of all patients eligible for at least one of the validated quality of care indicators were subject to possible allopurinol prescribing error, suggesting that inappropriate prescribing practices are widespread with this agent. Future interventions aimed at reducing inappropriate allopurinol use are needed and should be targeted towards high-risk groups, including older men and those receiving multiple concomitant medications.

Comment

Mikuls and colleagues examined physician adherence to evidence-based QIs related to allopurinol use using the UK GPRD. Prevalence of non-adherence to the following three QIs ranged from 25% to 57%: allopurinol dosing in renal failure; concomitant use with azathioprine or 6-mercaptopurine; and use in the treatment of asymptomatic hyperuricaemia. Patient factors such as older age, male gender, increase in medication and history of renal failure were associated with higher odds of inappropriate treatment of asymptomatic hyperuricaemia. This is the first study to examine these QIs in a patient care dataset. Further studies should examine adherence to these and other QIs in other populations and datasets. In addition, long-term studies should incorporate disease outcomes and examine how these QIs are related to the patient outcomes.

Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study.

Neogi T, Hunter DJ, Chaisson CE, *et al. J Rheumatol* 2006; **33**: 104–9 (epub 1 November 2005)

Background. To evaluate the patterns and determinants of medication use during recurrent gout attacks. Participants with documented gout were followed in an online prospective case crossover study. During an attack, subjects were asked if they had consulted a physician for the attack and what medications they were using. Definitely inappropriate therapy was defined as use of allopurinol or a uricosuric agent acutely without having used it as a prophylactic. Potentially inappropriate therapy was defined as use of analgesics alone, alternative remedies, or no medications. The risk of having one or more attacks in 1 year was

estimated using life-table methods. The relation of various risk factors to the risk of inappropriate therapy was examined using Poisson regression.

Interpretation. Among 232 participants (mean age 52 years, 81% male) with documented gout, the risk of having one or more attacks in a year was 69%. One hundred and ten participants consulted a physician for each attack, 49 did so for only some attacks, while 43 never consulted a physician for any attack. Fifty-three participants had definitely ($n = 10$) or potentially ($n = 43$) inappropriate therapy for their recurrent attacks. Physician consultation for an attack was associated with increased risk of inappropriate therapy (risk ratio 2.5, $P = 0.006$), whereas an increasing number of gout attacks was associated with lower risk of inappropriate therapy (risk ratio 0.8, $P = 0.01$). Given the high risk of recurrent attacks and the substantial number of persons whose attacks are not appropriately managed, further education about management of gout attacks for both patients and physicians may be warranted.

Comment

This is a prospective internet-based study of inappropriate management of recurrent acute gouty arthritis. Among a predominantly male cohort of 232 participants with gout, almost 25% had an inappropriate treatment. A physician consultation for an attack increased the likelihood of inappropriate treatment and an increasing frequency of gout attacks reduced the likelihood. This study suggests that education of physicians with regards to appropriate management of acute gouty arthritis is needed.

Sex differences in gout epidemiology: evaluation and treatment

Harrold LR, Yood RA, Mikuls TR, *et al. Ann Rheum Dis* 2006; **65**: 1368–72 (epub 27 April 2006)

Background. Little is known about the characteristics, evaluation and treatment of women with gout. The objective of this study was to examine the epidemiological differences and differences in treatment between men and women in a large patient population. Data from approximately 1.4 million people who were members of seven managed care plans in the USA for at least 1 year between 1 January 1999 and 31 December 2003 were examined. Adult members who had pharmacy benefits and at least two ambulatory claims specifying a diagnosis of gout were identified. In addition, men and women who were new users of ULT were identified to assess adherence, with recommended surveillance of serum urate levels within 6 months of initiating ULT.

Interpretation. A total of 6133 people (4975 men and 1158 women) with two or more International Classification of Disease-9 codes for gout were identified. As compared with men with gout, women were older [mean age 70 (SD 13) vs. 58 (SD 14), $P < 0.001$] and had comorbidities and received diuretics more often (77% vs. 40%,

$P < 0.001$). Only 37% of new users of ULT had appropriate surveillance of serum urate levels post initiation of ULT. After controlling for age, comorbidities, gout treatments, number of ULT dispensings and health plan, women were more likely (odds ratio 1.36, 95% CI 1.11–1.67) to receive the recommended serum urate level testing. Women with gout were older, had greater comorbidities and more often used diuretics and received appropriate surveillance of serum urate levels, suggesting that the factors leading to gout as well as monitoring of treatment are very different in women and men.

Comment

This large population-based study used administrative data from several managed care plans to compare men and women with gout. Women with gout were older, had higher comorbidity load and were twice as likely to have received diuretics. After controlling for age, comorbidity and other factors, women were more likely than men to receive the recommended serum urate monitoring within 6 months of allopurinol initiation. This study confirms the previous reports of age, comorbidity and treatment differences between men and women with gout in a larger sample. Despite a better rate of serum urate monitoring in women, similar to the findings of an earlier study by Mikuls *et al.*, overall only 37% of the patients received the recommended serum urate monitoring.

Gout, not induced by diuretics? A case–control study from primary care

Janssens HJ, van de Lisdonk EH, Janssen M, *et al. Ann Rheum Dis* 2006; **65**: 1080–3 (epub 16 Nov 2005)

Background. It is taken for granted that diuretics may induce gout, but there is a general lack of evidence on this topic. The objective of this study was to determine the incidence of gout in patients who use diuretics, taking into account concurrent hypertension and cardiovascular diseases. A case–control study was designed. From a primary care population all patients with a first gout registration [59 men, 11 women; mean (SD) age 55.1 (13.5)] were identified as cases. To relate the occurrence of gout to diuretic use, a matched reference series of three control subjects for each case was compiled. Conditional logistic regression analyses were applied to estimate incidence rate ratios (IRRs) of gout, and 95% CIs, in subjects with and without diuretic treatment, hypertension, and cardiovascular diseases. Additional stratification analyses were made, particularly in the subjects not using diuretics.

Interpretation. The IRRs of gout in subjects with vs. those without diuretic treatment, hypertension, heart failure and MI were 2.8 (95% CI 1.2–6.6), 2.6 (95% CI 1.2–5.6), 20.9 (95% CI 2.5–173.8) and 1.9 (95% CI 0.7–4.7) respectively. After adjustment, the IRR of gout for diuretic use dropped to 0.6 (95% CI 0.2–2.0), while the IRRs of gout for hypertension, heart failure and MI were still > 1. This was also the case for subjects with hypertension or myocardial infarction, who had not used diuretics. The results suggest

that diuretics do not actually increase the risk of gout. Cardiovascular indications for treatment may have confounded previous inferences.

Comment

This case–control study challenges the findings of previous observational studies that have suggested a link between diuretic use and incident gout. After adjusting for the presence of hypertension, heart failure, and myocardial infarction, diuretic use was no longer significantly associated with incident gout. Analyses of data from large epidemiological studies such as NHANES, Framingham and BRFSS are needed to confirm/challenge this finding.

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Part III

Connective tissue disease

10

Systemic lupus erythematosus

RAM RAJ SINGH

Introduction

Autoimmune diseases such as systemic lupus erythematosus (SLE) are characterized by a striking female preponderance. The fundamental basis for such gender bias and how it affects the management of this disease has intrigued physicians and scientists alike for decades. In this chapter, we first review a series of papers that address some of the most frequently asked questions in this regard, i.e. how will exposure to hormones, such as oral contraceptives in young women and hormone replacement therapy in later years, affect the course of SLE? Three randomized controlled trials directly address this issue. Following these trials, we discuss two epidemiological studies that examine the associations between hormonal changes, such as menopause, menarche and pregnancy, and the development of SLE. To add a broader perspective to the gender issue in SLE, we discuss exciting new developments that suggest a role of sex chromosome and gene translocation in imparting the sex bias in SLE.

The second series of papers emphasize that hydroxychloroquine, a relatively safe drug, has a myriad of benefits in patients with SLE. Unfortunately, not all physicians taking care of patients with SLE use this medication. Reviewed here are a series of papers that highlight the value of hydroxychloroquine in reducing the risk of flares, organ damage, thrombosis and malignancy and in facilitating remission by immunosuppressive agents in patients with SLE. Most importantly, the use of hydroxychloroquine is associated with improved survival, as suggested in two papers reviewed here. Finally, we review a paper that addresses the safety and utility of hydroxychloroquine use in pregnancy.

Most clinical studies so far have assessed the effect of treatment on active ongoing inflammation in autoimmune diseases. Few papers have evaluated the effect of treatment on chronic organ damage. Reviewed here is a clinical trial that suggests the superiority of cyclophosphamide–corticosteroid combination over azathioprine-based therapy in reducing chronic renal damage in patients with lupus nephritis. The next set of papers emphasize that mycophenolate mofetil continues to show its value as a less toxic alternative for patients with mild to moderate proliferative and membranous lupus nephritis.

Biological therapies have generated a tremendous enthusiasm among rheumatologists. A large number of preclinical and clinical investigations have explored the effects of depleting a specific immune cell type or neutralizing a specific proinflammatory molecule in rheumatic diseases. Early short-term trials using rituximab, an antibody that depletes B-cells showed the utility of this method in treating SLE. More recent experience, including long-term studies with this agent, is reviewed in this chapter.

Finally, turning the clock of autoimmunity to time zero has been a long-cherished dream of rheumatology investigators. Stem cell transplantation appeared to provide a vehicle to realize this dream. Results of a clinical trial of autologous stem cell transplantation discussed here suggest that we have a long way to go in this regard.

Thus, I have tried to select papers that are likely to affect patient management and that address some of the most frequently asked questions in SLE. I hope that the readers will share my enthusiasm.

Hormone and gender matters in SLE: oral contraceptives and hormone replacement therapy

Gender differences in susceptibility to SLE are well known. The female sex bias for the development of lupus is seen in most genetically lupus-susceptible animals |**1**|. Even chemically induced lupus in animals injected with hydrocarbon oils displays a female preponderance |**2**|. A temporal association between oestrogen exposure and the development of SLE in a previous observational cohort study |**3**| triggered several major studies to investigate the effects of oestrogen in SLE. Several recent studies have also begun to question the role of sex hormones as the sole basis for sex bias in SLE. A few studies describing the effect of hormones, gender and sex chromosomes are reviewed in this article.

The effect of combined oestrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial

Buyon JP, Petri MA, Kim MY, *et al. Ann Intern Med* 2005; **142**: 953–62

Combined oral contraceptives in women with systemic lupus erythematosus

Petri M, Kim MY, Kalunian KC, *et al. N Engl J Med* 2005; **353**: 2550–8

A trial of contraceptive methods in women with systemic lupus erythematosus

Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, *et al. N Engl J Med* 2005; **353**: 2539–49

The effect of menopause on disease activity in systemic lupus erythematosus

Urowitz MB, Ibanez D, Jerome D, Gladman DD. *J Rheumatol* 2006; **33**: 2192–8

Reproductive and menopausal factors and risk of systemic lupus erythematosus in women

Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW. *Arthritis Rheum* 2007; **56**: 1251–62

A female preponderance for chemically induced lupus in SJL/J mice

Smith DL, Dong X, Du S, *et al. Clin Immunol* 2007; **122**: 101–7

The XX sex chromosome complement, as compared to the XY, confers greater susceptibility to experimental autoimmune diseases – EAE and SLE

Smith DL, Du S, Tiwari-Woodruff S, *et al. Clin Immunol* 2007; **123**: S178–9

Autoreactive B-cell responses to RNA-related antigens due to TLR7 gene duplication

Pisitkun P, Deane JA, Difilippantonio MJ, *et al. Science* 2006; **312**: 1669–72

A Tlr7 translocation accelerates systemic autoimmunity in murine lupus

Subramanian S, Tus K, Li QZ, *et al. Proc Natl Acad Sci USA* 2006; **103**: 9970–5

Interpretation

The SELENA (Safety of Estrogens in Lupus Erythematosus, National Assessment) trial measured the effect of hormone replacement therapy (HRT) on disease activity in lupus |**4**|. The study sample consisted of 351 menopausal patients with SLE, a high percentage of whom had inactive or stable-active disease. The patients were randomly assigned to receive placebo or 0.625 mg of conjugated oestrogen (Premarin, Wyeth-Ayerst Pharmaceuticals) every day of the month plus 5 mg of medroxyprogesterone (Provera, Wyeth-Ayerst Pharmaceuticals) on days 1–12. The randomization was stratified by disease status: inactive or stable-active. The disease flares were identified using a modified index, SELENA-SLEDAI. The rates of severe flares were 0.081 in the HRT group vs. 0.049 in the placebo group, which was not statistically significant. However, rates of mild to moderate flares were 1.14 flares per person-year in the HRT group and 0.86 flares per person-year in the placebo group. Although this difference is statistically significant, it is quite small. These data led the authors to conclude that HRT is associated with a small risk for increasing disease flares. There could be a concern with this inference, because there were high rates of dropout and loss to follow-up in this trial. Of the 173 women in the HRT group, 70 discontinued the treatment and 32 were lost to follow-up. Of 177 women in the placebo group, 55 discontinued the treatment and 23 were lost to follow-up. Further data in the dropout and loss to follow-up cases would have reassured that the composition of the two study groups did not differ as the study progressed. Although the study included fewer patients with active disease, patients with active lupus and those with renal disease had a greater chance of a severe flare than patients with inactive disease on HRT. There were few adverse events in the HRT group. In the HRT group, one woman died, one had a stroke, one developed thrombosis in an arteriovenous graft and two had deep venous thrombosis. In the placebo group, one woman developed deep vein thrombosis. It is important to emphasize that the trial did not include patients with anti-cardiolipin antibodies, lupus anticoagulant or history of vascular thrombosis. The trial did not address the beneficial effects of HRT in menopausal women with SLE, but one can infer that benefits of HRT in SLE patients should be similar to benefits in women in the general population.

In premenopausal women, effective birth control, preservation of ovarian function during cyclophosphamide therapy, and prevention of steroid-induced osteoporosis would be valid reasons to prescribe oral contraceptives. A retrospective study, however, found a high rate of flares in patients receiving oral contraceptives |**5**|. The safety of oral contraceptives in premenopausal women with SLE has now

been examined in two large prospective studies – Oral Contraceptives-SELENA (OC-SELENA) |**6**| and Sanchez-Guirrero and colleagues |**7**| – which are reviewed here. The OC-SELENA study was a multicentre double-blind, randomized, non-inferiority trial involving 183 women who had inactive disease (76%) or stable-active disease (24%). Patients with ongoing active disease or those with lupus anticoagulant, high-titre anti-cardiolipin antibodies, or a history of vascular thrombosis were excluded. The women were randomly assigned to receive either combined oral contraceptives or placebo, and all of them were asked to use an additional method of birth control during the trial. The rates of severe flare were similar between the two groups – 7.7% and 7.6%. The 12-month rates of severe flare were also similar between the two groups: 0.84 and 0.87. The rates for mild to moderate flares were 1.40 flares per person-year in the oral contraceptive group and 1.44 flares per person-year in the placebo group. There were two thrombotic events in the oral contraceptive group and three thrombotic events in the placebo group. These findings led the investigators to conclude that oral contraceptives do not increase the risk of flares among women with mild to moderate and stable SLE. As evident, these findings are not applicable to SLE patients with ongoing disease activity and to patients at risk for vascular thrombosis.

Another study from Mexico City at the same time examined the effect of combined oral contraceptives on disease activity in SLE |**7**|. In this single-blind, uncontrolled randomized clinical trial, 162 women with SLE were enrolled to receive combined oral contraceptives, a progestin-only pill or a copper intrauterine device. Patients in this trial had more active disease at study entry than patients enrolled in the above OC-SELENA trial. The overall flare rates per person-year were similar in the three groups: 0.86 in the oral contraceptive group, 1.14 in the progestin-only pill group, and 0.91 in the intrauterine device group. Rates of severe flares were also similar in the three groups. Four patients, two in each of the two groups receiving hormones developed vascular thrombosis during the trial. Severe infections were more frequent in the intrauterine device group. The patient population in this study was ethnically homogeneous, whereas the OC-SELENA study had patients of diverse ethnic backgrounds.

Analyses of data on SLE patients from the University of Toronto Lupus Clinic indirectly support the above hormone intervention studies |**8**|. Urowitz and colleagues showed that, although premenopausal women with SLE have more disease activity than postmenopausal women with SLE, changes in SLE disease activity or damage indices or numbers of flares were not associated with menopausal status.

From the above studies, one might begin to think that hormonal factors play a minimal role, if any, in the development and progression of SLE. To address this issue further, Costenbader and colleagues examined associations between female reproductive and menopausal factors and the development of SLE |**9**|. Using data from the largest cohorts of women who have been followed up prospectively for rheumatic diseases, the authors found 262 incident cases of SLE among 238 308 women from the Nurses' Health Study and Nurses' Health Study II. Early age at menarche (≤10 years), oral contraceptive use [relative risk 1.5, 95% confidence

interval (CI) 1.1–2.1], early age at menopause (<47 years), surgical menopause and postmenopausal use of hormones (relative risk 1.9, 95% CI 1.2–3.1) were each associated with an increased risk of SLE. Age at first birth, parity and total duration of breastfeeding were not associated with SLE. These data showing increased risk of SLE among women using oral contraceptives and HRT are in apparent conflict with conclusions drawn in SELENA and other studies. However, there are several concerns with the assessment of SLE risk in the Nurses' Health Study. For example, although supported by detailed questionnaire and chart review, the illnesses were based on self-diagnosis in the absence of verification studies of control subjects who did not self-diagnose SLE. Another important concern is that a recall bias in patients with an illness may have affected some of the data in this report. Additionally, the authors used modified American College of Rheumatology criteria for SLE to label a diagnosis of SLE. Another issue concerns the false-positive and false-negative rates of SLE diagnosis. Only 7% of subjects who screened positive by questionnaire and only 1.8% of women who initially stated that they had been diagnosed as having SLE were actually accepted as incident disease. Nevertheless, this report is the best available study of this type showing a doubled risk of developing SLE in white women who possess certain surrogates for oestrogen exposure, such as early age at menarche and oral contraceptive use.

Although the above Nurses' Health Study suggests an influence of oestrogen on the development of SLE, the increase in risk is relatively small and insufficient to explain a 9:1 female to male sex ratio in SLE. These data may indicate that oestrogen is not a critical determinant of the sex ratio in SLE. Recent studies in animal models of SLE have begun to clarify this further. For example, we in collaboration with Voskuhl's group used transgenic mice that were created to permit a comparison between XX and XY within a common gonadal type, thereby avoiding the confound of differences in sex hormones |**10**|. Mice of the XX sex chromosome complement, as compared with XY, demonstrated greater susceptibility to lupus. This suggests that the XX sex chromosome complement, as compared with XY, confers greater susceptibility to SLE. Using another mouse strain in which male mice develop lupus, two groups have shown that enhanced susceptibility of male mice to develop lupus is due to a translocation of the Toll-like receptor (TLR) *Tlr7* gene from the X chromosome onto the Y chromosome |**11,12**|. Another study suggested a role of epigenetic factors in the development of SLE. For example, women with SLE might have more activated genes in two X chromosomes due to abnormally low total T-cell DNA methylation |**13**|. Thus, it remains to be determined as to which extent each of these factors – genes, epigenetic factors and hormones – confer the female sex bias in SLE.

Comment

Based on the results of the SELENA HRT study, the modestly increased risk of mild to moderate flares during short-term HRT might be a small price to pay for relief from menopausal symptoms in patients with SLE. However, until further studies

are conducted it is prudent for patients with active disease and life-threatening manifestations of SLE to avoid HRT, although some women may accept the small risk of disease exacerbation in order to get relief from severe menopausal symptoms. Patients with a history of venous or arterial thrombosis or high-titre anti-cardiolipin antibody or lupus anticoagulant should also avoid HRT, until further research becomes available. Thus, the decision to prescribe HRT should be considered on an individual basis. The current evidence, however, does not adequately address the safety of long-term HRT, which has been used by some physicians to treat osteoporosis in patients who cannot use other osteoporosis medications.

The findings of the OC-SELENA and Mexico City studies suggest that SLE patients with inactive or moderately active stable disease can safely use oral contraceptives. However, these studies do not address the issue of the use of combined oral contraceptives in patients at risk for vascular thrombosis and those with severe disease, although more than one-third of the patients in the OC-SELENA study had a history of lupus nephritis. Thus, patients with active and severe SLE and those at risk for thrombosis should probably avoid the use of oral contraceptives until further data are available in these groups of patients.

In addition to the above concerns, a more serious cautionary note emanates from a more recently published Nurses' Health Study, which suggested increased risk of SLE among users of oral contraceptives and HRT. Although this observational study has several limitations, discussed above, it does highlight that the issue of safe use of hormones in patients with SLE is far from settled.

Finally, recent laboratory data suggest that female susceptibility to SLE cannot be fully explained by hormonal factors alone. Genes and epigenetic factors probably play important roles in the development of SLE.

Hydroxychloroquine should be given to all patients with SLE

Several lines of evidence, including a randomized, double-blind, placebo-controlled study, have demonstrated the effectiveness of hydroxychloroquine in reducing the risk of clinical SLE flares |**14**|. The use of hydroxychloroquine, however, continues to be limited to about 50% of patients in most reported clinical trials. The following recent studies emphasize the value of hydroxychloroquine in reducing exacerbations and organ damage, and improving survival.

Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual

Fessler BJ, Alarcon GS, McGwin G Jr, *et al.*, LUMINA Study Group. *Arthritis Rheum* 2005; **52**: 1473–80

Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus

Costedoat-Chalumeau N, Amoura Z, Hulot JS, *et al. Arthritis Rheum* 2006; **54**: 3284–90

Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis

Kasitanon N, Fine DM, Haas M, *et al. Lupus* 2006; **15**: 366–70

Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus

Ruiz-Irastorza G, Egurbide MV, Pijoan JI, *et al. Lupus* 2006; **15**: 577–83

Effect of hydroxychloroquine in the survival of patients with systemic lupus erythematosus: data from LUMINA, a multi-ethnic US cohort (LUMINA L)

Alarcon GS, McGwin G, Bertoli AM, *et al. Ann Rheum Dis* 2007 (epub ahead of print 27 Mar 2007)

Antimalarials may influence the risk of malignancy in systemic lupus erythematosus

Ruiz-Irastorza G, Ugarte A, Egurbide MV, *et al. Ann Rheum Dis* 2007; **66**: 815–17

Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus

Costedoat-Chalumeau N, Amoura Z, Hulot JS, *et al. Ann Rheum Dis* 2007; **66**: 821–4

Hydroxychloroquine in lupus pregnancy

Clowse ME, Magder L, Witter F, Petri M. *Arthritis Rheum* 2006; **54**: 3640–7

Interpretation

The LUMINA (Lupus in Minorities: Nature vs. Nurture) study is a longitudinal study of outcome in lupus patients from Alabama, Texas and Puerto Rico. Using patients enrolled in this study, Fessler and colleagues examined whether hydroxychloroquine use is associated with a reduced risk of damage accrual in patients with SLE |**15**|. Five hundred and eighteen patients who met the American College of Rheumatology criteria for diagnosis of SLE and had ≤5 years disease duration at study entry were followed up annually. Fifty-six per cent of the patients in the study were treated with hydroxychloroquine at the time of study enrolment. Disease activity and damage were assessed using the Systemic Lupus Activity Measure (SLAM) and the Systemic Lupus International Collaborating Clinics Damage Index (SDI) respectively. Patients who were treated with hydroxychloroquine on enrolment had lower SLAM and SDI scores than patients who were not treated. Untreated patients were significantly more likely to have major organ involvement such as renal disease ($P<0.0001$) or central nervous system disease ($P<0.003$). Hydroxychloroquine-treated patients were less likely to develop new damage and to accrue damage, even after adjustment for differences in treatment assignment ($P\leq0.05$). Importantly, patients receiving hydroxychloroquine who had no damage at study entry had a significant decrease in the risk of damage accrual (hazard ratio 0.55, 95% CI 0.34–0.87, $P=0.01$), whereas those receiving hydroxychloroquine who had damage at study entry did not (hazard ratio 1.106, $P=0.6$). Thus, hydroxychloroquine use is independently associated with a reduced risk of damage accrual in SLE patients who had not yet accrued damage at the time of treatment initiation.

Further proof for the value of hydroxychloroquine in SLE came from another study |**16**| that examined the possible relationship between levels of hydroxychloroquine in whole blood and its clinical efficacy in patients with SLE. These authors measured concentrations of hydroxychloroquine in whole blood from 143 unselected patients with SLE who had been receiving hydroxychloroquine 400 mg daily for at least 6 months. They found that the mean whole-blood

hydroxychloroquine concentration was significantly lower in patients with active disease than in the 120 patients with inactive disease at entry as well as during follow-up. The hydroxychloroquine concentration was found to be the only predictor of exacerbation in multivariate logistic regression. These authors concluded that low whole-blood hydroxychloroquine concentrations are associated with SLE disease activity and are a strong predictor of disease exacerbation. In a subsequent study, the same investigators found that very low levels of hydroxychloroquine were associated with prolonged poor compliance with the drug |**17**|.

A recent study designed to identify clinical predictors of response to initial mycophenolate mofetil (MMF) therapy for membranous lupus nephritis (MLN) analysed clinical outcomes of patients in the Hopkins Lupus Cohort |**18**|. The study identified 29 MLN patients within the first year of initiation of treatment with MMF therapy for newly diagnosed MLN. Membranous lupus nephritis was classified according to the new International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification. Complete renal remission was defined as proteinuria less than 500 mg/24 h. Eleven (38%) patients achieved complete renal remission by 12 months. Of those taking hydroxychloroquine, 7/11 (64%) were in remission within 12 months compared with only 4/18 (22%) of those not on hydroxychloroquine ($P < 0.05$ based on a log-rank test). Although the size is small and patients were followed for only 1 year, these data make a case for the use of hydroxychloroquine for inducing renal remission when MMF is used as the initial therapy for MLN.

The above effects of hydroxychloroquine on reducing disease activity, flares and damage are important in improving long-term outcomes, as found in two separate studies that showed improved survival in patients taking antimalarials. Ruiz-Irastorza and colleagues analysed a prospective cohort including 232 patients with SLE for death due to any cause in relation to antimalarial usage |**19**|. Cumulative 15-year survival rates were 0.68 for never-treated ($n = 82$) vs. 0.95 for ever-treated ($n = 150$) patients ($P < 0.001$). Twenty-three patients died, 19 of whom (83%) had never received antimalarials. No patient treated with antimalarials died of cardiovascular complications. They also showed that taking antimalarials was also protective against thrombosis (hazard ratio 0.28, 95% CI 0.08–0.90).

The same authors also examined the effect of antimalarials on the development of cancer in an observational prospective cohort study involving 235 patients with SLE |**20**|. Two out of 156 (1.3%) ever-treated patients compared with 11/79 (13%) never-treated patients had cancer ($P < 0.001$). Cumulative cancer-free survival in treated and not-treated patients was 0.98 and 0.73 respectively ($P < 0.001$). Adjusted hazard ratio for cancer among malaria drug users compared with non-users was 0.15 (95% CI 0.02–0.99). Confirmation of these data in a larger sample size would be highly desirable for long-term management of SLE.

The protective effect of hydroxychloroquine in the survival of patients with SLE was reproduced in a case–control study in the LUMINA cohort |**21**|. Of 608 patients in this study, 61 patients had died. Hydroxychloroquine had a protective effect on survival. The OR and 95% CI were 0.128 and 0.054–0.301, respectively, for

hydroxychloroquine alone and 0.319 and 0.118–0.864 respectively after taking into consideration the factors associated with treatment decisions.

Finally, Clowse and colleagues examined the effect of hydroxychloroquine treatment on pregnancy outcomes and lupus activity in a prospective study |**22**|. This study involved 163 cases with no exposure to hydroxychloroquine during pregnancy, 56 cases with continuous use of hydroxychloroquine during pregnancy, and 38 cases with cessation of hydroxychloroquine treatment either in the 3 months prior to or during the first trimester of pregnancy. The authors found no difference in rates of miscarriage, stillbirth, pregnancy loss and congenital anomalies among the three groups. The degree of lupus activity during pregnancy, however, was significantly higher in women who stopped taking hydroxychloroquine.

Comment

The take-home lesson from the LUMINA study is that hydroxychloroquine use should begin as soon as the diagnosis of SLE is made. Once the patients have developed organ damage, its use is less likely to reduce the risk of damage accrual in SLE patients. The beneficial effect of hydroxychloroquine is probably due to its effects on disease activity, as low levels of hydroxychloroquine in whole blood are associated with SLE disease activity and are a strong predictor of disease exacerbation. These data make a case for further studies to determine the need for regular drug assays to detect non-compliance and individual tailoring of treatment to improve the efficacy of hydroxychloroquine treatment in patients with SLE. Hydroxychloroquine also appears to protect against thrombosis, cardiovascular complications and malignancies in patients with SLE. Finally, hydroxychloroquine has a protective effect on survival that is evident even after taking into consideration the factors associated with treatment decisions. Based on the available literature and personal clinical experience, the author suggests that unless contraindicated, hydroxychloroquine should be given to all patients with SLE. Hydroxychloroquine treatment should continue during pregnancy.

Focus on chronic organ damage: cyclophosphamide is superior in averting chronic kidney damage than azathioprine plus methylprednisolone

Background

Traditionally, most investigators have focused on mechanisms of development of autoantibodies and inflammation in SLE. Recent studies in animals and humans in several laboratories including ours have begun to focus on mechanisms that perpetuate fibrosis leading to chronic tissue destruction (reviewed in |**23**|). The presence of chronic tissue lesions portends a poor prognosis in patients with lupus

nephritis. It is unclear whether current treatments affect the development of chronic tissue lesions. A clinical trial discussed in this section has attempted to address this question.

SLE: translating lessons from model systems to human disease

Singh RR. *Trends Immunol* 2005; **26**: 572–9

Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial

Grootscholten C, Ligtenberg G, Hagen EC, *et al*. *Kidney Int* 2006; **70**: 732–42

Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis

Grootscholten C, Bajema IM, Florquin S, *et al*. *Arthritis Rheum* 2007; **56**: 924–37

Interpretation

Grootscholten and colleagues |**24**| report a controlled trial involving 87 patients with proliferative lupus nephritis randomly assigned to receive either cyclophosphamide pulses (750 mg/m^2, six i.v. pulses at monthly intervals and then seven pulses at 3-month intervals) combined with oral prednisone, or to azathioprine (2 mg/kg/day in 2 years) combined with i.v. pulses of methylprednisolone (3×3 pulses of 1000 mg) and oral prednisone. Although both treatment regimens induced high response rates (~90%), relapses were less frequent in the cyclophosphamide group. Patients in the azathioprine group were also more likely to develop non-sustained doubling of their baseline serum creatinine. In concordance with this, patients in the azathioprine group had more severe progression of chronic renal histological lesions compared with the cyclophosphamide group |**25**|. These conclusions were guided by findings in 39 pairs of renal biopsy samples, obtained at baseline and after 2 years of treatment.

Comment

The above findings make a case for cyclophosphamide regimen for patients with proliferative lupus nephritis in order to prevent chronic renal fibrosis. However, most patients in their study had a relatively less aggressive disease with minimal crescents, as patients with creatinine clearance rates < 25 ml/min were excluded. Also, most patients in this study were Caucasians, so findings may not be generalizeable to other ethnic groups, in particular to African-Americans, who generally develop a more severe renal fibrosis.

Mycophenolate mofetil continues to impress in lupus nephritis

Background

As discussed above, combined cyclophosphamide and corticosteroid treatment is not only effective in inducing remission and maintaining long-term renal function in Asian and Caucasian patients, it also appears to curtail chronic end-stage renal damage. Treatment-related adverse effects, however, have been a major limiting factor with this therapy, which can be curtailed to some extent by limiting the dosage and/or duration of cyclophosphamide treatment. Since the first clinical trial of mycophenolate mofetil in lupus nephritis in 2000, several reports have found it to be effective and well tolerated.

Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis

Ginzler EM, Dooley MA, Aranow C, *et al. N Engl J Med* 2005; **353**: 2219–28

Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis

Chan TM, Tse KC, Tang CS, *et al. J Am Soc Nephrol* 2005; **16**: 1076–84

Mycophenolate mofetil for remission induction in severe lupus nephritis

Cross J, Dwomoa A, Andrews P, *et al. Nephron Clin Pract* 2005; **100**: c92–100

Induction therapy for active lupus nephritis: mycophenolate mofetil is superior to cyclophosphamide

Elliott JR, Manzi S. *Nat Clin Pract Rheumatol* 2006; **2**: 354–5

Interpretation

In Chinese patients with class IV lupus nephritis, a combination of mycophenolate mofetil and prednisolone induced >90% response rate and a 6.3% incidence of serum creatinine doubling over a period of 63 months |**26**|. Efficacy data on mycophenolate mofetil plus prednisone are less impressive (~50% response rates) in a multicentre US trial involving predominantly black patients, but still superior to pulse cyclophosphamide-based induction or maintenance treatment |**27**|. However, this study excluded patients with creatinine clearance rates <30 ml/min, thus excluding patients with the most severe disease, including rapidly progressive glomerulonephritis. A favourable response rate and tolerability profile with mycophenolate mofetil and prednisone has also been reported in Caucasian patients in UK |**28**|. Mycophenolate mofetil is also effective in reducing proteinuria in patients with membranous lupus nephritis |**29**|. However, it remains to be fully resolved whether mycophenolate mofetil should be used after cyclophosphamide dosing for 6 months as maintenance therapy or whether it should be implemented as induction therapy. The duration of treatment with mycophenolate mofetil also remains to be resolved.

Comment

Until further data on long-term outcome with mycophenolate mofetil compared with other therapies are available for lupus nephritis, the available studies have guided the author to follow the following treatment strategies. For patients with newly diagnosed, mild to moderately severe lupus nephritis, especially those for whom fertility is a major concern, it is reasonable to start treatment with mycophenolate mofetil plus prednisone. For patients with severe, rapidly progressive glomerulonephritis with renal failure, pulse cyclophosphamide plus corticosteroid appears to be the appropriate choice at this time. Patients with moderate to severe lupus nephritis but with less fulminant course, in whom fertility is not a concern, can be treated with cyclophosphamide plus corticosteroid regimen to induce remission, followed by mycophenolate mofetil to maintain remission. Treatment, however, should be individualized, as some patients may respond better to one treatment than to the other. Thus, it may be prudent to switch the treatment to another regimen in patients with inadequate response to one regimen.

Therapies targeted at B-cells: rituximab may emerge as a promising safe drug in SLE

Background

B-cell depletion is emerging as a major advance in the treatment of autoimmune diseases. Over 150 patients with SLE have been treated with rituximab, a chimeric monoclonal antibody specific for CD20.

Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse and retreatment

Smith KG, Jones RB, Burns SM, Jayne DR. *Arthritis Rheum* 2006; **54**: 2970–82

Clinical and immunological effects of rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study

Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, *et al. Arthritis Res Ther* 2006; **8**: R83 (epub 5 May 2006)

Rituximab therapy for childhood-onset systemic lupus erythematosus

Willems M, Haddad E, Niaudet P, *et al. J Pediatr* 2006; **148**: 623–7

B-lymphocyte depletion therapy in children with refractory systemic lupus erythematosus

Marks SD, Patey S, Brogan PA, *et al. Arthritis Rheum* 2005; **52**: 3168–74

Histopathological and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis

Gunnarsson I, Sundelin B, Jonsdottir T, *et al. Arthritis Rheum* 2007; **56**: 1263–72

Interpretation

In a prospective study, 11 patients with active or refractory SLE were treated with a course of therapy with rituximab along with a single dose of cyclophosphamide and followed for a median of 24 months |**30**|. Six patients had a complete remission and five had a partial response. B-cell return preceded relapses in seven patients, who responded to further treatment with rituximab. Similar data have been reported in refractory childhood lupus |**31,32**|. However, serious adverse events, including serious infections and cytopenias occurred in 5 of 11 patients in one study |**32**|.

In another study, seven patients with cyclophosphamide-resistant proliferative lupus nephritis were treated with rituximab plus cyclophosphamide |**33**|. At 6 months' follow-up, all patients had responded clinically as well as histopathologically to this treatment.

Comment

The results of these small case series suggest that for SLE patients who fail to respond to conventional immunosuppressive therapy, combined treatment with rituximab and cyclophosphamide may constitute a new treatment option. Long-term efficacy and safety, however, need to be tested in large clinical trials.

Stem cell transplantation for SLE

Background

With the hope that transplantation of stem cells may turn the clock of autoimmunity to time zero, Traynor and colleagues mobilized and collected stem cells from patients with severe lupus before giving high-dose cyclophosphamide and then reinfused the stem cells 2 days after the completion of the chemotherapy. At median follow-up of 25 months, all seven patients in this phase I study underwent complete remission |**34**|. In 53 European patients, high-dose cyclophosphamide followed by peripheral stem cell transplantation was associated with remission in 66% of patients at 6 month follow-up; however, 32% of these patients with remission subsequently relapsed and 12 deaths occurred within 6 weeks after the procedure |**35**|.

Non-myeloablative haematopoietic stem cell transplantation for systemic lupus erythematosus

Burt RK, Traynor A, Statkute L, *et al*. *JAMA* 2006; **295**: 527–35

Interpretation

In the paper reviewed here, Burt and colleagues report the long-term outcome of treatment with autologous non-myeloablative haematopoietic stem cell transplantation and high-dose cyclophosphamide |**36**|. This single-arm non-randomized study included 50 patients with severe refractory lupus with either organ- or life-threatening visceral involvement. Patients were followed for a median of 29 months (range 6 months to 7.5 years). This treatment resulted in significant amelioration of disease activity. Overall survival was 84% and the probability of 5-year disease-free survival (prednisone dose of < 10 mg/day and no immunosuppressive medications) was 50%. Serological studies, complement levels, renal function and SLE disease activity index (SLEDAI) all demonstrated clinically meaningful improvement.

However, two patients (4%) died after mobilization, including one patient who died a week after stem cell mobilization, but before starting stem cell transplantation (treatment-related mortality of 2%). Four patients (8%) developed bacteraemia during stem cell mobilization. Furthermore, many patients continue to have lupus autoantibodies.

Comment

This non-randomized study suggests that autologous haematopoetic stem cell transplantation with high-dose cyclophosphamide therapy has benefit in patients with severe refractory lupus. It remains to be determined in randomized controlled trials whether this approach is superior to other less effort-intensive treatment modalities.

Conclusion

No new drugs have been approved by the US Food and Drug Administration for SLE since 1966, because we understand little about the pathogenesis of this disease. Comfortingly, however, we have learnt to make the best use of 'old' drugs such as antimalarials, and have learnt to borrow from our colleagues in transplant medicine and oncology medicines such as mycophenolate mofetil and rituximab. Although we are yet to find the exact basis for the most obvious observation, i.e. female sex preponderance in SLE, several clinical trials, large epidemiological studies and reverse translational studies in animal models have shed some light on this issue.

Tremendous efforts in the laboratory as well as in the clinical arena, are trying to solve important questions, such as what causes SLE, how to diagnose it, how best to assess the extent and severity of this disease, and what are the important new drug targets. Not all articles describing these developments can be reviewed in this chapter. The author hopes that discussion of a few arbitrarily selected articles in this chapter will provide a snapshot of the current clinical developments in SLE.

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11

Systemic sclerosis

ARIANE HERRICK

Several hundred papers that reflect the expanding clinical and scientific understanding of the systemic sclerosis (SSc) disease process have been published over the last 18 months. However, for the practising clinician, the key question is not the number of publications but 'Are we any nearer to identifying treatment(s) that can modify the underlying disease process?' The answer for the last 18 months must be 'yes'. Although we still do not have drugs that have been proven to reverse the fibrotic and vascular abnormalities that are together responsible for the cutaneous, peripheral vascular, and internal organ involvement of the disease, significant progress has been made. In this review I have selected ten papers that together highlight some of the major challenges in understanding the different elements of the SSc disease process and/or describe key clinical advances. All are directly or indirectly relevant to the practising clinician. Many others could equally well have been chosen, but those selected give a flavour of how clinicians and scientists are collaborating in studies of pathogenesis, measurement and treatment.

Whereas in Volume 5 of *The Year in Rheumatic Diseases* the emphasis was mainly on clinical assessment and treatment, this year I have chosen a broader remit and subdivided the chapter as follows:

1 pathogenesis;
2 the effect of statins on the SSc disease process, as an exemplar of how increased understanding of the pathobiology of SSc allows identification of novel mechanisms of action;
3 measurement of disease process;
4 pulmonary arterial hypertension;
5 clinical trials.

Also to highlight during the period under review:

1 In Volume 5, one of the papers selected discussed survival benefit from renal transplantation in patients with SSc. This year further data from the US United Network for Organ Sharing are reported, this time describing outcomes of lung transplantation. The 1- and 3-year survival rates were 68% and 46% respectively, similar to those of patients receiving transplants for other conditions |**1**|. Therefore, lung transplantation should be considered

in carefully selected patients and this is confirmed in a paper published just after the review period |**2**|.

2 The risk of malignancy amongst patients with SSc was revisited. Studies continue to give conflicting results, probably due to differences in study design and case ascertainment. Chatterjee and colleagues |**3**| reported no increase in cancer rates, with the exception of an increased incidence of liver cancer, whereas Derk and colleagues found that in SSc the incidence of cancer was increased and that this was statistically significant for oesophageal and oropharyngeal cancers |**4**|. The high reported prevalence of Barrett's oesophagus in SSc (12.7%) |**5**| highlights the need for careful monitoring of patients at risk of upper gastrointestinal malignancy, and for prospective studies investigating this risk in patients with SSc.

Finally, it is worth remembering that in recent years a major advance has been the recognition of the importance of subtyping SSc into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) |**6**|, as these two main subtypes have different natural histories, autoantibody associations and prognoses. Therefore, progress in SSc relies heavily upon clinicians documenting disease process, working along scientists who have a widening armamentorium of molecular and cellular biological techniques to investigate the mechanisms that initiate and drive disease and that are responsible for the different phenotypes.

Pathogenesis

During the period under review there has been continued interest in the roles of endothelin-1, the renin–angiotensin system and transforming growth factor-β (TGF-β), and in identifying points in their 'pathways' that might be amenable to therapeutic intervention |**7**|. Multiple other potential inciting factors/regulators have also been examined in studies of immunogenetics, circulating markers, skin biopsies and cell cultures. The paper selected for review demonstrates how novel techniques can provide new insights into pathogenesis.

Gene profiling of scleroderma skin reveals robust signatures of disease that are imperfectly reflected in the transcript profiles of explanted fibroblasts

Gardner H, Shearstone JR, Bandaru R, *et al. Arthritis Rheum* 2006; **54**: 1961–73

Background. Skin involvement is one of the most characteristic aspects of the SSc disease process and affords an accessible 'window' into the disease in that skin is easy to biopsy. Gene expression profiling allows identification of

genes that are differentially regulated in diseased tissue compared with healthy tissue. The aim of this study was threefold: (a) to examine the gene profile of sclerodermatous skin compared with healthy forearm skin; (b) to examine whether this gene profile is maintained in cultured SSc dermal fibroblasts. This is a key issue because many studies investigating the pathogenesis of SSc involve dermal fibroblast cultures, and it is therefore important to understand as fully as possible the strengths and weaknesses of this approach; and (c) to examine whether robust collection protocols allow results of gene expression profiling studies to be combined between centres. Forearm skin biopsies from nine patients with early SSc (eight dcSSc) and from nine healthy control subjects were examined.

Interpretation. A large number of qualifiers distinguished between SSc and control biopsies – 1839 at a univariate *P*-value of < 0.01 and 506 at a value of < 0.001. Clustering of all the biopsies showed that disease status (SSc vs. control) was the most important parameter in classifying the samples, and was not confounded by gender, race, age or origin (samples from two centres – in South Carolina and Texas – were included). Class-distinguishing genes for SSc included those from the TGF-β and Wnt pathways, extracellar matrix proteins (examples included collagens XI, X, V and IV), and from the CCN family (including connective tissue growth factor). The number of qualifiers distinguishing between SSc and control fibroblasts was smaller – 223 at a *P*-value of < 0.01 and 21 at a value of < 0.001.

Comment

This paper is one of the first to examine gene expression profiling in sclerodermatous skin. As anticipated, a large number of genes were differentially expressed compared with healthy control skin. Many of these genes were as anticipated, for example connective tissue growth factor, others unanticipated and therefore worthy of further investigation using other methodologies. The authors suggested three interpretations of the fact that there was a smaller number of qualifiers in cultured fibroblasts than in biopsies:

(a) A cell type other than the fibroblast, for example the endothelial cell or pericyte, is a key driver of SSc. The roles of both endothelial cells and pericytes are currently being intensively researched.

(b) a small population of cells creates an altered cytokine milieu and matrix that is subsequently lost in culture.

(c) Fibroblast-synthesized matricellular proteins contribute to an autocrine loop in which fibroblasts exhibit abnormal behaviour, but that the relevant signals are lost in the process of cell culture.

It is likely that further gene profiling studies will be reported in the next few years, as it will be of interest to look at gene profiles from different sites, from different disease subtypes (all but one of the patients studied by Gardner and colleagues had early diffuse disease) and at different time points in the natural history of the disease. A key point in this study was the comparison between biopsies and

fibroblast cultures – the implication being that studies using fibroblast cultures must be interpreted in context: other cells probably contribute to pathogenesis and/or some key fibroblast characteristics are progressively lost in culture.

Statins – their potential role in disease modification

It is well recognized that statins have effects additional to lowering lipid levels: they downregulate expression of several adhesion molecules, inhibit the migration of lymphocytes to areas of inflammation, increase production of the vasodilator nitric oxide and (in fibrotic disorders) inhibit overproduction of extracellular matrix components |**8**|. Therefore statins might modify all three aspects of the SSc disease process: the fibrosis, the vasculopathy and the immune dysfunction. Two papers have been selected for review. The paper by Louneva and colleagues examined effects on collagen production and the paper by Kuwana and colleagues effects on blood vessels. A recent small study suggested that 8 weeks' treatment with pravastatin was associated with a reduction in von Willebrand factor activity |**9**|, further support (but needs to be confirmed in larger studies) that statins might have a beneficial effect on the vasculature.

Inhibition of systemic sclerosis dermal fibroblast type I collagen production and gene expression by simvastatin

Louneva N, Huaman G, Fertala J, Jimenez S. *Arthritis Rheum* 2006; **54**: 1298–308

Background. The aim of this study was to examine whether statins could influence collagen gene expression in SSc fibroblasts (which produce excess amounts of various collagens). The rationale was that statins are known to influence the synthesis of lipid intermediates involved in isoprenylation reactions, which play a role in the regulation of collagen genes. Experiments were conducted in fibroblast cultures from three patients with early dcSSc and from three age-/sex-matched control subjects. The studies included examining the effects of simvastatin on cell morphology, on cytotoxicity, and on type I collagen production and messenger RNA (mRNA).

Interpretation. Simvastatin (in a number of different concentrations) had no effects on cell morphology or cytotoxicity. However, simvastatin (5–10μmol/l) reduced type I collagen expression and mRNA levels in both normal and SSc fibroblasts in a dose-dependent manner. These inhibitory effects of simvastatin were abbrogated by mevalonate [of which intracellular levels are reduced by statins via inhibition of hydroxymethylglutaryl-coenzyme A (HGM-CoA) reductase] and by geranylgenanyl pyrophosphate, but not by farnesyl pyrophosphate. Geranylgenanyl pyrophosphate and farnesyl pyrophosphate are both lipids downstream of HMG-CoA. Further studies with

COL1A1 promoter constructs showed that the statin effects occurred at the transcriptional level and involved the proximal *COL1A1* promoter region including –174hp.

Comment

This elegant set of experiments demonstrated that simvastatin inhibits *COL1A1* expression in SSc and normal fibroblasts. The fact that farnesyl pyrophosphate failed to reverse this inhibition suggests the involvement of geranylgeranylation (rather than farnesyl prenylation). Also simvastatin exerts its effects at a transcriptional level via *COL1A1* promoter elements, which are well recognized as being involved in the up-regulation of collagen gene expression in SSc.

The key contribution of this paper for the clinician is to demonstrate that the possible beneficial effects of statins in SSc are not confined to vascular protection. A potential antifibrotic effect is very exciting, because drugs that will prevent fibrosis early on in disease are urgently required. Future clinical trials should therefore examine statin therapies in patients with different disease subtypes: the wide-ranging effects of statins mean that different subgroups of patients with SSc may benefit via different mechanisms.

Increase in circulating endothelial precursors by atorvastatin in patients with systemic sclerosis

Kuwana M, Kaburaki J, Okazaki Y, *et al. Arthritis Rheum* 2006; **54**: 1946–51

BACKGROUND. These authors had previously proposed that defective vasculogenesis (the formation of blood vessels) contributes to the vascular abnormalities of SSc. The aim of this study was to investigate whether statin therapy could increase the number of bone marrow-derived circulating endothelial cell precursors (CEPs, reduced in SSc and required for vasculogenesis) and improve vascular symptoms in patients with SSc. Fourteen patients were prescribed 10 mg of atorvastatin for 12 weeks in an open study and studied at weeks 0, 4, 8, 12 and 16 (4 weeks post treatment). Endpoints included numbers of CEPs, the potential of CEPs to differentiate into mature endothelial cells, clinical parameters of Raynaud's and circulating markers of endothelial activation/injury.

INTERPRETATION. The numbers of CEPs increased significantly on atorvastatin (mean $\pm$ SD increase 3.8-fold $\pm$ 1.9, $P < 0.0001$) but returned to baseline levels 4 weeks post treatment. Maturation capacity in response to angiogenic stimuli was evaluated in cell cultures from five patients: maturation potential was reduced in the SSc patients, and was not improved after atorvastatin. Raynaud's condition score and patient's self-assessment by visual analogue scale (VAS) improved with atorvastatin, and there were significant falls in both the angiogenic factors measured (vascular endothelial growth factor and basic fibroblast growth factor) and in both the markers of endothelial activation/injury (soluble vascular cell adhesion molecule and soluble E-selectin).

Comment

This was a small open study of only 14 patients and, as such, its findings, particularly the improvements in Raynaud's phenomenon, need to be interpreted with caution. Nonetheless, the key finding – that atorvastatin can increase CEPs in patients with SSc – is of considerable clinical interest, especially when coupled with a reduction in the upregulated levels of angiogenic factors and endothelial activation/injury markers. The wider implications of these findings are discussed in an accompanying editorial |**10**|. If the findings are confirmed in larger studies, then this would be a powerful argument as to why statin therapy could be benefical in patients with SSc. Therefore, the need for larger multicentre studies is highlighted.

At present there is considerable interest not only in redressing the abnormal balance between vasoconstriction and vasodilation in SSc-related vascular disease, but also in exploring the effects of different drugs on vascular protection/remodelling. Thus, this paper is also important because it adds further support for the role of defective angiogenesis in SSc, and highlights how CEPs might be a biomarker for the vasculopathy of SSc. Clinical trials of SSc, including those of SSc-related digital vascular disease, have been plagued by a lack of valid outcome measures that are sensitive to change. As demonstrated by this study, measuring CEPs may prove to be useful not only in providing insights into pathogenesis but also as a marker of disease progression and of treatment response.

Outcome measures

One of the challenges to clinicians with an interest in SSc is the identification of robust endpoints to facilitate clinical trials, and this continues to be an area of active research within the international research community |**11**|. In the last volume of *The Year in Rheumatic Disorders*, measurement methods relating to hand function, computed tomographic (CT) patterns of lung disease and nailfold capillaries (reflecting the microvascular component of SSc) were discussed. This year a paper describing assessment of skin involvement has been selected.

Durometry for the assessment of skin disease in systemic sclerosis

Kissin EY, Schiller AM, Gelbard RB, *et al. Arthritis Rheum (Arthritis Care Res)* 2006; **55**: 603–9

Background. The authors' aim was to assess the validity of durometry to measure skin hardness in patients with SSc, including assessment of its sensitivity to change. Durometers are hand-held devices that measure hardness by applying an indentation load on surfaces. Durometry was assessed in three studies. The first study measured intra- and inter-observer reliability in five patients with SSc and one healthy control subject. Five physicians participated.

The second study was a longitudinal study of 13 patients with SSc and five control subjects, studied on two occasions 3–12 months apart. Both these studies involved durometry at nine sites and a 17-site modified Rodnan skin score (MRSS). The third study compared durometry, ultrasound skin thickness and clinical skin score at four upper-limb sites (fingers, hands, forearms, upper arms) in 30 patients with SSc and 12 healthy control subjects.

Interpretation. The intra-observer intraclass correlation coefficients (ICCs) were higher for durometry than for skin scores – 0.97 for the overall nine-site durometry score compared with 0.85 for the MRSS. Durometry reliability was high at all nine sites measured (range 0.86–0.94), whereas skin score reliability was only moderate in upper arms, abdomen and thighs. Inter-observer variability was similar for durometry and MRSS when overall scores were considered (0.75 and 0.73 respectively). Whereas inter-observer ICCs for durometry were high at all sites (range 0.61–0.85), they were lower for skin score at certain sites including abdomen (0.08), feet (0.09) and fingers (0.27). There was a wide range of durometry scores within each clinical skin score at each body site (Fig. 11.1). Durometry score was higher for uninvolved skin in patients with SSc (mean±SD 23±7 durometry units) compared with healthy control subjects (19±6, $P < 0.0001$). In the longitudinal study, there was a strong correlation between the change in nine-site durometry score and 17-site MRSS ($r = 0.77$, $P = 0.002$). Durometry scores correlated with MRSSs and with ultrasonic skin thickness measurements, although this varied between sites with low correlations at the fingers.

Comment

In patients with diffuse cutaneous disease, skin involvement predicts survival, and at present the gold standard measure of skin involvement is the MRSS. Yet there are problems inherent in the MRSS: there is considerable intra- and inter-

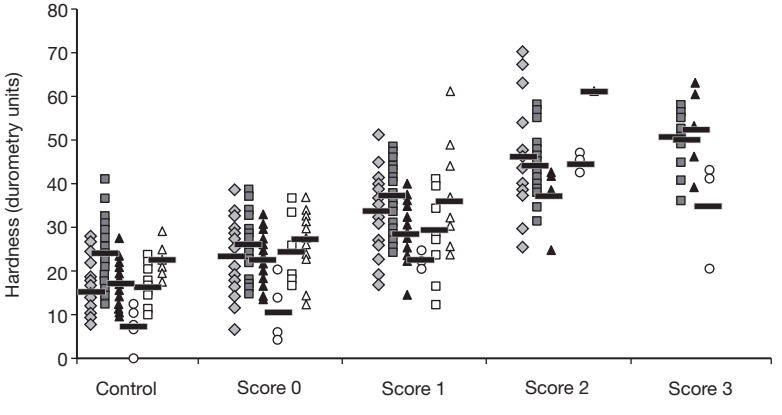

Fig. 11.1 Durometer measurements of skin hardness at various body sites in healthy control subjects and patients with systemic sclerosis; data are subdivided by clinical skin score. While skin became progressively harder with increasing clinical skin scores, for each clinical skin score there was a wide range of skin hardness measurements. Solid diamonds, hand; solid squares, forearm; solid triangles, upper arm; open diamonds, leg; open squares, thigh; open circles, abdomen; solid bars, mean. Source: Kissin *et al.* (2006).

observer variability, it is imprecise (at any one site there are only four possibilities of scoring – 0 to 3), and it is generally recognized that training is required. Against this background the authors assessed the use of durometry, comparing it with the MRSS (both as a total score and at individual sites) and with ultrasound skin thickness. The study design was somewhat complicated by comprising three separate studies, with three separate patient cohorts, and the paper would have been easier to read (and the conclusions perhaps more easily drawn) had the investigators examined a single cohort of patients and control subjects, studying all landmark sites in all patients, correlating with MRSS and ultrasound in all patients, and then restudying a subgroup of the original cohort 3–12 months later. Nonetheless, the authors make the point that durometry gives precise, reliable measures of skin hardness and that durometry correlated with both clinical skin score and ultrasound skin thickness, although at some sites better than at others. The poor correlations at the fingers probably reflect how durometry measurements over bone are unreliable, and also the low reliability of skin scoring at the fingers. Careful selection of sites is likely to maximize the usefulness of durometry in future clinical trials.

Pulmonary arterial hypertension

In recent years, pulmonary hypertension has attracted enormous interest amongst those with an interest in SSc because of treatment advances with prostanoids, endothelin-1 receptor antagonists and phosphodiesterase inhibitors. It is important to recognize that pulmonary hypertension can occur in patients with SSc for two main reasons: pulmonary *arterial* hypertension (PAH), which often develops after many years of disease, and pulmonary hypertension secondary to interstitial lung disease |**12**|. Most of the new therapies have focused on PAH. I have selected four papers on the basis that they address a number of issues:

- Are all those patients who might benefit from treatment being identified?
- Does a high estimated pulmonary artery pressure have the same prognostic significance in patients with interstitial lung disease as in those without?
- Survival – is this improving?

The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary healthcare level of community-based rheumatologists (the UNCOVER study)

Wigley FM, Lima JA, Mayes M, *et al. Arthritis Rheum* 2005; **52**: 2125–32

Background. Estimates of PAH prevalence in connective tissue disease vary widely, in part related to criteria for diagnosis and to differences in the denominator population. The aim of this study was to determine the point prevalence of undiagnosed PAH, in patients with SSc or mixed connective tissue disease (MCTD) in community based rheumatology practices using Doppler echocardiography. The study had both retrospective and prospective components: patients known to have PAH had their data examined retrospectively, whereas those not known to have PAH were examined prospectively (dypsnoea questionnaire, Doppler echocardiography if not done in the previous 6 months).

Interpretation. Nine hundred and nine patients were screened at 50 centres, and of these 815 met the inclusion criteria and were not lost to follow-up (715 SSc, 100 MCTD). Of these, 122 already had a diagnosis of PAH. Of the remaining 693 patients, 24 did not undergo Doppler echocardiography leaving 669 with complete data. Of these 669 patients, 89 (13.3%) had an estimated right ventricular systolic pressure of ≥40 mmHg, of whom 20 (22.5% of these 89) had a very high estimated pressure of ≥50 mmHg. Thus, the total prevalence of PAH (known and undiagnosed) in the cohort was 211/791 (26.7%). Of the 89 newly diagnosed patients, 82 had SSc and seven MCTD. Among patients in the prospective group, those with an estimated right ventricular systolic pressure of ≥40 mmHg were more likely to have mild or severe functional impairment (76/89, 85%) than those with pressure < 40 mmHg (320/580, 55%).

Comment

The key finding of this study is that significant numbers of patients with SSc and MCTD may have undiagnosed pulmonary hypertension (point prevalence in this study 13.3%). While it is important to recognize that this conclusion is made on the basis of estimated pressures on Doppler echocardiography, and that echocardiography is a *screening* test that must be followed by right heart catheterization to make the diagnosis, it seems likely that with the cut-off set at 40 mmHg a significant proportion of these cases would have been confirmed on right heart catheter. As cited by the authors, a study by Mukerjee and colleagues |**13**| reported that the threshold value of 40 mmHg had a positive predictive value of 92% and a negative predictive value of 44%. The total prevalence of PAH of 27% reported in this study might seem high. It is possible that results may have been influenced by the fact that echocardiograms will have been performed by a large number of individuals with different levels of experience, although the authors had predefined criteria by which to interpret the echocardiography results.

The study is based on 50 community rheumatology practices in North America, and as healthcare systems vary between countries conclusions may not be generalizable to other countries with different referral systems for echocardiography. Nonetheless, a key point is that many patients with connective tissue disease are breathless, and that estimated pulmonary artery pressure may be high both in those with breathlessness and those without. Now that treatments are available, it is important to make the diagnosis of PAH in order to implement an appropriate investigation and treatment plan. The message for clinicians is to ensure that they

have a system in place to screen all patients with scleroderma-spectrum disorders, be they hospital or community based – otherwise patients will be 'missed'.

Early detection of pulmonary arterial hypertension in systemic sclerosis. A French nationwide prospective multicentre study

Hachulla E, Gressin V, Guillevin L, *et al. Arthritis Rheum* 2005; **52**: 3792–800

Background. The aim of this study was to develop an algorithm for screening of PAH in patients in France with SSc. The algorithm was based on symptoms, Doppler echocardiography [peak velocity of tricuspid regurgitation (VTR) of

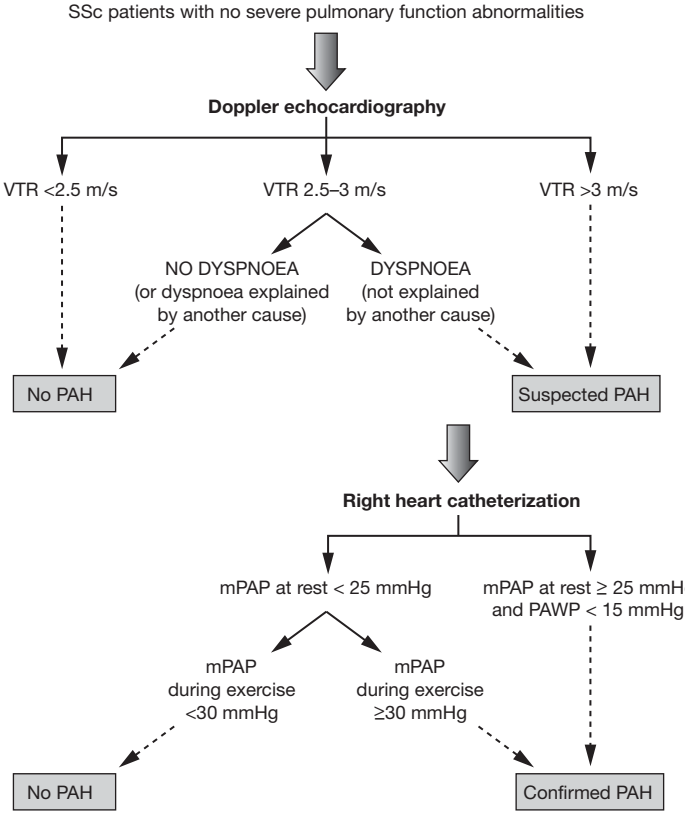

Fig. 11.2 Screening algorithm for diagnosis of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc). VTR, peak velocity of tricuspid regurgitation; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure. Right heart catheterization was performed except when Doppler echocardiography provided evidence of left heart disease. Source: Hachulla *et al*. (2005).

> 3 m/s or 2.5–3 m/s with unexplained dyspnoea] and right heart catheterization (Fig. 11.2). Five hundred and ninety-nine patients (434 lcSSc, 165 dcSSc) without severe abnormalities on pulmonary function tests were recruited from 21 SSc centres. Patients with forced vital capacity, total lung capacity or forced expiratory volume in 1 s < 60% predicted were excluded.

Interpretation. Twenty-nine of the 599 patients were already known to have PAH, leaving 570 to be screened. Thirty-seven patients were found to have either VTR > 3 m/s or VTR 2.5–3 m/s with unexplained dyspnoea. Of these 37 patients, four had left ventricular dysfunction on echocardiography. Of the 33 remaining patients who underwent right heart catheterization, 18 had PAH (mean ± SD pulmonary artery pressure 30 ± 9 mmHg). Peripheral arterial hypertension was excluded in the remaining 15 patients, three of whom had postcapillary pulmonary hypertension. Seven were in New York Heart Association functional class III or IV. Overall, 47/599 patients therefore had PAH [prevalence 7.85%, 95% confidence interval (CI) 5.70–10.00]. The authors concluded that their algorithm identified patients with PAH at a mild stage. The cohort is being followed up over 3 years to see whether early identification improves prognosis.

Comment

Although this study and the one described above by Wigley and colleagues both address the issue of early detection of PAH in patients with SSc, they are of different design and consider different patient populations. Thus, the two studies give complementary information and together highlight many of the key points surrounding screening for PAH.

Hachulla and colleagues' study was a hospital-based study including only centres with an interest in SSc. The authors emphasize how their focus was to develop an algorithm, and this they have successfully done, showing that they were able to detect PAH at a mild stage. By doing this in the context of a large multicentre study they have also (although not specifically discussed by them) achieved consensus amongst different centres on how to screen. This is a very important step in providing the infrastructure for further prospective work, to which the authors refer.

The authors emphasize the importance of the echocardiographic technique. In their study all echocardiograms were undertaken by an experienced cardiologist. They also discuss the different echocardiographic methods of estimating pulmonary artery pressure, and are careful to state that the purpose of their study was not to establish optimal criteria and thresholds for screening. Their algorithm worked well, and identified patients likely to benefit from treatment. One concern is that (as discussed by the authors) patients with severe pulmonary function abnormalities were excluded (43 patients did not fulfil the entry criteria on this basis) and so the study is not generalizable to patients with significant interstitial lung disease or other respiratory problems.

It is likely that the difference in the prevalences in PAH (estimated or confirmed) reported between the two studies selected in this review reflect the very different populations studied and the different methods used to screen for PAH. Nonetheless, both studies emphasize that without screening protocols, the diagnosis of PAH

will be missed in a significant proportion of patients with scleroderma-spectrum disorders.

Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease

Trad S, Amoura Z, Beigelman C, *et al. Arthritis Rheum* 2006; **54**: 184–91

Background. The aim of this retrospective study was to investigate whether PAH predicts mortality in patients with the diffuse cutaneous subtype of SSc, independent of interstitial lung disease. In addition, the authors examined, in a subset of patients, the effect of cyclophosphamide on outcome. Patients with dcSSc were included on the basis that they had been seen between 1980 and 2004, and had had both high-resolution computed tomography (HRCT) and echocardiography at the time of diagnosis of SSc. Interstitial lung disease was defined on the basis of appearances on HRCT. Peripheral arterial hypertension was defined as an estimated pulmonary artery systolic pressure on echocardiography of ≥45 mmHg.

Interpretation. Eighty-six patients with dcSSc were included. Fifty-two (60%) had interstitial lung disease on HRCT and 18 (21%) had PAH as defined above (median pulmonary artery systolic pressure 48 mmHg, range 45–106), all except three in association with interstitial lung disease. Seventeen patients (20%) died, 10/52 (19%) with interstitial lung disease and 9/18 (50%) with PAH, including all three with 'isolated' PAH. By univariate analysis, survival was reduced in patients with PAH compared with those without ($P = 0.004$) but not in those with interstitial lung disease compared with those without ($P = 0.62$) (Fig. 11.3a and b). Multivariate analysis showed that in both the whole cohort of 86 patients and in the 52 patients with interstitial lung disease, age at SSc diagnosis and PAH were the only two independent risk factors for death, with PAH the more significant: hazard ratio for PAH was 4.09 (95% CI 1.47–11.5, $P = 0.007$) for

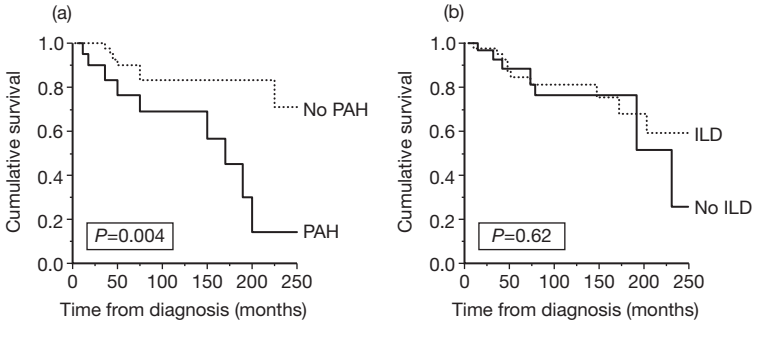

Fig. 11.3 Kaplan–Meier graphs of survival in patients with diffuse cutaneous systemic sclerosis, according to the presence or absence of pulmonary arterial hypertension (PAH) (a) and interstitial lung disease (ILD) (b). Survival analysis was performed by univariate analysis using a log-rank test. Source: Trad *et al.* (2006).

the whole cohort, and 5.07 (95% CI 1.09–23.8, $P = 0.038$) for those with lung disease. Comparison of lung function and HRCT findings in the 52 patients with interstitial lung disease with and without PAH showed: (a) similar lung volumes but reduced diffusing capacity of the lung for carbon monoxide (DLCO) (% predicted) in the group with PAH; and (b) no significant differences in the extent of interstitial lung disease, the proportion of ground-glass shadowing and the extent of fibrosis, although there was a trend ($P = 0.09$) towards greater 'disease extent' in the PAH subset. Of the 20 patients with interstitial lung disease treated with cyclophosphamide, eight had PAH. Pulmonary artery pressure rose during and after cyclophosphamide treatment.

Comment

Most of the recent interest in pulmonary hypertension in SSc has focused on patients with 'isolated' PAH. This study is therefore of interest because it seeks to investigate some of the inter-relationships between pulmonary hypertension and interstitial fibrosis, both life-threatening complications of disease, in patients with the dcSSc. A key issue is whether there is a significant pulmonary vascular component to the raised pulmonary artery pressure in patients with dcSSc. This is an interesting question because, as a generalization, patients with dcSSc tend to have a more fibrotic component to their disease, whereas patients with lcSSc tend to have more marked vascular abnormalities, including severe Raynaud's phenomenon and telangiectases.

The authors interpret their findings as showing that raised pulmonary artery pressure is a major predictor of survival in dcSSc. There is no doubt that those with raised estimated pulmonary artery systolic pressure on echocardiography of ≥45mmHg did badly: 9 of 18 patients in this group died. What is more difficult to be confident about from the data presented is the (lack of) inter-relationship between this raised pressure and the extent of interstitial disease because of: (a) the reliance of a single estimated pulmonary artery pressure to define two groups within the interstitial lung disease cohort; and (b) the relatively small numbers (only 15 patients with raised estimated pulmonary artery pressure). Regarding the data on cyclophosphamide, again these have to be viewed in the context of a retrospective study without a control group. Nonetheless, the data provide some evidence that pulmonary artery pressure continues to rise despite treatment with cyclophosphamide.

Despite its limitations, the study has been selected not only because it emphasizes that a raised estimated pulmonary artery pressure in a patient with dcSSc is a bad prognostic sign, but also because it highlights the complexities of disentangling the relative contributions of interstitial lung disease and pulmonary vascular disease to prognosis. Prospective studies are required to elucidate further the natural history and pathophysiology of pulmonary hypertension in dcSSc in order to inform new treatment approaches, which, as suggested by the authors, might include vasoactive treatments.

Systemic sclerosis associated pulmonary hypertension: improved survival in the current era

Williams MH, Das C, Handler CE, *et al. Heart* 2006; **92**: 926–32

Background. The aim of this longitudinal study was to measure survival, haemodynamic function and functional class in patients with SSc-associated PAH in two treatment eras (before and after 2002) and to compare results between groups. From a total population of 185 patients with SSc–PAH diagnosed between 1998 and 2004, 93 were excluded on the basis of being in World Health Organization (WHO) functional class I or II, having significant pulmonary fibrosis, or having significant haemodynamic compromise. Of the 92 remaining patients, 47 were included in the 'historical control' group and 45 in the 'current treatment' group. Data were collected both retrospectively and prospectively. All patients were treated with standard treatment (diuretics, digoxin, oxygen and warfarin). 'Advanced' treatment was added when clinically indicated: prostanoid therapy in the historical control group and one of a range of treatments (usually bosentan) in the current treatment group.

Interpretation. Survival (Kaplan–Meier) at 1 and 2 years was 68% and 47% in the historical control group, and 81% and 71% in the current treatment group ($P = 0.016$) (Fig. 11.4). Pulmonary vascular resistance increased in the historical control group but remained stable in the current treatment group ($P < 0.006$). Two patients in the historical control group received bosentan. Fourteen patients in the current treatment group who were initially commenced on bosentan were subsequently treated with prostanoid. The authors interpreted their findings as the first to show survival advantage in SSc–PAH in the current treatment era.

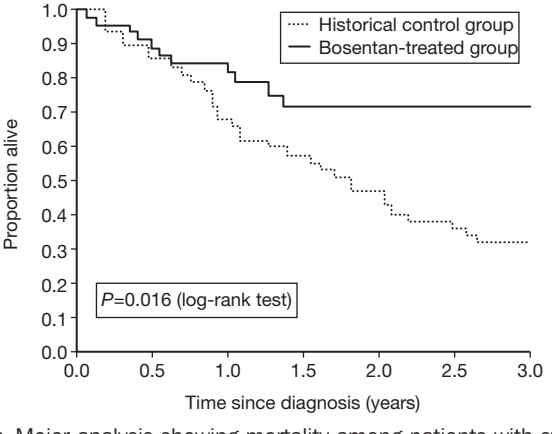

Fig. 11.4 Kaplan–Meier analysis showing mortality among patients with systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH). Historical group: 1-year survival 68%, 2-year survival 47%; current treatment era group: 1-year survival 81%, 2-year survival 71%. Source: Williams *et al.* (2006).

Comment

This was not a controlled clinical trial, but rather an open study that included a large retrospective component, and it therefore has a number of limitations, as discussed by the authors. Nonetheless, its findings are of considerable interest, the key point being that they suggest that survival in moderately severe SSc-PAH (WHO functional classes III and IV) is improved in the current treatment era. The authors are careful to state that it is not possible, because of the design of the study, to ascribe this improved survival to any one particular agent but rather it should be attributed to the more aggressive general approach to treatment. An important point is that the interval between diagnosis of PAH and commencement of advanced treatment (either prostanoid or bosentan) was significantly shorter in the current treatment group (mean delay in the current treatment group 36 days compared with 72 days in the historical control group, $P < 0.0001$), and the delay of 72 days in the historical control group relates only to the 27 patients in this group selected to commence prostanoid. The earlier treatment in the current treatment group may have had an important bearing on results. The conclusions of the study (as discussed by the authors) are not applicable to those patients who did not satisfy the entry criteria – those with less severe (WHO functional classes I and II) or end-stage disease.

The take-home message for the practising rheumatologist is that these findings complement those of controlled clinical trials suggesting that patients with SSc-PAH may benefit from 'advanced' treatments, and emphasize the need for early diagnosis and assessment to allow optimization of treatment protocols.

Clinical trials

In the past 18 months only a small number of clinical trials has been published. Both those included here relate to specific or 'organ-based' manifestations – interstitial lung disease and Raynaud's phenomenon – rather than to modification of the underlying disease process, although the distinctions between these are not absolute. For example, cyclophosphamide is likely to have had a beneficial effect on disease process beyond the lungs as evidenced, in the paper by Tashkin and colleagues, by the fall in skin score in the active treatment group.

Cyclophosphamide versus placebo in scleroderma lung disease

Tashkin DP, Elashoff R, Clements PJ, *et al. N Engl J Med* 2006; **354**: 2655–66

Background. The aim of this multicentre, double-blind, randomized, controlled clinical trial was to examine efficacy and safety of oral cyclophosphamide in SSc-related interstitial lung disease. Thirteen centres in the USA participated. Patients were prescribed oral cyclophosphamide (≤2mg/kg) or matching placebo for 12

months then followed for a further year. The primary endpoint was the forced vital capacity (FVC) at 12 months, adjusted for baseline FVC. Other endpoints included (adjusted for baseline values) total lung capacity, DLCO, the disability index of the Health Assessment Questionnaire (HAQ) and the Short Form-36 (SF-36).

Interpretation. One hundred and fifty-eight patients were included on the basis of their bronchoalveolar lavage fluid, appearances on HRCT scanning, or both. Of these, 145 completed at least 6 months' treatment and were included in the analysis. The adjusted mean difference in FVC at 12 months between the cyclophosphamide and placebo groups was 2.53% (95% CI 0.28–4.79) in favour of cyclophosphamide ($P < 0.03$). In the placebo group, there was a greater fall in FVC over time among those who had the more severe fibrosis scores at baseline (Fig. 11.5a), suggesting that cyclophosphamide protected against the decrease in FVC in patients with fibrosis. A greater percentage of patients in the cyclophosphamide group had an improvement from baseline in FVC ($P < 0.01$) (Fig. 11.5b). Significant differences between the two treatment groups (favouring cyclophosphamide) were also seen in total lung capacity, dyspnoea, HAQ and skin scores, but not in gas transfer. There were more adverse events in the cyclophosphamide group but the difference between groups in the number of serious adverse events was not significant.

Comment

This is the first double-blind, placebo-controlled clinical trial to report on safety and efficacy of cyclophosphamide in SSc-related interstitial lung disease and during the period under review is probably the most important clinical trial in SSc from the practising clinician's perspective. In the past, many clinicians have treated SSc-related lung disease with cyclophosphamide on the basis of retrospective series and anecdotal reports. This study provides a stronger evidence base for this approach, and its findings are supported by those of a UK study |**14**|, published after the review period, which showed some benefit with intravenous cyclophosphamide (switching after 6 months to azathioprine) in combination with low-dose prednisolone.

It should be noted, however, that, as the authors themselves state and as discussed in an accompanying editorial |**15**|, the benefit from oral cyclophosphamide was only modest and must be weighed against the substantial potential toxicity of cyclophosphamide. Although serious adverse effects were not increased in the cyclophosphamide group, as the authors point out the potential long-term side-effects of cyclophosphamide were not evaluated, and even within the study period three patients in the cyclophosphamide group developed malignancies. Ten patients developed haematuria, one of whom required urinary diversion. Consideration should be given to intravenous administration of cyclophosphamide, as used in the UK study, as the cyclophosphamide is then given in lower dosage and is less likely to be associated with serious adverse effects. With this in mind, an important finding from the study is the interaction between fibrosis and treatment (Fig. 11.5a) suggesting that patients with the more severe fibrosis scores were most likely to benefit. Therefore, this is a factor to be taken into account when deciding whether or not to recommend cyclophosphamide. A limitation of the study was the high drop-out rate: of the 79 patients assigned to cyclophosphamide, only 54 completed, and of the 79 assigned to placebo, only 55 completed.

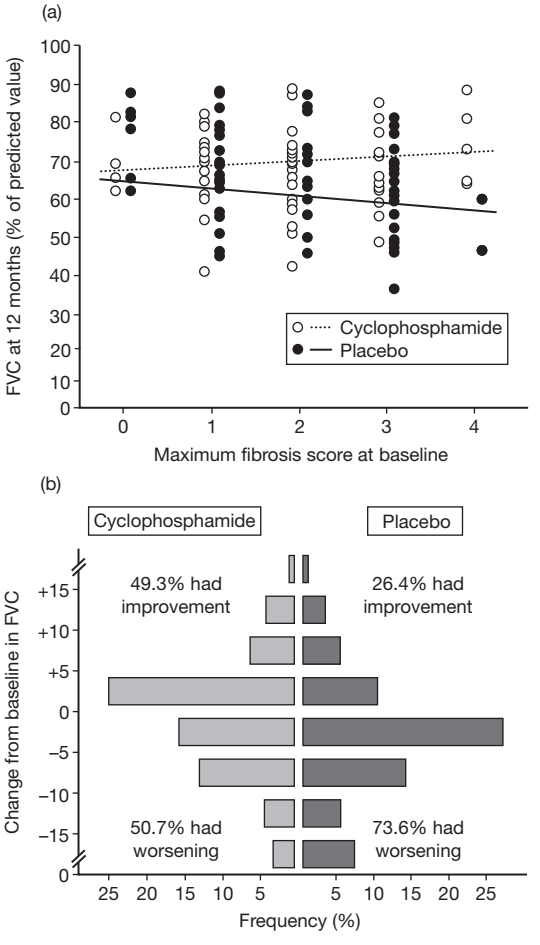

Fig. 11.5 The percentage of predicted FVC at 12 months and changes in the percentage of predicted FVC from baseline to 12 months. (a) Scattergram of the FVC at 12 months (adjusted for the baseline FVC) according to treatment compared with the maximal fibrosis score as determined on baseline thoracic high-resolution CT in 69 patients in the cyclophosphamide group and 71 in the placebo group whose scans were scored by two independent radiologists who were unaware of the treatment assignments. The slope of the regression is significant in the placebo group (−2.01% of the predicted FVC per unit score for fibrosis, $P = 0.006$) but not in the cyclophosphamide group (0.96% of the predicted FVC per unit score for fibrosis, $P = 0.26$); the difference in the slopes between the two groups was significant ($P = 0.009$). (b) The change in the FVC from baseline to month 12 in each of 145 patients who could be evaluated is displayed as a histogram according to treatment and absolute increments or decrements of 5% of the predicted value. All changes of 15% or more are grouped, and imputed values were used for patients who completed at least the 6-month evaluation but did not return for the 12-month visit. A significantly greater percentage of patients in the cyclophosphamide group than in the placebo group (49.3% vs. 26.4%) exhibited any improvement in the FVC ($P < 0.01$); conversely, a significantly greater percentage of those in the placebo group than in the cyclophosphamide group (73.6% vs. 50.7%) exhibited any worsening of the FVC ($P < 0.01$ by Fisher's exact test). Source: Tashkin *et al.* (2006).

In conclusion, as a result of this study and of the UK Fibrosing Alveolitis in Scleroderma Trial |**14**|, clinicians may feel more comfortable about recommending cyclophosphamide in carefully selected patients with SSc-related interstitial lung disease, especially in those with significant fibrosis on HRCT. However, benefit was modest and clinicians and scientists must continue to strive together to identify more effective management strategies, which will probably involve early identification of those patients most likely to progress.

Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy

Fries R, Shariat K, von Wilmowsky H, Bohm M. *Circulation* 2005; **112**: 2980–5

Background. Sildenafil is a phosphodiesterase-5 inhibitor, which vasodilates by enhancing the effect of nitric oxide through inhibition of the degradation of cyclic guanosine monophosphate. The aim of this study was to examine its efficacy in Raynaud's phenomenon in a double-blind, placebo-controlled cross-over study. Twenty patients were recruited, but results are presented only from the 18 who completed the 8-week study period. Patients were randomized to 4 weeks of either sildenafil 50 mg twice daily or placebo then crossed over (after a 1-week washout) to the other treatment. Fourteen patients had SSc, two mixed connective tissue disease and two primary Raynaud's phenomenon. All patients had previously reported no benefit from at least two other vasodilators.

Interpretation. Among the 16 patients with secondary Raynaud's, frequency of attacks was lower ($P = 0.0064$), cumulative attack duration shorter ($P = 0.0038$) and Raynaud's Condition Score lower ($P = 0.0386$) on sildenafil compared with placebo. These symptomatic improvements were associated with significant increases in capillary perfusion as measured by a laser Doppler anemometer (approximately fourfold increases on sildenafil). The two patients with primary Raynaud's also experienced improvements in symptoms and in microvascular flow. Of the six patients with digital ulcers, all were reported to experience some healing on sildenafil (in two healing was complete), whereas ulcer healing was not observed with placebo. All patients were able to state correctly in which order they received the two treatments. Two patients discontinued treatment because of side-effects (headache, muscle pain).

Comment

This was a small study and not truly blinded, all patients correctly 'guessing' their order of treatment, therefore its findings must be interpreted with caution. Nonetheless, its findings are of considerable interest because there is a good rationale for phosphodiesterase inhibition in Raynaud's phenomenon, as it seems likely that at least in a proportion of patients there is a relative deficiency in nitric oxide |**16**|, and inhibition of phosphodiesterase-5 will maximize nitric oxide effect. A controlled trial of phosphodiesterase inhibition in Raynaud's phenomenon is, therefore, long overdue.

The authors included among their endpoints an objective measure of microvascular flow, which was fortunate given the problems in blinding of treatment. Although the degree of blood flow increase with sildenafil is very striking, it would have added to the study to have reported the authors' experience of the reliability of the technique, because measures of microvascular flow, even under controlled conditions, can be highly variable. The report of ulcer healing is of considerable interest but could be prejudiced by the failure of blinding. While the authors state that the patients studied were 'resistant' to other vasodilators, it is difficult to comment upon this without knowing the dosages and durations of previous therapies.

In conclusion, despite its limitations the study is sufficiently encouraging to suggest that phosphodiesterase inhibitors should be further studied in Raynaud's phenomenon. Future studies should be of longer duration, should include patients over the winter months (the study was performed during summer), and should include a variety of endpoints including objective measures of digital artery and microvascular function.

Conclusion

The 10 papers discussed provide a small window into the intense research activity currently ongoing into the SSc disease process and its treatment. From these papers the following conclusions can be drawn:

1. Huge strides are being made into the molecular and cellular (patho)biology of SSc, and advances in knowledge are suggesting targets for new therapies.
2. Statins may favourably modify both the fibrosis and the vascular abnormalities of SSc, and are an exemplar of how drugs licensed for other indications may have mechanisms of action that favourably influence the SSc disease process.
3. Development and validation of outcome measures for the different aspects of SSc continue to be a major area of international effort.
4. The development of new therapies for PAH means that clinicians must screen all patients – with either lcSSc or dcSSc – to identify those eligible for treatment, some of whom will have concomitant interstitial fibrosis. Peripheral arterial hypertension has a high mortality and identifying predictors for which patients with early/mild PAH are likely to progress, and how best to treat such patients with early but progressive disease, will be a focus of clinical research over the next 10 years.
5. Two recent clinical trials have suggested modest benefit from cyclophosphamide in SSc-related interstitial lung disease. In addition, these two studies demonstrate the high level of collaboration between centres with an interest in SSc, auguring well for further clinical trials investigating treatment response. These trials will include those investigating newer vasoactive treatments for SSc-related Raynaud's phenomenon.

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12

Anti-neutrophil cytoplasmic antibody-associated vasculitis

SANDEEP BAWA, CHETAN MUKHTYAR, RAASHID LUQMANI

Introduction

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS) are idiopathic vasculitides characterized by inflammation of small vessels and their subsequent occlusion, leading to tissue necrosis. Histologically, they are united by their pauci-immune nature, which differentiates them from other small vessel vasculitides like Henoch–Schonlein purpura and cryoglobulinaemia. Together they are termed anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AASV). Anti-neutrophil cytoplasmic antibody was described in the 1980s |**1**|, and the presence of specific patterns of ANCA (cytoplasmic ANCA directed against proteinase 3 and perinuclear ANCA directed against myeloperoxidase) is 85% sensitive and 99% specific for the diagnosis of AASV |**2**|. Clinically, the presence of ANCA in the setting of a pulmonary–renal syndrome should raise the suspicion of AASV. Anti-neutrophil cytoplasmic antibody may be negative in a significant proportion of patients, especially certain subsets of the AASV, e.g. localized WG, CSS |**3,4**|.

The incidence of AASV is 10–20/million per year |**5**|. Northern hemispheric data suggest that WG is commoner than MPA in the northern latitudes and the opposite is true nearer to the equator |**5**|. The average survival of patients with untreated WG is 5 months |**6**|. The introduction of cyclophosphamide and glucocorticoids made remission an achievable outcome |**7**|. As a result of the high morbidity of cyclophosphamide there is a continuous search for alternative therapies to induce and maintain remission in vasculitis. Co-trimoxazole (trimethoprim/sulfamethoxazole), methotrexate, azathioprine, mycophenolate mofetil, etanercept, infliximab, rituximab, immunoglobulin, have all been used with varying success |**8–15**|. The current standard of care for AASV is remission induction with intravenous or oral cyclophosphamide and glucocorticoids in most cases. In some instances it may be acceptable to treat with glucocorticoid monotherapy |**16**|. Remission is usually maintained with azathioprine or methotrexate |**13,17**|.

Epidemiology

The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a southern hemisphere region

Gibson A, Stamp LK, Chapman PT, O`Donnell JL. *Rheumatology* 2006; **45**: 624–8

Background. Three hospital clinical databases and the immunology laboratory database were searched and case notes reviewed for patients fulfilling either the 1990 American College of Rheumatology criteria for WG or a modification of those criteria that allowed for ANCA positivity in the absence of granulomatous vasculitis. Microscopic polyangiitis was defined by the Chapel Hill consensus definition; however, in the absence of histological evidence of pauci-immune glomerulonephritis, ANCA positivity in association with evidence of active glomerular disease was included as a criterion. The point prevalence at 31 December 2003 and the 5-year period prevalence for the interval 1 January 1999 to 31 December 2003 were calculated using 2001 census data as the denominator. Ninety-one per cent of the Canterbury population from which the study was conducted, described themselves as New Zealand-European.

Interpretation. Seventy-three patients with WG and 28 patients with MPA fulfilled the inclusion criteria. The 5-year period prevalence for WG was 152 cases/million (95% confidence interval [CI] 117–186) and for MPA, 58 cases/million (95% CI 37–80). Nineteen patients with WG and 10 patients with MPA died during the study period, resulting in a point prevalence for survivors at 31 December 2003 of 112 cases/million (95% CI 82–142) and 37 cases/million (95% CI 20–55) respectively. Using unmodified ACR criteria the 5-year period and point prevalence for WG were 131/million (95% CI 99–163) and 93.5/million (95% CI 66–121) respectively. Apart from respiratory tract involvement in WG, which formed part of the case definition and was therefore always present, organ involvement was similar in both diseases.

Comment

The prevalence of WG and MPA has been calculated to be 24–157/million and 9–66/million, respectively, from a number of studies |**5**|. The data vary depending on the application of different classification systems and the lack of a clear definition of MPA until 1994 |**18**|. There may be a latitudinal effect on the prevalence of AASV. Wegener's granulomatosis is reported to be more common than MPA in northern Europe than it is in southern Europe or Asia |**5**|. Geographically, Christchurch, New Zealand (43°S), is comparable with Lugo, Spain (43°N), but the disease profiles as reported from Christchurch are closer to that of Norwich, UK (52° N) (Table 12.1). The data are not directly comparable and further reporting from the southern hemisphere may help to clarify the latitudinal effect.

Table 12.1 A comparison of incidence and prevalence rates of Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) in Christchurch, Lugo and Norwich

Place	Latitude	Incidence		Prevalence	
		WG	MPA	WG	MPA
Christchurch	43ºS	No data	No data	112	37
Lugo (Gonzalez-Gay |**19**|)	43ºN	4.9	11.6	No data	No data
Norwich (Watts |**5**|)	52ºN	10.2	5.8	109	28

Figures are per million population.

Investigations

Prevalence and clinical significance of anti-neutrophil cytoplasmic antibodies in CSS

Sinico RA, Di Toma L, Maggiore U, *et al. Arthritis Rheum* 2005; **52**: 2926–35

Background. Churg–Strauss syndrome is classified among the ANCA-associated systemic vasculitides because of its clinico-pathologic features that overlap with the other AASV. However, while ANCAs are consistently found in 75–95% of patients with WG or MPA, their prevalence in CSS varies widely and their clinical significance remains uncertain. This study was undertaken to examine the prevalence and antigen specificity of ANCA in a large cohort of patients with CSS. Moreover, the relationship between ANCA positivity and clinico-pathologic features was evaluated. Immunofluorescence and enzyme-linked immunosorbent assays were used to determine the presence or absence of ANCA in 93 consecutive patients at the time of diagnosis. The main clinical and pathologic data, obtained by retrospective analysis, were correlated with ANCA status. Due to the high prevalence of asthma, this feature was not compared in the analysis.

Interpretation. Anti-neutrophil cytoplasmic antibodies were present by immunofluorescence in 35 of 93 patients (37.6%). A perinuclear ANCA (P-ANCA) pattern was found in 26 of 35 patients (74.3%), with specificity for myeloperoxidase (MPO) in 24 patients, while a cytoplasmic ANCA (C-ANCA) pattern, with specificity for proteinase 3 (PR3), was found in 3 of 35 patients (8.6%). Atypical patterns were found in 6 of 30 patients with anti-MPO antibodies (20.0%). Anti-neutrophil cytoplasmic antibody positivity was associated with higher prevalence of renal disease (51.4% vs. 12.1%, $P < 0.001$) and pulmonary haemorrhage (20.0% vs. 0.0%, $P = 0.001$) and, to a lesser extent, with other organ system manifestations (purpura and mononeuritis multiplex), but with lower frequencies of other lung manifestations (34.3% vs. 60.3%, $P = 0.019$) and cardiac involvement (5.7% vs. 22.4%, $P = 0.042$).

Anti-neutrophil cytoplasmic antibodies and CSS

Sable-Fourtassou R, Cohen P, Mahr A, *et al.* for the French Vasculitis Study Group. *Ann Intern Med* 2005; **143**: 632–8

Background. Although testing for ANCA is widely available in routine practice, there are no large studies of the prevalence of ANCA in CSS. The objective of this study was to define the clinical and biological characteristics of newly diagnosed CSS, according to the presence or absence of ANCA. A cross-sectional analysis of manifestations was performed on 112 patients with CSS. The authors compared principal demographic, clinical, and laboratory features according to ANCA status at diagnosis.

Interpretation. Anti-neutrophil cytoplasmic antibodies were present in 43 (38%) patients. Thirty-nine patients had a perinuclear ANCA staining pattern and four patients had cytoplasmic ANCA staining patterns. Of the 34 patients with P ANCA who were tested for specificity, 100% had anti-MPO specificity. Anti-neutrophil cytoplasmic antibody-positive patients showed higher rates of biopsy proven vasculitis (79% vs. 39%) compared with ANCA-negative patients. Anti-neutrophil cytoplasmic antibody-positive patients had a higher incidence of peripheral neuropathy (84% vs. 65%), and renal involvement (35% vs. 4%) compared with ANCA-negative patients, but a lower incidence of cardiac manifestations (12% vs. 49%) and symptoms of fever (30% vs. 55%).

Comment

Although clinical trials of AASV have often excluded CSS, there is ample evidence that CSS is associated with ANCA |**4**|. These two studies have shown the presence of the typical diagnostic pattern of ANCA in a significant number of cases of CSS. Combining these two studies, 205 patients with CSS were tested for ANCA and a classic cytoplasmic or perinuclear immunofluorescence was seen in 72 patients (35%). Of the 200 patients who also underwent ELISA testing for MPO or PR3 specificity, 60 patients (30%) had the typical pattern of C/PR3 ANCA or P/MPO ANCA (Table 12.2). This pattern has been shown to be 89% sensitive and 99% specific for a diagnosis of AASV, including CSS in a meta-analysis |**2**|. The above studies have also shown a relationship between the presence of typical ANCA positivity and a more aggressive phenotype of CSS. Renal involvement and especially rapidly progressive glomerulonephritis appears to be strongly associated with the presence of ANCA (Table 12.3). However, care has to be taken in interpreting the phenotypic relationship of the disease with ANCA as all the relationships are univariate, and thus prone to statistical errors. The Italian study (Sinico *et al.*) reports that lung manifestations (apart from asthma which was present in almost all the patients), were more common in ANCA-negative patients.

Table 12.2 Pooled analysis of incidence of anti-neutrophil cytoplasmic antibody (ANCA) in Churg–Strauss syndrome

Study	No. of patients tested	Classical C- or P-ANCA on IIF	C/PR3 ANCA or P/MPO ANCA
Sinico *et al.* 2005	93	29 (31%)	27 (29%)
Sable-Fourtassou *et al.* 2005	112	43 (38%)	33 (31%)*
Total	205	72 (35%)	60 (30%)†

*Five patients were not tested for antigen specificity; the figures are based on an analysis of 107 patients.
†Figures based on 200 patients.
C ANCA, cytoplasmic anti-neutrophil cytoplasmic antibody; IIF, indirect immunofluorescence; MPO, myeloperoxidase; P ANCA, perinuclear anti-neutrophil cytoplasmic antibody; PR3, proteinase 3.

Serial ANCA determinations for monitoring disease activity in patients with ANCA-associated vasculitis: systematic review

Birck R, Schmitt W, Kaelsch A, van der Woude FJ. *Am J Kidney Dis* 2006; **47**: 15–23

Background. Anti-neutrophil cytoplasmic antibodies are considered to be sensitive markers of disease activity and have been suggested to predict relapse and guide therapeutic decisions. Studies using serial ANCA monitoring in patients with AASV have yielded controversial results during the last 15 years. A systematic review was conducted to assess the diagnostic value of serial ANCA testing in the follow-up of patients with AASV. Studies were identified by a comprehensive search of the Pubmed and BIOSIS+/RRM databases, as well as hand-searching. Method quality of all eligible studies was assessed with respect to external and internal validity according to established criteria for diagnostic studies.

Interpretation. Twenty-two studies including a total of 950 patients, out of 3611 papers, met the inclusion criteria. Assessment of internal validity showed that only four studies reported the combination of consecutive patient recruitment, prospective data collection, and independent determination of both index and reference tests, considered as the ideal for diagnostic test studies. Quantitative meta-analyses were not conducted because of the presence of considerable method heterogeneity.

Comment

The main purpose of monitoring a patient is to identify a change in the clinical state. A rise in the titre of C/PR3 ANCA during remission is an independent risk factor for relapse of disease in WG |**20**|. Similar disease-specific data are lacking for MPA and CSS. The toxicity of the remission-induction regimens precludes their use in

Table 12.3 Phenotypic differences between ANCA-positive and negative patients (with permission from Sinico *et al.* 2005)*

	ANCA-positive ($n = 35$)	ANCA-negative ($n = 58$)	P†
Asthma	34 (97.1)	55 (94.8)	1.00
Constitutional symptoms	30 (85.7)	33 (56.9)	0.006
Sinusitis	27 (77.1)	45 (77.6)	1.00
Skin involvement	21 (60.0)	28 (48.3)	0.29
Purpura	9 (25.7)	4 (6.9)	0.015
Lung involvement, all kinds	12 (34.3)	35 (60.3)	0.019
Pulmonary haemorrhage	7 (20.0)	0 (0.0)	0.001
Heart involvement	2 (5.7)	13 (22.4)	0.042
Gastrointestinal involvement	7 (20.0)	13 (22.4)	1.00
Peripheral neuropathy, all kinds	25 (71.4)	35 (60.3)	0.37
Mononeuritis multiplex	18 (51.4)	14 (24.1)	0.013
CNS involvement	6 (17.1)	7 (12.1)	0.54
Renal involvement	18 (51.4)	7 (12.1)	< 0.001
RPGN	10 (28.6)	3 (5.2)	0.004
ACR criteria	30 (85.7)	55 (94.8)	0.15
Lanham's criteria	30 (85.7)	47 (81.0)	0.78
Eosinophilia > 10%	32 (91.4)	56 (96.6)	0.36
Eosinophils/mm^3, median (range)	4881 (1074–28815)	3544 (600–25637)	0.51
BVAS, 0–63, median (range)	22 (7–40)	17 (6–40)	0.15
DEI, 0–21, median (range)	6 (3–10)	6 (3–10)	0.85
VDI, 0–11, median (range)	0 (0–2)	0 (0–5)	0.30
FFS ≥ 2	9 (25.7)	7 (12.1)	0.15

*Except where otherwise indicated, values are the number (%) of patients.
†Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables.
ANCA, anti-neutrophil cytoplasmic antibody; ACR, American College of Rheumatology; BVAS, Birmingham Vasculitis Activity Score; CNS, central nervous system; DEI, Disease Extent Index; FFS, five-factor score; RPGN, rapidly progressive glomerulonephritis; VDI, Vasculitis Damage Index.
Source: Sinico *et al.* (2005).

patients simply based on a rise in the ANCA titre, because a significant proportion of patients with a rise in the ANCA titre will not develop a relapse |**20**|. A meta-analysis of the validity of serial ANCA monitoring was needed to clarify the issue. The authors were unable to comment on the issue due to the heterogeneity of the studies that did not allow for adequate comparisons to be made. Anti-neutrophil cytoplasmic antibody associated vasculitis is rare with an estimated incidence of 10–20/million per year |**5**|. In the past, this meant that clinical trials were single-centred and underpowered with heterogeneous cohorts. The results derived from such studies were often inconclusive; collaborative clinical trials have solved some of these problems. The European League Against Rheumatism (EULAR) and the European Vasculitis Study group (EUVAS) have also developed recommendations for the conduct of clinical trials in vasculitis, which should make future meta-

analyses meaningful |**21**|. Although no conclusions could be reached regarding the efficacy of serial ANCA monitoring, based on currently available evidence (Birck *et al.* 2006), there is no current evidence to support a role for serial ANCA testing as a sole guide to therapy. This is controversial and will remain so until it has been adequately addressed in a well-designed, prospective analysis.

Urine IgM excretion predicts outcome in ANCA-associated renal vasculitis

Bakoush O, Segelmark M, Torffvit O, *et al. Nephrol Dial Transplant* 2006; **21**: 1263–9

Background. Renal function at diagnosis is a strong predictor not only of renal survival but also of patient survival in patients with AASV. Apart from abnormal renal function at diagnosis, there are no other established risk factors for renal outcome in AASV. It has been previously reported that in other forms of glomerular diseases, an increased urine excretion of IgM is an early marker of poor renal outcome. In this single-centre observational study, the prognostic significance of urine IgM excretion and other selected prognostic markers was studied in 83 consecutive patients (49 males, 34 females) with AASV with renal involvement.

Interpretation. Patient survival at 1 and 5 years was 93 and 77%, respectively, and the corresponding figures for renal survival censored for death were 84 and 76%. Univariate analysis indicated that patient survival was inversely associated with older age, male gender, raised serum creatinine, low serum albumin and high urine IgM excretion at presentation. Renal survival was inversely associated with raised serum creatinine, and the presence of albuminuria and urine IgM at presentation. In multivariate analysis, older age (> 65) and high urine IgM excretion were independent predictors of patient survival [odds ratio (OR) = 11.2 and 4.4, respectively, $P < 0.01$]. Urine excretion of IgM was the only independent predictor of end-stage renal disease (OR = 19.8, $P = 0.004$). Overall, 35% had a poor outcome of either death or renal replacement therapy. Urine IgM excretion was the strongest individual predictor of such an outcome (OR = 7.7, $P = 0.009$).

Comment

Proteinuria > 1g/day is an independent risk factor for developing renal failure in WG |**22**|. It is also part of the five-factor score and thus its presence confers an adverse prognosis for overall survival |**23**|. Other renal factors that adversely influence either renal or overall survival in WG are dialysis dependence at diagnosis |**22**|; a rise in serum creatinine of 100 μmol/l |**22**|; and renal involvement at diagnosis |**24**|. Renal impairment is a risk factor for mortality in MPA |**25**|. Urinary IgM was calculated as a spot urine sample in this study by Bakoush and colleagues. Patients who were high urine IgM excretors (> 0.05 mg/l) were at an increased risk of renal failure and death compared with low urine IgM excretors in multivariate analysis (Fig. 12.1).

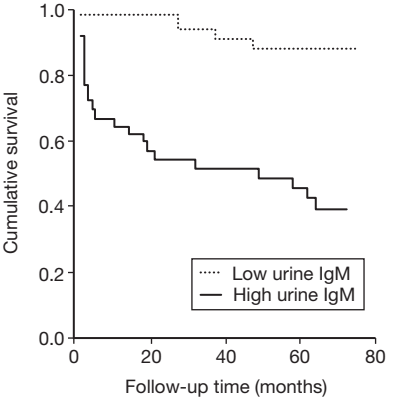

Fig. 12.1 Cumulative composite outcome of death or end-stage renal disease (ESRD) for 83 patients with AASV, as a function of urine IgM excretion < 0.05 or > 0.05 mg/l. Source: Bakoush *et al.* (2006).

It would have been interesting to compare the urinary IgM excretion with 24-h urinary protein, which has been the traditional form of laboratory investigation, with a view to using the spot urine test in place of the more cumbersome 24-h collection. The authors postulate that urine IgM excretion is a marker of active disease, while serum creatinine reflects cumulative glomerular damage. This finding needs to be corroborated in further clinical trials with an assessment of its likely impact on treatment and a direct comparison with more traditional forms of monitoring of renal disease.

Treatment

Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic anti-neutrophil cytoplasmic antibody-associated vasculitis

De Groot K, Rasmussen N, Bacon PA, *et al*. *Arthritis Rheum* 2005; **52**: 2461–9

Background. Standard therapy for AASV with cyclophosphamide and prednisolone is limited by toxicity. A non-blinded, prospective, randomized, controlled trial was undertaken to determine whether methotrexate could replace cyclophosphamide in the early treatment of AASV. Patients with newly diagnosed AASV, with serum creatinine levels $< 150\,\mu$mol/l, and without critical organ manifestations of disease were randomized to receive either standard oral

cyclophosphamide, 2 mg/kg/day or oral methotrexate, 20–25 mg/week; both groups received the same prednisolone regimen. All drug treatments were gradually tapered and withdrawn by 12 months. Follow-up continued to 18 months. The primary endpoint was the remission rate at 6 months (non-inferiority testing).

Interpretation. One hundred patients were recruited from 26 European centres; 51 patients were randomized to the methotrexate group and 49 to the cyclophosphamide group. At 6 months, the remission rate in patients treated with methotrexate (89.8%) was not inferior to that in patients treated with cyclophosphamide (93.5%) ($P = 0.041$). In the methotrexate group, remission was delayed among patients with more extensive disease ($P = 0.04$) or pulmonary involvement ($P = 0.03$). Relapse rates at 18 months were 69.5% in the methotrexate group and 46.5% in the cyclophosphamide group; the median time from remission to relapse was 13 months and 15 months respectively ($P = 0.023$, log-rank test). Two patients from each group died. Adverse events (mean 0.87 episodes/patient) included leukopenia, which was less frequent in the methotrexate vs. the cyclophosphamide group ($P = 0.012$), and liver dysfunction, which was more frequent in the methotrexate group ($P = 0.036$).

Comment

The use of oral cyclophosphamide for remission induction of WG and MPA has never been subjected to the scrutiny of a randomized, controlled trial. But the evidence from open-labelled studies has been convincing |**26,27**|. The use of cyclophosphamide is associated with significant toxicity leading to a search for alternative agents. Prior to this trial, the use of methotrexate in WG was supported by an open-label study |**14**|. The study by de Groot and colleagues (2005) provides further evidence for the role of methotrexate in non-renal WG and MPA. The outcome measures from the two arms are summarized in the table below (Table 12.4). One of the criticisms of the study is the inclusion of six patients with MPA, and the failure to stratify the results purely for WG. The difference in the remission rates of the two arms is not statistically significant and probably would remain so on disease specific subanalysis. The higher relapse rate in the methotrexate group suggests that patients should continue remission maintenance therapy for at least 12 months

Table 12.4 Outcome measures in a trial comparing cyclophosphamide and methotrexate as remission induction therapy for anti-neutrophil cytoplasmic antibody associated vasculitis (AASV) (De Groot *et al.*, 2005)

	Remission rate	Time to remission	Relapse	Time to relapse
Cyclophosphamide	43/46 (93%)	3 months (1–9)	20/43 (47%)	15 months (4–17)
Methotrexate	44/49 (90%)	2 months (1–5)	32/46 (70%)	13 months (2–17)
P-value		0.28		0.023

Time to remission and relapse are median values with figures in parentheses representing ranges.
Source: De Groot *et al.* (2005).

following induction of remission |**13**|. More importantly, the study succeeded in finding less toxic remission induction therapy (i.e. avoiding cyclophosphamide) for a subset of WG patients.

Mycophenolate mofetil in anti-neutrophil cytoplasmic antibodies-associated systemic vasculitis

Koukoulaki M, Jayne D. *Nephron Clin Pract* 2006; **102**: c100–7

Background. Mycophenolate mofetil is an immune suppressive initially introduced for the prevention of solid organ allograft rejection that is increasingly used in autoimmune conditions, including vasculitis. This retrospective study evaluated the efficacy and tolerability of mycophenolate mofetil in 51 sequential patients with AASV treated in a single centre between 2001 and 2004.

Interpretation. The mean age of the patients was 54 years and median disease duration was 36 months. A mean of 3.5 systems were involved and the previous median exposure to cyclophosphamide was 9 g. Mycophenolate mofetil was administered either as remission maintenance therapy (29/51, 56.9%) or as treatment for active disease (22/51, 43.1%). The mean duration of mycophenolate mofetil therapy was 20 months and the mean mycophenolate mofetil dose during the first year was 1.6 g/day. Fourteen of 29 (48.3%) of those receiving mycophenolate mofetil for remission maintenance therapy eventually relapsed with a mean time to relapse of 14 months. Of those receiving mycophenolate mofetil for relapsing disease, three failed to respond to therapy while the rest achieved remission by 3.9 months. However, nine of these subsequently flared; mean time to disease flare was 14 months. Mycophenolate mofetil was withdrawn in 28 patients (54.9%) because of treatment inefficacy in 21, severe adverse events in five and intolerance in two. Of the 51 treated, 36 (70.6%) experienced at least one side-effect, namely infections in 24, gastrointestinal side-effects in 12 and psychological events in six patients.

Comment

The use of mycophenolate mofetil for remission induction as well as maintenance in vasculitis has been reported previously in three small studies ($n = 11–14$) |**12,28,29**|. In this retrospective study (Koukoulaki and Jayne 2006), 22 patients with AASV (heterogeneous cohort of WG, MPA and CSS) received mycophenolate mofetil as remission induction therapy; 18 (82%) achieved remission. This result is comparable with the remission rate achieved with oral cyclophosphamide (78%) and i.v. cyclophosphamide (89%) |**30**|. Along with these 18, who continued to receive mycophenolate mofetil, 29 other patients received mycophenolate mofetil as remission maintenance therapy. Of these 47 patients, 12 (26%) relapsed at 12 months with an overall median time to relapse of 14 months (Fig. 12.2). This is higher than the rate of relapse with azathioprine (15.5% at 18 months) |**13**|. The incidence of adverse events was similar to that found with currently used immunomodulator therapies. However, this was a retrospective study and these

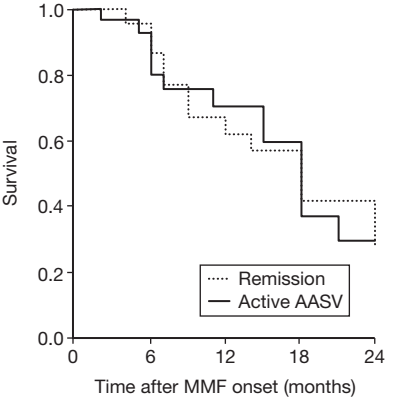

Fig. 12.2 Kaplan–Meier analysis of the time to disease flare following commencement of MMF for remission therapy and active disease. Source: Koukoulaki *et al.* (2006).

results need to be validated in randomized controlled trials. There is evidence that the relapse rates are different for WG and MPA |**13**| and therefore any future trial for remission maintenance therapy should report a disease specific subanalysis |**21**|.

Outcome measures

Deaths occurring during the first year after treatment onset for polyarteritis nodosa, MPA, and CSS: a retrospective analysis of causes and factors predictive of mortality based on 595 patients

Bourgarit A, Le Toumelin P, Pagnoux C, *et al.* for the French Vasculitis Study Group. *Medicine (Baltimore)* 2005; **84**: 323–30

Background. Although combining corticosteroids and cyclophosphamide has greatly improved the prognoses of severe necrotizing vasculitides, some patients continue to have fulminating disease and die within the first year of diagnosis. To evaluate the characteristics of these patients, the files of 60 patients who died within the first year [20 patients with hepatitis B virus-associated polyarteritis nodosa (PAN), 18 with PAN, 13 with MPA, and 9 with CSS] and 535 first-year survivors (89 patients with HBV-PAN, 182 with PAN, 140 with MPA, and 124 with CSS) were studied retrospectively. The two groups were compared for prognostic factors (defined by the five-factor score and Birmingham Vasculitis Activity Score at baseline), clinical signs, treatment, outcome and causes of death.

Interpretation. For first-year non-survivors, the clinical signs predictive of death were as follows: renal involvement (HR 1.6, 95% CI 1.09–2.3) or central nervous system involvement (HR 2.3, 95% CI 1.5–3.7), and there was a trend towards cardiomyopathy

(HR 1.4, 95% CI 1.000–2.115). Older patients died earlier than younger patients (HR 1.04, 95% CI 1.023–1.051). Gastrointestinal symptoms were most frequently associated with early death from HBV-PAN, while 83% of CSS patients died of cardiac involvement. Treatment had no significant impact on early death, except for patients with five-factor score ≥2, for whom glucocorticoid monotherapy was associated with early deaths ($P < 0.05$). The major cause of early death was uncontrolled vasculitis (58%), followed by infection (26%). Cyclophosphamide-induced cytopenia and infection were responsible for two deaths.

Comment

The 1-year survival rates of MPA and CSS in this study were 92% (140/153) and 93% (124/133) respectively. While this is similar to the reported 1-year survival of WG of 85–99% |**22,24,31–33**|, in two other prospective cohorts MPA had a statistically significant poorer survival than WG (5-year survival of 45% vs. 76%, and 63% vs. 91.5%) |**34,35**|. Two risk factors were found to be of particular interest on disease specific subanalysis. They are renal impairment in MPA (HR 3.69, 95% CI 1.006–13.4) and cardiomyopathy in CSS (HR 3.39, 95% CI 1.6–7.3). Renal impairment has previously been identified as a risk factor for mortality in WG (HR 4.45, 95% CI 1.48–13.65) |**24**|. This is the first time that renal insufficiency has been identified as a risk factor for early death in MPA. Cardiac involvement in CSS has previously been identified as a poor prognostic indicator |**36**|. It is also a constituent of the five-factor score which is a prognostic score, along with serum creatinine >1.58 mg/dl, proteinuria >1g/24 h, gastrointestinal tract involvement and central nervous system involvement |**23**|. Twenty-six per cent of deaths occurring in the first year were iatrogenic (Table 12.5). Even though patients with more aggressive disease will have been treated more aggressively, causing inadvertent consequences, this reflects the toxicity of the medication necessary to treat vasculitis and is an incentive to find safer therapies for inducing remission in vasculitis. For those patients who survived the first year, a quarter died from malignancies. None of the malignancies was bladder-related as would have been expected with cyclophosphamide exposure. A longitudinal study looking at long-term outcomes would be interesting to further elucidate the incidence of malignancies in vasculitis.

Damage caused by WG and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET)

Seo P, Min YI, Holbrook JT, *et al.* for WGET Research Group. *Arthritis Rheum* 2005; **52**: 2168–78

Background. This paper examined the occurrence of damage in patients with WG enrolled in the WG Etanercept Trial and correlated the accumulation of damage with disease activity, adverse events, and quality of life. The Vasculitis

Table 12.5 Causes of death of first-year non-survivors and survivors who subsequently died*

Cause of death	First-year non-survivors ($n = 60$)	First-year survivors ($n = 85$)	*P*
Unknown	3/60 (5)	15/85 (18)	
Related to vasculitis	33/57† (58)	26/70† (37)	< 0.05
Acute vasculitis alone	19	13	
Vasculitis plus infection	12	1	
Other	2	12	
Organ-specific involvement			
GI tract	16	1	
Liver	3	0	
Heart	4	8	
Lungs	1	3	
CNS	4	2	
Diffuse vasculitis	5	12	
Treatment side-effect	15/57† (26)	5/70† (7)	< 0.005
Infection	13	3	< 0.005
Cytopenia plus infection	2	0	
Infection site			
Lungs	6	1	
Septicaemia	7	1	
CNS	2	0	
Other	0	3	
Other side-effect	0	2	
Miscellaneous	9/57† (16)	39/70† (56)	< 0.001
Cancer	1 (2)	17 (24)	< 0.005
Bedridden	0	3	
Cardiac insufficiency	0	8	
Other	8	11	

*Values are expressed as *n* (%).
†The denominator is the number of patients for whom the cause of death is known.
CNS, central nervous system; GI gastrointestinal.
Source: Bourgarit *et al.* (2005).

Damage Index (VDI) was applied to all 180 patients at trial entry and every 6 months throughout the trial. Items of damage were analysed by presumed aetiology (i.e. secondary to WG, to therapy, or both) and time of occurrence. The VDI scores 1 point for each item of damage to a maximum of 64. Spearman's rank correlation coefficients were calculated between VDI scores and the Birmingham Vasculitis Activity Score (BVAS) for WG, frequency of flares, number of adverse events, and the patients' quality-of-life assessments.

Interpretation. The mean VDI score was 1.3 at the study enrolment and 1.8 at the end of the trial. This increase was due to damage that occurred despite (or because of) therapy. Damage items included visual impairment, hearing loss, nasal blockade, pulmonary fibrosis, hypertension, renal insufficiency, peripheral neuropathy, gonad failure, and diabetes mellitus. Eighty-nine per cent of the patients had suffered at least one item of damage after 1 year of enrolment. When adjusted for baseline VDI, the baseline BVAS/

WG correlated with the VDI score at 1 year ($r = 0.20$, $P = 0.015$). Increases in adjusted VDI scores also correlated with the number of adverse events, particularly among patients with limited WG ($P = 0.06$).

Comment

Damage in vasculitis is defined as irreversible scarring. In its original concept, all medical events that occurred following the onset of vasculitic symptoms could be recorded as damage if they had been persistent for more than 3 months. Using that principle, the VDI was designed and validated as a typical item list of damage that could be seen in vasculitis or due to its treatment |**37**|. The application of the VDI in this study deviated from the validated pathway in two main respects – the time-limited definition of damage was extended to 6 months from 3 months, and only events that could be attributed to vasculitis or its therapy were recorded. Therefore, by comparison with previous studies of VDI, there is likely to have been an under-reporting of damage in these patients. Previous studies have shown that the presence of a single item of damage increases the resistance to treatment (OR 1.53, 95% CI 1.03–2.27) and reduces survival (HR 5.54, 95%CI 1.28 – 24.05, $P = 0.022$) |**22**|. We also know that early accrual of damage is linked to a poor prognosis. A 6-month VDI score >4 has been shown to be associated with increased mortality rate (OR 12.4, 95%CI 4.2–36.9) |**38**|. This study (Seo *et al.* 2005) has demonstrated that damage is a function of the number of relapses and adverse events. Previous studies have identified that quality of life remains unsatisfactory in WG in spite of clinical remission |**39**|. This study proves that irreversible changes of vasculitis result in an adverse quality of life irrespective of disease activity. The items of damage that have been identified (Table 12.6), including free text items in the 'other' section can be utilized to design an improved damage index |**40**|.

Predictors of relapse and treatment resistance in anti-neutrophil cytoplasmic antibody associated small-vessel vasculitis

Hogan SL, Falk RJ, Chin H, *et al. Ann Intern Med* 2005; **143**: 621–31

Background. Predictors of treatment resistance and relapse have not been well described in AASV. The authors conducted a study to identify clinical, pathological, and serological predictors of treatment resistance and relapse in a community-based cohort of patients with AASV. Patients (350) were identified at or near the time of biopsy diagnosis and followed for a median of 49 months. Patients were categorized according to whether they had anti-PR3 antibodies or anti-MPO antibodies. Organ involvement was determined by biopsy or by well-defined clinical criteria. Treatment resistance was defined as progressive decline in kidney function with active urine sediment or the persistence or appearance of

extra-renal manifestations. Relapse was defined as the time to the resurgence of vasculitic symptoms.

Interpretation. Treatment resistance affected 23% of 334 treated patients and was associated with female sex, black ethnicity, and presentation with severe kidney disease [OR per serum creatinine elevation of 100μmol/l (1.13 mg/dl), 1.28 (95% CI 1.16–1.39)]. The following factors were associated with relapse in 258 (77%) patients who attained remission: the presence of anti-PR3 antibodies [hazard ratio, 1.87 (CI, 1.11–3.14)] lung involvement [hazard ratio, 1.71 (CI 1.04–2.81)] or upper respiratory tract involvement [hazard ratio, 1.73 (CI 1.04–2.88)]. Relapses occurred in 26% of patients who did not have these identified risk factors versus 73% of patients with all three risk factors (HR 3.7, CI 1.4–9.7). Among 143 patients attaining remission who subsequently stopped all immunosuppressant therapy, relapse rates were similar for those who had received cyclophosphamide therapy for 6 months or less (34%) compared with those treated for a longer duration (35%), even after adjusting for risk factors for relapse (HR 1.41 CI 0.80–2.50).

Comment

The identified risk factors are summarized in Table 12.7. This study showed that women were more likely than men to be refractory to treatment; however, men are known to have a higher mortality than women |**35,41**|. Although it is logical to assume that disease which progresses in spite of therapy may be more likely to result in death, there is no evidence of this being the natural course of refractory disease. The authors showed that MPO ANCA-related disease is less likely to respond to treatment, and that PR3 ANCA-related disease is more likely to relapse. For a patient to be considered to have relapsed, he or she must have achieved remission at some point during treatment. Therefore, flares (or exacerbations) that occur in the course of already grumbling disease cannot be defined as relapses. This reflects difficulty in defining current disease states. Upper respiratory tract involvement was associated with a higher rate of relapse in the study by Hogan and colleagues (2005); this contrasts with prior reports suggesting that the presence of upper respiratory tract involvement is a beneficial factor for survival |**42**|. Upper respiratory tract manifestations are more likely to be a feature of WG than of MPA. It has been hypothesized that WG involves a spectrum of disease with granulomatous disease and vasculitic disease at opposite ends |**43**|. Upper respiratory features typify the granulomatous end of the spectrum whilst renal involvement signifies the vasculitic end of the spectrum. Granulomatous disease is difficult to treat and therefore more prone to a relapsing course; at the vasculitic end of the spectrum, the abnormalities often need urgent aggressive intervention because they can be life-threatening. Besides upper respiratory involvement and the presence of PR3 ANCA, lung involvement was the third factor found to be associated with relapsing disease. The combination of these three features fits the disease profile of WG, rather than MPA, and there is prior evidence from a prospective cohort that WG is more likely to relapse than MPA |**13**|.

Table 12.6 Items of damage as reported in the WGET trial (reproduced with permission from Seo *et al.*, 2005)

		Other items			
Items of damage	**%**	**Item**	**%**	**Item**	**%**
Hearing loss	25.6	Lung nodule	3.3	Easy bruisability	0.5
Proteinuria ≥ 0.5 g/24 h	18.9	Striae	3.3	Glaucoma	0.5
Nasal blockade/chronic discharge/crusting	17.8	Anxiety	2.2	Glottic stenosis	0.5
Nasal bridge collapse/septal perforation	17.8	Weight gain	2.2	Hypopituitarism	0.5
GFR ≤ 50% of premorbid baseline	17.8	Depression	2.2	Hypothyroidism	0.5
Subglottic stenosis	17.8	Bilateral tympanic membrane scarring	2.2	Ageusia	0.5
Chronic sinusitis/radiological damage	12.2	Fibromyalgia	2.2	Palate defect	0.5
Diastolic hypertension	9.4	Nasolacrimal duct obstruction	2.2	Vasculitic neuropathy	0.5
Pulmonary fibrosis	7.2	Proptosis	2.2	Corneal scarring	0.5
Diabetes mellitus	7.2	Scleral scarring/thinning	2.2	Overwhelming fatigue	0.5
Significant muscle atrophy/weakness	7.2	Bone marrow hypoplasia	0.5	Pulmonary artery stenosis	0.5
Impaired lung function	7.2	Breast deformity from WG	0.5	Pulmonary infiltrate	0.5
Chronic breathlessness	6.7	Carcinoma in situ, vulva	0.5	Renal transplantation	0.5
End-stage renal disease	6.7	Chronic episcleritis	0.5	Right ventricular hypertrophy	0.5
Cataract	6.1	Chronic endobronchial dysfunction	0.5	Right ventricular hypertension	0.5
Osteoporosis/vertebral collapse	5.0	Eustachian tube dystrophy	0.5	Rotator cuff tear	0.5
Gonadal failure	5.0	Testicular atrophy	0.5	Scarring on chest radiograph	0.5
Alopecia	4.4	Chronic rhinitis	0.5	Tinnitus	0.5
Visual impairment/diplopia	3.9	Coronary artery bypass	0.5		

Blindness in one eye	3.9	Cold sensitivity	0.5
Malignancy	3.3	Systolic hypertension	0.5
Cranial nerve lesion	2.8	Diabetes insipidus	0.5
Chemical cystitis	2.2	Erectile dysfunction	0.5
Pleural fibrosis	2.2	Deep venous thrombosis	0.5
Complicated venous thrombosis	2.2	Cutaneous ileostoma	0.5

GFR, glomerular filtration rate; WGET, Wegener's Granulomatosis Etanercept Trial.
Source: Seo *et al.* (2005).

Table 12.7 Multivariate predictors of treatment resistance and relapse

Predictor	**Prediction of treatment resistance ($n = 334$)**		**Prediction of relapse ($n = 258$)**	
	Odds ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Female vs. male	1.80 (1.10–3.30)	0.048	1.05 (0.70–1.56)	0.97
Black vs. non-black	3.10 (1.19–7.85)	0.013	1.70 (0.83–3.90)	0.163
PR3 ANCA vs. MPO ANCA	0.47 (0.25–0.90)	0.023	1.87 (1.11–3.14)	0.022
Lung involvement	1.46 (0.64–3.36)	0.37	1.71 (1.04–2.88)	0.034
Upper respiratory involvement	0.69 (0.29–1.63)	0.39	1.73 (1.04–2.88)	0.030
Serum creatinine level per 100 μmol/l	1.28 (1.16–1.39)	< 0.001	1.01 (0.91–1.13)	0.82

ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

Conclusion

The first report of prevalence of microscopic polyangiitis from the southern hemisphere is welcome. Further reports from the southern hemisphere may help us understand the possible latitudinal effect on the distribution of vasculitis, but there may be other environmental and genetic differences that will need to be evaluated.

The presence of C/PR3 ANCA or P/MPO ANCA in over a quarter of patients with CSS and the striking phenotypic differences dependent on serology strongly suggest CSS to be an AASV. Each of the three forms of AASV is a distinct syndrome. For this reason future clinical trials should include disease specific subanalysis if they recruit a heterogeneous cohort. Arguments against the need to study pure cohorts include the lack of absolute disease definitions and the fact that these diseases are treated with the same remission induction therapies. The use of similar induction regimens in primary systemic vasculitis is similar to the use of identical regimens to treat various inflammatory arthritides. This does not stop us from trying to differentiate them. So far, the plethora of studies with heterogeneous cohorts has meant that there is little disease-specific evidence. This cannot be taken to mean that such differences may not exist.

The role of methotrexate in non-renal WG has been supported. Although evidence for its use existed in the form of a longitudinal cohort, the study by de Groot and colleagues (2005) will give more justification for its widespread use. The use of mycophenolate mofetil does merit randomized controlled trials and presently the European Vasculitis Study Group is recruiting patients for a trial comparing mycophenolate mofetil with cyclophosphamide for remission induction |**44**|.

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13

Inflammatory myositis

STEVEN YTTERBERG

Introduction

The idiopathic inflammatory myopathies (IIM) comprise a group of related disorders including polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). A review of papers published relating to IIM over the past year has been both encouraging and disappointing. Encouragement comes from the number of studies that have provided detailed observations of clinical features of the disease and studies that have investigated basic mechanisms underlying the pathogenesis of IIM. These studies form the basis for improved understanding and, ultimately, treatment of patients with IIM. Disappointment comes from the lack of published studies that have built on the basic findings to provide evidence upon which to base clinical decision making. There have been few studies of sufficient size to be able to make evidence-based treatment decisions. Hope persists, however.

Classifying subgroups of IIM patients

Controversy continues about how to best group patients with diseases within the IIM category. This will continue to be a problem as long as the aetiology of the disorders remains unknown. Distinct subgroups can be defined clinically, and indeed this is the basis upon which subgroups were first categorized by Bohan and Peter |**1**|, and their classification criteria continue to be widely used. Criteria for IBM have stressed the pathological findings that are unique to this disorder |**2**|. Classification based on serological findings has been suggested |**3**|. This is a reasonable suggestion, but serological grouping and clinical features do not always coincide. For example, anti-Jo-1 antibodies can be found in patients with both DM and PM. Nonetheless, grouping patients based on specific features, be they clinical, histological or serological, makes sense to try to better understand the group of diseases. Several papers published recently have proposed other ways to classify IIM patients.

A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies

Gerami P, Schope JM, McDonald L, *et al. J Am Acad Dermatol* 2006; **54**: 597–613

BACKGROUND. Classically DM is defined by inflammatory myositis accompanied by cutaneous lesions. Indeed, certain skin manifestations can be pathognomonic for the disease. Some patients have typical skin lesions but little or no evidence of muscle involvement, historically termed as having 'dermatomyositis siné myositis', and more commonly 'amyopathic DM' (ADM). Dermatologists, rather than rheumatologists, most often see these patients. Lacking muscle involvement, ADM patients do not meet the Bohan and Peter criteria for DM, and typically have been excluded from series of IIM patients. This paper reports a systematic review of the published literature about such patients to assess the risks for developing systemic disease manifestations and overt myositis.

INTRODUCTION. Table 13.1 summarizes the terms and descriptions of the various subgroups of patients with ADM. There were 291 cases of adult-onset (age ≥18 years) clinically amyopathic DM (CADM). The average age of CADM patients was 50 years; 73% were female. The average duration of skin disease at the time of report was 3.7 years (range 6 months to over 20 years). Anti-nuclear antibody (ANA) was positive in 63% but myositis-specific antibodies (MSAs) were found in only 4%. Muscle weakness occurred,

Table 13.1 Terminology and descriptions used for patients with cutaneous features of dermatomyositis with little or no evidence of muscle involvement

Term	Description
ADM	Biopsy-proven cutaneous features of classical DM occurring for ≥6 months with no clinical evidence of muscle weakness and no abnormalities of serum levels of muscle enzymes. Exclusions include use of immunosuppressive therapy for 2 consecutive months within the first 6 months of cutaneous involvement
CADM	A group including patients classified as ADM or HDM. Clinically these patients have no apparent muscle involvement
HDM	Patients with classical cutaneous DM but no muscle weakness. On evaluation these patients may have abnormalities detected on measurement of muscle enzymes, EMG, muscle biopsy, or MRI. The same exclusions apply as for ADM
PRMDM	Patients with classical cutaneous DM and no muscle weakness but of duration < 6 months

ADM, amyopathic dermatomyositis; CADM clinically amyopathic dermatomyositis; DM, dermatomyositis; EMG, electromyography; HDM, hypomyopathic dermatomyositis; MRI, magnetic resonance imaging; PRMDM, premyopathic dermatomyositis.

after at least 6 months of CADM (range, 15 months to 6 years), in 37 patients (13%). Most notable were the findings of high rates of lung involvement (13%) and malignancy (14%) among these patients.

Comment

This is an important review of the topic of ADM but the findings have to be interpreted with caution because of reporting and publication bias. The incidence of ADM, or any of its subgroups, cannot be determined from this compilation, which included 90 reports, with 1–28 patients per report (median = 1). Insight into the incidence of ADM comes from a report from Mayo Clinic describing 37 patients with ADM, representing 5% of all patients with DM seen at the clinic during the study period |**4**|. Of adult patients, 24 had ADM and three hypomyopathic DM (HDM). Of 19 subjects for whom follow-up information was available, two (11%), both from the ADM group, developed clinical weakness within 5 years of disease onset. Cancer developed in 13.5%.

There are concerns about diagnosing ADM. It can be difficult to know that muscle involvement was adequately excluded. In this study it is difficult to determine how many of the subjects classified as having ADM might have had HDM, as standardized assessments to detect muscle involvement were not employed. Among HDM patients in whom specific tests were performed, muscle enzyme levels were elevated in 43%, electromyography was abnormal in 56%, in two of seven muscle biopsy was abnormal and in four of seven a magnetic resonance imaging (MRI) study of muscle was abnormal. Another issue relates to differentiating ADM from lupus. Anti-nuclear antibody was positive in 63% of patients with CADM. As the clinical and biopsy findings can overlap, there is concern that some patients classified as CADM may in fact have lupus.

Despite its shortcomings, this paper contains a couple of important messages. First, patients with CADM most often continue to be clinically amyopathic and do not develop overt muscle involvement. Only 37 subjects (13%) eventually developed clinically apparent muscle disease after at least 6 months of having CADM. Second, CADM is a systemic disease. Patients with CADM rarely develop calcinosis, but they are at risk for developing interstitial lung disease and malignancy. The lack of muscle disease should not lull clinicians into thinking that CADM is a benign disorder.

Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies. Analysis of 100 French Canadian patients

Troyanov Y, Targoff IN, Tremblay JL, *et al. Medicine* 2005; **84**: 231–49

Background. Patients with IIM often have features that overlap with other connective tissue diseases (CTDs). The objective of this study was to devise a new classification scheme for IIM taking into account signs and symptoms of other CTDs as well as presence of myositis-associated autoantibodies (MAAs) and MSA. This was a retrospective study of 100 adult patients. Patients were classified at the time of diagnosis and at the time of last follow-up using the original criteria of Bohan and Peter |1|, and modified criteria. The mean duration of follow-up was 8.7 years (range 0.17–33.6 years).

Interpretation. For the modified Bohan and Peter criteria, patients with any clinical overlap feature were classified as overlap myositis (OM). For the new clinicoserological classification, patients with any clinical overlap feature or an overlap autoantibody were classified as having OM. Results of reclassifying patients using the two new schemes are shown in Table 13.2. The biggest change affected patients classified as having PM, the largest group using the original Bohan and Peter criteria. The group classified as having OM increased most, rising from 24% of the cohort using the original criteria, to 68% with the revised classifications. Classification using the modified Bohan and Peter criteria and the clinicoserological criteria were similar.

Comment

Defining subgroups of IIM has been difficult. The original classification scheme proposed by Bohan and Peter |**1**| has been utilized extensively but has been questioned |**5,6**|. Defining subgroups based on the presence of specific MSAs has been advocated to define more homogeneous subgroups |**3**|, but even this approach has its weaknesses, as evidenced by the fact that anti-Jo-1 antibodies can be found in both PM and DM sera. Some have advocated the use of histological findings for diagnosing IIM |**5**|. The current retrospective study relies on clinical and serological features; indeed, muscle biopsies were not uniformly performed or independently reviewed.

Use of the proposed classification schemes raises a philosophical question. Should PM be considered a disorder that affects only muscle, or should systemic

Table 13.2 Classification of 100 IIM patients using different classification criteria

Classification scheme	At diagnosis				At last follow-up			
	PM	DM	CTM–OM	CAM	PM	DM	CTM–OM	CAM
Original B/P	45	28	24	3	33	30	31	6
Modified B/P	14	23	60	3	9	18	67	6
Clinicoserological	10	20	68	2	9	19	68	4

B/P, Bohan and Peter; CAM, cancer-associated myositis; CTM–OM, myositis in association with another connective tissue disease (used by original Bohan and Peter classification) or overlap myositis (used by the currently proposed modification); DM, dermatomyositis; PM, polymyositis.

involvement be considered part of the disease spectrum? A patient with typical clinical and histological features of PM who has anti-Jo-1 antibodies, inflammatory arthritis and interstitial lung disease would be classified as OM rather than PM. The authors accept that other CTDs can have systemic manifestations, e.g. lung and gastrointestinal involvement in scleroderma. Why should the anti-synthetase syndrome not be considered part of the spectrum of PM?

The most important questions for any disease classification schema are: How does the classification system aid understanding the pathogenesis of the disease? How does it help predict prognosis and plan treatment for an individual patient? Clinical outcomes of the groups are detailed in Table 13.3. In the end, using the new classification system, PM was found to be the most refractory to initial corticosteroid treatment. Dermatomyositis patients typically responded to corticosteroids but the course was almost always chronic. Patients with OM had a high rate of response to corticosteroids, but those with anti-synthetase, signal recognition particle (SRP), or nucleoporin antibodies had chronic myositis. Patients with antibodies to U1RNP, Pm-Scl, or Ku tended to have monophasic disease, but 55% of those with U1RNP antibodies died. Will the proposed classification matter for patient care? Whether patients are classified as having OM or PM with overlap features probably matters little. Treatment with steroids alone is most appropriate for OM patients with antibodies to U1RNP, Pm-Scl, and Ku. Those in the other patient groups should probably be treated early with an immunosuppressive agent in addition to corticosteroids.

Identification of novel autoantibodies in IIM patients

Myositis-specific autoantibodies are autoantibodies found predominantly in sera of patients with PM or DM. Those with high specificity for IIM include Jo-1 and other anti-synthetase antibodies, anti-SRP antibodies and antibodies to Mi-2. They have been useful as markers of disease subgroups and are linked to specific clinical manifestations |**3,7**|. New autoantibodies continue to be defined, including two highlighted below that seem specific for DM.

Table 13.3 Outcomes of 100 patients with IIM classified according to the clinicoserological classification (%)

Clinical group (*n*)	Steroid responsive	Monophasic course	Death
Total (100)	88	32	23
PM (9)	50	0	44
DM (18)	87	8	5
OM (67)	93	42	24
CAM (6)	n/a	n/a	50

CAM, cancer-associated myositis; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; n/a, not applicable; OM, overlap myositis; PM, polymyositis.

A novel autoantibody to a 155-kDa protein is associated with dermatomyositis

Targoff IN, Mamyrova G, Trieu EP, *et al.*, for the Childhood Myositis Heterogeneity and International Myositis Collaborative Study Groups. *Arthritis Rheum* 2006; **54**: 3682–9

Background. The authors sought to identify novel autoantibodies in patients with IIM. Sera from 244 juvenile and adult IIM patients meeting the Bohan and Peter criteria were evaluated. Cases were classified as juvenile onset if the age at disease onset was < 18 years. Sera from normal subjects and patients with other connective tissue were examined as well. Testing was by immunoprecipitation and results were confirmed by immunoblotting of immunoprecipitates.

Interpretation. By immunoprecipitation, an antibody reacting with a 155-kDa protein (anti-p155) was detected in the sera of several patients with DM. In contrast to anti-synthetase and anti-SRP positive sera, anti-p155 sera did not precipitate nucleic acid. On indirect immunofluorescence testing of the anti-155-kDa sera using Hep-2 cells, a nuclear speckled pattern was observed. The antibody was found in 21% of 244 sera from subjects with IIM (Table 13.4). It was associated with DM, including juvenile DM and cancer-associated myositis. Caucasian patients with anti-p155 had HLA DQA1*0301 as a unique risk factor. Interstitial lung disease was not seen in patients having anti-p155 antibodies.

Table 13.4 Frequency of anti-p155 autoantibodies in patients with IIM and control subjects

Clinical group	Number positive/number tested	Per cent positive
All IIM	51/244	21
Juvenile DM	30/103	29
Juvenile PM	0/9	0
Juvenile CTD-IIM	5/15	33
Adult DM	8/39	21
Adult PM	0/48	0
Adult CTD-IIM	2/13	15
Adult cancer-IIM	6/8	75
Control groups	1/138	0.7
SLE	1/49	2
Scleroderma	0/18	0
Other CTD	0/8	0
Other myopathies	0/41	0
Healthy control subjects	0/22	0

CTD, connective tissue disease; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; PM, polymyositis; SLE, systemic lupus erythematosus.
Source: Targoff *et al.* (2006).

Comment

The observations made in this paper are unique on several fronts. First, anti-p155 is among the most frequent autoantibodies in patients with IIM. Anti-Jo-1 antibody is generally considered the most common MSA, occurring in about 20–30% of adult patients with PM and DM |**3,7**|. Anti-p155 was found with a similar frequency. Moreover, anti-p155 is highly specific for IIM, being detected in no sera from healthy control subjects and only one of 116 sera from patients with CTD, a patient with lupus. Second, anti-p155 is present in a large proportion of patients with juvenile DM (JDM). Compared with adult patients, autoantibodies are infrequently found in JDM patients. A study of 42 patients with JDM and seven with other IIM found only five with defined autoantibodies – two with anti-Mi2 and three with anti-PM-Scl antibodies |**8**|. Fourteen of the JDM sera had unidentified bands on immunoprecipitation, and it is possible that many of these may have represented anti-p155 antibodies. In the current study, anti-p155 was found in 29% of juvenile and 21% of adult DM patients. Third, anti-p155 is highly associated with malignancy. It was present in six of eight adult patients with malignancy, all of whom had DM. Viewed another way, six of 16 (37.5%) adult patients with anti-p155 antibodies had malignancy.

From the viewpoint of the practising rheumatologist, the discovery of this antibody will not change practice in the near future. It may become a clinically useful tool, however, for the diagnosis of DM, especially in children, and it may be useful as a marker of patients who need more extensive screening for malignancy. A more recent paper, published after the time frame for this review, described a similar antibody recognizing 155- and 140-kDa proteins in the sera of patients with DM. This autoantibody was also restricted to patients with DM and was associated with development of malignancy |**9**|.

Autoantibodies to a 140-kDa polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis

Sato S, Hirakata M, Kuwana M, *et al. Arthritis Rheum* 2005; **52**: 1571–6

Background. This study was undertaken to identify autoantibodies in patients with CADM. The authors screened sera from 298 untreated Japanese patients with various CTDs or idiopathic pulmonary fibrosis, as well as 16 control subjects, for autoantibodies. Immunoprecipitation was used to identify antibodies and positive sera were followed up using immunoblotting and indirect immunofluorescence.

Interpretation. Of the sera examined, eight were found to recognize a 140-kDa protein. All eight patients with the antibody had DM ($n = 42$, 19%). The antibody was not detected in control subjects, patients with other CTDs or patients with idiopathic pulmonary fibrosis. Notably, all DM patients with the antibody had CADM, resulting in the antigen being named 'CADM-140' and the autoantibody 'anti-CADM-140'. Other than

the obvious difference in muscle manifestations, clinical features were identical between DM patients with and without the antibody with one major exception, those with anti-CADM-140 had an increased risk of developing rapidly progressive interstitial lung disease (ILD).

Comment

Finding unique autoantibodies can help identify specific subsets of patients. It remains to be determined whether anti-CADM-140 is pathogenic or simply a marker of disease, but simply recognizing the clinical association with CADM is important. Indeed, the details of the manuscript indicate that several patients had HDM. None had muscle weakness, but two had elevated levels of creatine kinase (CK) and four had increased levels of aldolase. Anti-CADM-140 is an infrequent MSA but was detected in over half of patients (8/15, 53%) with this condition. It is specific for CADM, however. Among IIM patients having MSAs, typically only a single MSA occurs and the observations with anti-CADM-140 continue this pattern. No patients with anti-CADM-140 had another MSA, although MAA were present in these patients.

This paper helps support the idea that CADM is a unique and likely important entity along the spectrum of DM. The most significant use this antibody might play clinically is to identify patients at risk for developing rapidly progressive ILD. Rapidly progressive ILD has been noted in some patients with CADM |**10**|. Among the cohort studied for the present paper, ILD was present in other patients, but rapidly progressive ILD occurred only in patients with anti-CADM-140 antibodies. Indeed, 5 of the 15 patients with CADM developed ILD, and it was rapidly progressive in four of the five. To the extent that aggressive therapy may benefit such patients, the ability to use autoantibody screening to identify patients at risk for poor outcome, as represented by rapidly progressive ILD, is a real plus.

Pathogenesis of IIM

Signs of inflammation in both symptomatic and asymptomatic muscles from patients with polymyositis and dermatomyositis

Dorph C, Englund P, Nennesmo I, Lundberg IE. *Ann Rheum Dis* 2006; **65**: 1565–71

Background. Muscle involvement in the IIM is typically symmetric but not diffuse. This is best exemplified by the characteristic proximal muscle weakness with distal sparing seen in PM and DM. This study examined relationships of

weakness and histological features of inflammation and immunological reactivity in muscle biopsies of patients with IIM. Biopsies from clinically involved (weak) and uninvolved muscles of patients with PM and DM were examined and compared with muscle biopsies from control subjects. Most IIM patients were untreated but two had received corticosteroids prior to biopsy. Steroid use did not seem to affect the findings.

Interpretation. From each muscle sampled, biopsies were collected for diagnostic and research purposes. Histological findings in the two samples were not always identical. Findings from the most abnormal specimen for each muscle are shown in Table 13.5. Inflammatory infiltrates and class I and II major histocompatibility complex (MHC) antigen expression were found in both symptomatic (proximal) and asymptomatic (distal) muscles of patients with PM and DM, but not in control muscle specimens. CD3+ T-cells and CD163+ macrophages were found in affected and unaffected muscle of patients but not in control subjects. Interleukin 1α (IL-1α) was expressed in both symptomatic and asymptomatic muscle. Capillaries expressing IL-1α were increased in both affected and unaffected muscles and overall IL-1α content was similarly increased.

Comment

This is a fascinating study that raises as many questions as it answers. Obtaining a biopsy from a clinically involved muscle to try to understand disease pathogenesis is an obvious step. As a control specimen, what would be better than a biopsy from an uninvolved muscle from the same patient? This is apparently the first study to explore this issue. The number of subjects included in the study is relatively small, but the findings seem valid. The findings in involved muscle samples confirm observations this group has made previously, showing that muscle from patients

Table 13.5 Muscle histology findings in symptomatic and asymptomatic muscle biopsies from patients with polymyositis and dermatomyositis and control subjects

	Number (%) of biopsy specimens showing feature		
	PM and DM patients		
Histological finding	**Symptomatic muscle (*n* = 11)**	**Asymptomatic muscle (*n* = 11)**	**Control muscle (*n* = 6)**
Inflammation	9 (82)	8 (73)	1 (17)
Degenerating fibres	7 (64)	5 (45)	0 (0)
Regenerating fibres	6 (55)	5 (45)	0 (0)
Muscle fibre atrophy	8 (73)	9 (82)	1 (17)
Central nuclei	0 (0)	2 (18)	4 (67)

DM, dermatomyositis; PM, polymyositis.

with weakness but no inflammatory infiltrates has increased expression of IL-1α in the endothelium of capillaries |**11**|.

Why are there similar immunopathological changes in symptomatic and asymptomatic muscles? Does this mean that inflammation and infiltration of T-cells and macrophages has nothing to do with weakness in a particular muscle? Muscle inflammation, muscle fibre necrosis or atrophy, and presence of inflammatory cytokines in muscle may all have nothing to do with weakness. Perhaps symptoms are related to the physical demands on specific muscle groups or the muscle fibre composition of different muscle groups.

If the immunological changes in muscle are generalized, why are biopsies from patients with active IIM sometimes normal? Normal muscle biopsies were found in 12.5% of patients with PM and DM in one series |**12**|. Magnetic resonance imaging studies can show differences in inflammation in adjacent muscle groups. Procurement of negative muscle biopsies in patients with convincing clinical features of IIM is often attributed to having biopsied an uninvolved muscle. These observations are difficult to square with the findings of the present study but raise interesting questions.

Seasonal influence on the onset of idiopathic inflammatory myopathies in serologically defined groups

Sarkar K, Weinberg CR, Oddis CV, *et al. Arthritis Rheum* 2005; **52**: 2433–8

Background. Several lines of evidence suggest the possibility that environmental factors, perhaps including infectious agents, might play an aetiological role in the development of the IIM. A previous study from this group suggested a seasonal influence for some serologically defined subgroups of IIM. The current study was a cross-sectional retrospective review at multiple referral centres to determine the time of onset of disease of patients with IIM. Included patients had probable or definite PM or DM according to the Bohan and Peter criteria and had information available concerning the time of symptom onset and MSA status.

Interpretation. Data were available for 503 patients (268 with PM and 235 with DM). No seasonal pattern was identified for the overall group of IIM patients or for subgroups defined by gender, race, or specific form of myositis. Among patients with anti-synthetase autoantibodies, disease tended to begin in March to April for non-black patients. This pattern was not observed among black patients. The seasonal association in this group was apparent for patients with PM but not DM, and for males but not females. Among patients with no MSA present, disease onset tended to be in June to July, mostly based on a relationship in DM, but not PM, patients.

Comment

This is an important study because of the large number of well-characterized subjects that were included, but understanding the findings is difficult. Because multiple associations were examined, individual subgroups of patients were small, limiting the power of the observations. The study is also limited by being retrospective. We cannot know whether data about potential exposures were collected systematically.

The initial report from this group found a seasonal influence of disease onset for serologically defined groups of IIM patients |**13**|. Patients with Jo-1 antibodies had disease onset between February and July, with a peak in April and those with anti-SRP antibodies had onset between September and February, with a peak in November. In the current study there was a trend for patients with Jo-1 antibodies to have onset in March to April, but this was not statistically significant. A seasonal pattern among patients with anti-SRP antibodies was not observed.

Observations continue to suggest that environmental agents may contribute to the aetiology or pathogenesis of the IIM |**14**|. Seasonally related factors might include specific exposure to infectious agents or possibly simple exposure to ultraviolet radiation |**15**|. The differences observed for various genders or races in the current study might relate to differences in exposure or to differences in immunological responses to a triggering factor. Although tantalizing, direct evidence linking specific environmental aetiologies to development of IIM remains elusive.

Outcomes in IIM

Long-term outcome in polymyositis and dermatomyositis

Bronner IM, van der Meulen MFG, de Visser M, *et al. Ann Rheum Dis* 2006; **65**: 1456–61

Background. The prognosis of PM and DM is not well understood. The authors of this study examined mortality and clinical outcomes of 163 adult patients (> 16 years old) with PM and DM for at least 1 year. Care was taken to exclude patients with IBM and non-inflammatory myopathies. Patients were defined as having cancer-associated myositis if cancer occurred within 2 years of the diagnosis of myositis. At the time of the study 34 patients had died and 110 of the 131 surviving patients were re-examined.

Interpretation. The cohort included 120 women and 45 men. The mean age was 45 years and median follow-up 5 years (range 1–23 years). Prednisone treatment was given to 95% and at least one immunosuppressive agent to 57%. Among patients who could be traced, 34 patients (21%) had died after a median follow-up of 4 years. Death was related to myositis in 18 patients. At follow-up, considerable disability was present

in 24% and muscle weakness was present in 25%. The duration of follow-up was not related to disability or muscle strength. At follow-up, 20% of patients were in remission off medications, but disease course was polycyclic or chronic in 80%.

Comment

This is a complicated study but one with important implications for those who care for patients with PM and DM. The definitions of disease utilized in the study create some difficulty interpreting the findings. The group classified as having PM is small because patients had to have specific histological features (autoaggressive invasion of muscle fibres) in addition to typical clinical features |**6**|. Thus, the largest group was patients classified as having 'unspecified myositis' – patients having clinical features of PM but not the required pathological finding. In the end, however, no significant differences were found for the disease subgroups.

Factors causing disability are not always clear. In PM and DM it is presumed that muscle weakness is the principal factor, but this may be a simplistic interpretation. Indeed, in this study, 65% of patients had normal strength as assessed on clinical examination, but only 34% reported no or slight disability and 16% had normal quality-of-life scores. These observations suggest an important disconnect between muscle strength testing and patients' disability and perceived quality of life. Altered muscle endurance, and not strictly muscle weakness, may be a cause of impaired function in patients with PM and DM. Easy-to-use tools to assess functional impairment of muscle activity have been proposed and might be considered for the regular assessment of patients with IIM |**16**|. Further research in this area is clearly needed.

The study detailed causes of death. Of the 18 patients considered to have myositis-related deaths, death was associated with cancer in seven, pulmonary complications in four, adverse effects of drugs in four, CTD in two and cardiac complications of myositis in one. The survival data are similar to those from another recent study of patients with IIM |**17**|. Four deaths related to treatment might seem small, but only about half of patients in this cohort received immunosuppressive therapy. Treatment-related morbidity is a major concern. An earlier study of patients with IIM found that disability increased with disease duration and corticosteroid complications contributed significantly to disability |**18**|.

Inclusion body myositis

Inclusion body myositis. Clinical features and clinical course of the disease in 64 patients

Badrising UA, Maat-Schieman MLC, van Houwelingen JC, *et al. J Neurol* 2005; **252**: 1448–54

Background. Recent publications about sporadic IBM have focused on its pathological findings and potential underlying pathogenetic mechanisms, with less attention directed towards clinical features. This cross-sectional study was performed to characterize the clinical features of sporadic IBM. A single investigator examined a cohort of 64 patients with IBM in the Netherlands using a standard evaluation protocol. Patients had probable or definite IBM. The study group was a representative sample of all known patients with IBM in the Netherlands.

Interpretation. Among the 64 patients (43 men and 21 women), the mean ages at the time of evaluation were 67 ± 8 and 73 ± 10 years respectively. The ages at symptom onset were 57 ± 9 and 59 ± 10 years respectively. Weakness began most commonly in quadriceps muscles (63%), finger flexors (14%) and pharyngeal muscles (9%). Falls were common and 13% of patients had sustained a fracture, prompting the majority to use an assistive device for ambulation. No patients had to leave work permanently because of disease and all but one continued to live at home. Myalgia was uncommon, present in only three patients.

Comment

This is the largest clinical series of patients with IBM reported to date. The study did not use the generally accepted Griggs criteria for IBM |**2**|, but instead used criteria promulgated by the European Neuromuscular Centre. The criteria used for diagnosis and epidemiology for this cohort have been reported previously |**19**|.

The age of onset among the cohort is notable. Sporadic IBM is generally considered to be a disorder of older subjects. In this study 20% of patients (10 men and three women) were younger than 50 years old when symptoms began, the youngest being 39 years old. This is not a new observation. Previous series have found that 17–19% of patients had symptom onset before age 50 |**20**|. Inclusion body myositis needs to be considered even in patients younger than 50. Younger age at onset, though, tended to be associated with slower disease progression.

A strength of this paper is the detail included about specific muscle group involvement. The most frequently and severely affected muscles were located ventrally, including flexors of the arms and extensors of the legs. Sparing of specific muscle groups allowed for long maintenance of ambulation and independence. Contractures were common. Nearly all patients had CK values below 12 times the upper limit of normal, but early in the disease course, some patients, men especially, had higher values. The authors also noted that reflex findings could not distinguish IBM from motor neurone disease. A diagnosis of IBM cannot be based on clinical and laboratory manifestations of disease alone.

The patients in this cohort generally continued to function independently despite the fact that at the time of evaluation the average duration of disease was 10 years for men and 14 years for women. Scores on functional scales and the fact that all but one continued to live at home at the time of follow-up demonstrated independence.

There continues to be controversy about treatment of patients with IBM and this report adds little insight. Little comment is made about the therapies these

patients received. At the time of final examination only four were receiving immunomodulating therapies. Overall, 41 had never received immunosuppressive therapy and 19 had received only short-term treatment.

Conclusion

Progress continues to be made in understanding IIM. The area is attracting more research interest. Our ability to separate subgroups of patients is improving, but there continues to be debate about how to define subgroups of patients, especially when it comes to identifying polymyositis. It is most important to be able to differentiate PM from IBM. Better availability of autoantibody testing for MSA may also enhance our ability to identify more homogenous groups of patients. The ultimate aim of better stratification of patients is to facilitate therapeutic decision making.

Validated outcome measures are starting to be applied. The issue around differences in muscle strength test findings and patients' functional difficulties needs further research.

The one major area of research not included in this review relates to therapeutic studies. The size of studies published during the review period did not warrant inclusion of any of them in this review. Several papers reported results of use of immunosuppressive agents including tumour necrosis factor inhibitors, mycophenolate mofetil, and rituximab, in small series of patients. We are in need of larger studies, which will of necessity be multicentre, to provide evidence to use for clinical decision-making.

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14

Interstitial lung disease in the rheumatic diseases

LEROY GRIFFING

Introduction

One of the most common features of illness to affect patients with rheumatic diseases is interstitial lung disease (ILD). Interstitial lung disease is a large and diverse group of pathological conditions including usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP) which was formerly known as bronchiolitis obliterans with organizing pneumonia (BOOP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), and desquamative interstitial pneumonia (DIP)/ respiratory bronchiolitis-associated interstitial lung disease (RB-ILD). This classification of ILD was developed by the American Thoracic Society conjointly with the European Respiratory Society |**1**| in 2002 and excluded patients with rheumatic diseases. However, similar histopathological lung changes do occur in patients with rheumatic disease, most commonly scleroderma (systemic sclerosis), rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and poly-/dermatomyositis.

The method of diagnosis of ILD varies considerably depending on the specific circumstances. Pulmonary function test results typically reveal restrictive defects with reduced forced vital capacity (FVC), total lung capacity (TLC), and gas exchange/diffusion capacity (DLCO). High-resolution computed tomography (HRCT) scanning of the lungs is an integral part of the initial evaluation. In some instances, a lung biopsy will be needed to help distinguish the precise lung illness. Biopsy findings alone may point to a specific aetiological diagnosis but, in many instances, the histopathology is non-specific and must be correlated with clinical and radiographical findings to arrive at a specific diagnosis. Despite the limitations, the histological findings of the lung may provide information about the aetiology, activity, reversibility, and prognosis of a given ILD |**2**|. Idiopathic pulmonary fibrosis (IPF/ UIP) is typically unresponsive to treatment with a poor prognosis, while NSIP is considered more responsive to immunosuppressive therapy and has a better prognosis (Figure 14.1).

Because rheumatic disease-ILD is more commonly caused by NSIP than UIP, the prognosis and outcome for rheumatic disease patients has been thought better

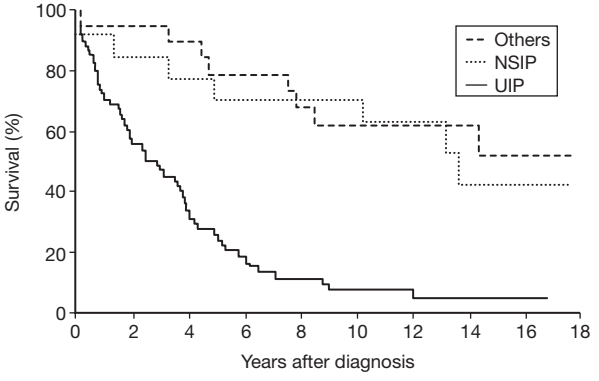

Fig. 14.1 Observed survival according to histopathological subgroups. Patients with usual interstitial pneumonia (UIP) had a significantly worse survival ($P < 0.001$, rank sum test) than patients with non-specific interstitial pneumonia/fibrosis and others subgroups. Median survival for UIP patients was 2.8 years. Reproduced from |**2**|: JA Bjoraker *et al.* (1998) *Am J Resp Crit Care Med;* **157***:* 199–203.

than IPF. But there have been very few studies carefully examining the prognosis and mortality for specific types of ILD in the context of specific rheumatic diseases, and most of the studies have been retrospective with small numbers of patients. Because of differences in patient populations reported, compounded by differences in rheumatic disease severity and duration, as well as differences in the techniques, investigations and criteria used to define ILD, results of studies have been conflicting. Additionally, treatment for rheumatic disease-ILD continues to be largely empiric in the absence of any prospective, randomized, controlled therapeutic trials.

The following papers help to improve our understanding of the frequency, pathogenesis, natural history, clinical relevance, prognosis and treatment of interstitial lung disease in the rheumatic diseases.

Cyclophosphamide versus placebo in scleroderma lung disease

Tashkin DP, Elashoff R, Clements PJ, *et al. N Engl J Med* 2006; **354**: 2655–66

Background. Tashkin and colleagues |3| evaluated the efficacy of oral cyclophosphamide on lung function, dyspnoea, and other health-related symptoms in a multicentre, prospective, randomized, double-blind, placebo-controlled study of patients with early scleroderma-related interstitial lung disease and active alveolitis. The Scleroderma Lung Study (SLS) involved 158 patients with diffuse or limited scleroderma of 3.1 years mean duration. All patients had restrictive lung physiology with moderate ventilatory restriction (mean FVC 68.1% predicted) and moderate to severe diffusion impairment (mean DLCO 47.4% predicted) in addition to moderate breathlessness (average Mahler Baseline Dyspnea Index 5.7; scale 0–12). Evidence of inflammatory ILD was based on bronchoalveolar

lavage fluid and/or ground glass opacity detected on HRCT. Patients received either cyclophosphamide orally (≤2 mg/kg body weight per day with adjustments for treatment-related toxicities) or matching placebo for 1 year and were followed for an additional year. Prednisone up to 10 mg/day was permitted. The primary endpoint was the FVC (% predicted) at 12 months, after adjustment for the baseline FVC.

Interpretation. One hundred and forty-five patients completed at least 6 months of treatment and were included in the analysis. One year of oral cyclophosphamide had statistically significant but modest beneficial effects on lung function, dyspnoea and health-related quality of life. The FVC mean change showed a statistically significant smaller decline favouring cyclophosphamide [–1.0% vs. –2.6%; adjusted mean absolute difference 2.53%, with 95% confidence interval (CI) 0.28–4.79; $P < 0.03$]. No difference in DLCO was seen. An unexpected finding was the lack of correlation between the response to CTX and the presence of ground glass opacities on HRCT. In addition, patients in the placebo group with the greatest severity of fibrosis had a greater decline in FVC while, in contrast, change in FVC in the cyclophosphamide-treated group was not influenced by the severity of interstitial fibrosis on baseline HRCT (Fig. 14.2). Treatment-related differences favouring cyclophosphamide were additionally seen for secondary study endpoints including self-reported dyspnoea, disability (Health Assessment Questionnaire Disability Index, HAQ DI) and Short Form (SF)-36 domains of vitality and health-transition. Side-effects of haematuria, leukopenia, neutropenia, anaemia and pneumonia were more common in the cyclophosphamide group.

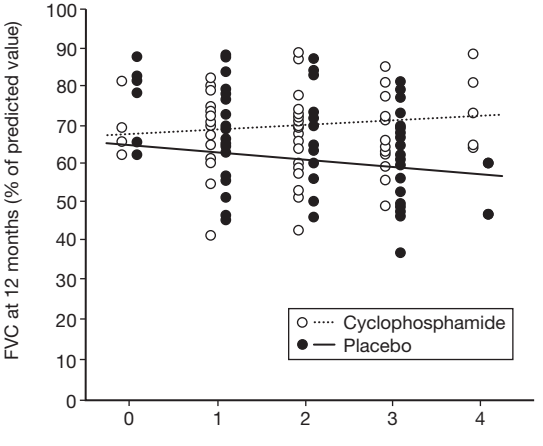

Fig. 14.2 The percentage of predicted forced vital capacity (FVC) at 12 months. This shows a scattergram of the FVC at 12 months (adjusted for the baseline FVC) according to treatment, compared with the maximal fibrosis score as determined on baseline thoracic high resolution computed tomography (HRCT). The slope of the regression is significant in the placebo group (–2.01% of the predicted FVC per unit score for fibrosis, $P = 0.006$), but not in the cyclophosphamide group (0.96% of the predicted FVC per unit score for fibrosis, $P = 0.26$); the difference in the slopes between the two groups was significant ($P = 0.009$). Source: Tashkin *et al.* (2006).

Comment

Even though the difference in FVC was quite modest and of uncertain clinical significance by itself, this is the first positive, randomized, placebo-controlled therapeutic trial for scleroderma-related lung disease. The fact that secondary outcomes additionally favoured cyclophosphamide supports the use of immunosuppressive medications. Interestingly, responsiveness to cyclophosphamide was not predicted by baseline HRCT ground glass opacities or bronchoalveolar lavage results, i.e. those tests that are often used in research studies to designate 'alveolitis', which has been thought more likely to respond to immunosuppressive treatment than fibrosis. This emphasizes the point that not all ground glass opacities seen on HRCT signify alveolitis. How to best identify 'treatment-responsive' lung disease remains imprecise but, based on the observations of this study, the standard methods often used to distinguish clinically significant scleroderma-ILD that would be most responsive to treatment will probably have to be revised.

Although a treatment-related difference in the reduction of skin thickness favouring cyclophosphamide was also found, it was noted this change would not account for the beneficial effect seen on FVC, as truncal skin involvement is not present in limited scleroderma. The beneficial effect on FVC was similar in patients with either the limited or diffuse forms of scleroderma.

One limitation of the study is the high dropout rate. Six patients withdrew prior to receiving any treatment. A disparity in the number of subsequent dropouts also occurred, with 21 in the cyclophosphamide group withdrawing after at least one dose study medication, compared with only 13 placebo group withdrawals. The larger number of cyclophosphamide group withdrawals, which also tended to occur earlier than placebo group withdrawals, was presumably caused by treatment-related adverse events. Should a longer period of cyclophosphamide treatment have been necessary in order to attain maximal effect, this may have created a bias towards not showing a treatment difference. The authors noted that, if this were to be the case, the study represents a 'real-world' outcome, by taking into account the net benefit of cyclophosphamide while simultaneously reflecting its lack of tolerability. The authors also noted caution is still warranted for the use of cyclophosphamide, as its potential long-term consequences were not evaluated.

Deciding which drug to use for treatment of scleroderma-associated ILD remains controversial. Corticosteroids are often considered, but proof of efficacy is lacking. Furthermore, there is concern that prednisone in doses higher than 15 mg per day promotes scleroderma renal crisis.

A multicentre, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma

Hoyles RK, Ellis RW, Wellsbury J, *et al. Arthritis Rheum* 2006; **54**: 3962–70

Background. Hoyles and colleagues |4| evaluated the effects of combination intravenous cyclophosphamide, azathioprine and low-dose prednisone on lung function, dyspnoea and HRCT findings in a multicentre, prospective, randomized, double-blind, placebo-controlled study of scleroderma patients with ILD. The Fibrosing Alveolitis in Scleroderma Trial (FAST) involved 45 patients with limited or diffuse scleroderma and ILD based on HRCT or thorascopic lung biopsy. All patients had restrictive lung physiology characterized by mild ventilatory restriction (mean FVC 81% predicted) and moderately severe diffusion impairment (mean DLCO 54% predicted value corrected for haemoglobin) in addition to mild to moderate breathlessness (mean modified American Thoracic Society respiratory questionnaire dyspnoea score 7.4; scale 0–20). Twenty-two patients were randomized to receive active treatment with prednisone 20 mg on alternate days combined with 6-monthly infusions of cyclophosphamide 600 mg/m² followed by oral azathioprine 2.5 mg/kg/day (maximum 200 mg/ day). Twenty-three patients received matching placebos. The study primary endpoints were change in FVC and DLCO at 12 months. Secondary outcome measures were change in dyspnoea score (≥1 grade) and change in the HRCT extent and pattern of disease at 1 year.

Interpretation. Twenty-eight patients (62%) completed the first year of the study. Treatment-related adverse events resulted in withdrawal of only two patients. There were no instances of haemorrhagic cystitis or bone marrow suppression. At 12 months, estimation of the relative treatment effect (active treatment vs. placebo), adjusted for the baseline severity of FVC and treatment centre, revealed a difference (improvement) in FVC of 4.19% (95% CI –0.57% to 8.95%). This between-group difference in FVC change showed only a trend towards statistical significance ($P = 0.08$). No significant or marginal difference was found in DLCO or in any of the secondary endpoints of dyspnea and HRCT change. The authors noted, however, that their results support several previous uncontrolled, open studies of intravenous and oral cyclophosphamide. Even though the response of the FVC did not achieve the same statistical significance as that found in the SLS study |**3**| above, the authors felt their findings were consistent.

Comment

This is the first placebo-controlled, randomized clinical trial using intravenous cyclophosphamide in scleroderma-ILD, and suggests that the combination of cyclophosphamide, azathioprine and low-dose prednisone might be helpful. The study did not demonstrate statistically significant improvement in its primary and secondary outcome measures; however, there was a trend towards significance

for change in FVC favouring treatment, similar in concept to the SLS study |3|. In terms of immediate toxicity, this combination would appear to be a more attractive alternative than oral cyclophosphamide.

Important limitations of this study are the small number of patients and the high dropout rate which, in part, may explain the failure to have achieved statistical significance. Only 28 (62%) patients completed the entire year of treatment. Of the 17 withdrawals, seven were in the treatment group and 10 in the placebo group. Nine patients (six in the placebo group and three in the treatment group) withdrew on account of significant decline in lung function, and were offered rescue medication. Because of the intent-to-treat analysis used, follow-up data included data obtained after rescue treatment, and this may have led to underestimating the benefit. Additionally, the study population had only mild interstitial lung involvement (mean FVC 81% compared with 68.1% in the SLS trial) with relatively stable disease. Consequently, only a minor therapeutic benefit might have been measurable. It is not known if the modest change in FVC might predict subsequent outcome or improved survival over a longer period of time.

Scleroderma lung: Initial forced vital capacity as predictor of pulmonary function decline

Plastiras SC, Karadimitrakis SP, Ziakas PD, *et al*. *Arthritis Care Res* 2006; **55**: 598–602

Background. Plastiras and colleagues |5| investigated the ability of baseline pulmonary function tests, and in particular FVC (% predicted), to predict subsequent pulmonary function deterioration in scleroderma patients, paying particular attention to analysing patients with similar lung involvement. Forced vital capacity, DLCO (% predicted) and various clinical and laboratory parameters were retrospectively studied on 78 patients with scleroderma and ILD based on HRCT. Separate Kaplan–Meier analyses were performed for 60 patients who were initially assessed within the first 3 years from disease onset (group A) and for 16 patients whose baseline FVC values were measured in the fourth or fifth year after disease onset (group B). Both groups were further subdivided into those with normal baseline FVC (≥80% predicted) and those with decreased FVC (<80% predicted). The primary outcome was a sustained decline in FVC by ≥15 points 5 years later.

Interpretation. Among patients in group A, 28 (46.7%) patients had normal baseline FVC (95.2 ± 10.1%, mean ± SD) and the remaining 32 patients (53.3%) had a decreased FVC (66.1% ± 12.4, mean ± SD). Kaplan–Meier analysis for group A is shown in Fig. 14.3. Eighty-nine per cent of patients with normal baseline FVC did not have a subsequent decrease in FVC at 5 years. In contrast, only 75% of patients with reduced baseline FVC did not have a significant further decrease in FVC (log-rank $P = 0.04$). Four patients with decreased baseline FVC developed severe respiratory failure (FVC < 50% predicted). In group A, the baseline FVC was also associated with subsequent deterioration of DLCO (Fig. 14.4). Eighty-nine per cent of patients with normal baseline

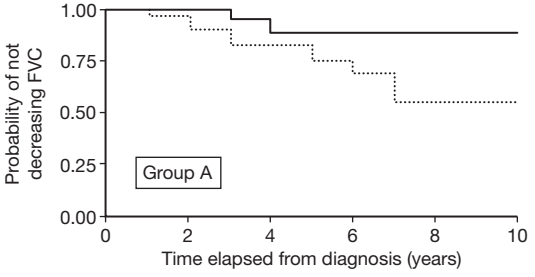

Fig. 14.3 Kaplan–Meier analysis of influence of initial forced vital capacity (FVC) measured within the first 3 years from disease onset on probability of subsequent decline of FVC in patients with scleroderma lung. Solid line indicates baseline FVC ≥80%; broken line indicates baseline FVC < 80%. Source: Plastiras *et al.* (2006).

FVC sustained a DLCO ≥40% predicted at 5 years, while only 68% of patients with a reduced baseline FVC did not have a decrease in DLCO to < 40%. Analysis of group B, whose baseline FVC was obtained during the fourth and fifth year after disease onset, showed no difference between patients with normal or decreased baseline FVC in the ability to predict further pulmonary function decline (log-rank $P = 0.13$) (Fig. 14.5). In contrast to the baseline FVC, no other clinical and laboratory parameters including age, male sex, baseline DLCO, anti-topoisomerase I antibody, and duration of Raynaud's phenomenon preceding the skin manifestations were associated with subsequent decline in pulmonary function.

Comment

Because many scleroderma patients will have milder ILD that will not necessarily progress, the challenge in treating is to determine when treatment should be started, in which patient, and with which drug. Treatment is most ideal and successful if progressive ILD can be stabilized early and effectively, while unnecessary and potentially toxic treatment is avoided for those patients whose ILD is less likely to

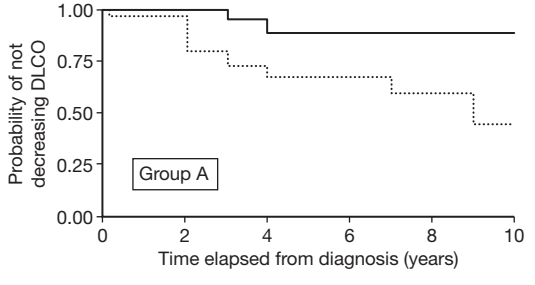

Fig. 14.4 Kaplan–Meier analysis of influence of initial forced vital capacity (FVC) measured within the first 3 years from disease onset on probability of subsequent severe diffusing capacity for carbon monoxide (DLCO) decline (< 40% of predicted) in patients with scleroderma lung. Solid line indicates baseline FVC ≥80%; broken line indicates baseline FVC < 80%. Source: Plastiras *et al.* (2006).

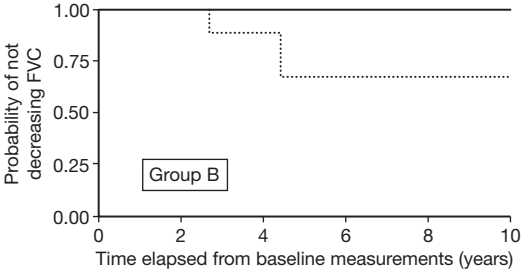

Fig. 14.5 Kaplan–Meier analysis of influence of initial forced vital capacity (FVC) measured after the first 3 years from disease onset on probability of subsequent decline of FVC in patients with scleroderma lung. Solid line indicates baseline FVC ≥80%; broken line indicates baseline FVC <80%. Source: Plastiras *et al.* (2006).

progress. However, there is little consensus regarding how best to assess scleroderma-related lung disease. No single predictor, including FVC, or set of predictors has been found consistently useful in predicting pulmonary function loss or survival, with discordant findings in part due to differences in patient populations and sizes studied, disease duration, illness criteria employed, and length of observation periods utilized.

This study paid particular attention to the timing of pulmonary function tests and found that FVC, when measured within the first 3 years from disease onset, may predict subsequent rate of change of lung function. Patients with normal FVC (≥80% predicted) early within illness had a greater likelihood of maintaining normal lung function than patients with abnormal FVC (<80% predicted) early on, similar to the report by Morgan |**6**|. Anti-topoisomerase I antibody is a risk factor for developing ILD but, as shown in this study, does not correlate with the severity of ILD over time.

The strengths of this study include the strict criteria used to define pulmonary function loss, which are more rigorous than that used in many other studies and higher than the within-individual variation of pulmonary function testing. Additionally, efforts were made to include a uniform patient group by excluding those with pulmonary hypertension. The main limitations to this study are the lack of description of HRCT abnormalities (ground glass opacities and/or fibrosis) used to identify patients, as well as its retrospective nature. Inclusion of a greater proportion of patients with more severe lung involvement and more frequent pulmonary function testing over time may have biased the results.

Mycophenolate mofetil is safe, well tolerated and preserves lung function in patients with connective tissue disease-related interstitial lung disease

Swigris JJ, Olson AL, Fischer A, *et al. Chest* 2006; **130**: 30–6

Background. Swigris and colleagues |7| evaluated mycophenolate mofetil (MMF) to treat ILD associated with a heterogeneous group of connective tissue diseases (CTDs) in a retrospective observational study. The primary outcome was safety and tolerability of MMF. The secondary objective was the impact of MMF on pulmonary physiology. Records of 28 patients who had received MMF for CTD-ILD and had returned for at least one follow-up visit were reviewed. Interstitial lung disease had been diagnosed by either lung biopsy (13/28) showing primarily fibrotic NSIP, or HRCT. The study examined the frequency and severity of side-effects associated with MMF and used longitudinal data analytical methods to determine the ability of MMF to maintain the lung function variables FVC (% predicted), total lung capacity (TLC,% predicted), and DLCO (% predicted). For each of these variables, the analytical models provided a mean value at three time points: before MMF initiation, at MMF initiation and after MMF initiation. With this approach, mean differences were compared in each variable measured over two specified time intervals – the first interval extending from before MMF up to its initiation, and the second interval from initiation of MMF to the most recent visit.

Interpretation. The most common underlying CTD was scleroderma (9/28), followed by poly-/dermatomyositis (5/28), and undifferentiated CTD (5/28). No patients had rheumatoid arthritis (RA). Twenty-two patients previously had received at least one other immunosuppressive drug (13 cyclophosphamide, nine azathioprine). The most common reason for initiating MMF (15/28) was intolerance to the initial agent. One patient stopped cyclophosphamide due to concern for length of exposure. In six patients, the treatment change was necessitated for progressive lung worsening, while in the remaining six patients, MMF was the first treatment used. The median dose of MMF was 2000 mg/day for a total of 35.9 patient-years. Six patients experienced side-effects, most commonly diarrhoea, after a median duration of 470 days (range 31–792 days), but side-effects resolved in all instances with dose reduction and no patient had to stop the drug on this account. Two did discontinue MMF for other reasons. Moderate restrictive lung physiology (median FVC 65% predicted) and severely reduced DLCO (median DLCO 38% predicted) were present when MMF was initiated. After MMF initiation, clinically significant increases in FVC of 2.6%, TLC of 4.0% and DLCO of 2.6% were observed (Table 14.1). There was also a trend towards a significant reduction in prednisone dose used between the first and second study intervals (15 mg/day vs.10 mg/day respectively, $P = 0.09$).

Comment

This is the first study evaluating MMF specifically for ILD associated with several CTDs. The recognized limitations of this retrospective study include the variability in therapeutic regimens that were used clinically, and the lack of systematic data collection. Notably, none of the patients had RA which is the most frequent CTD with which ILD may occur. The absence of RA patients may have been in part due to MMF having little clinically recognized benefit for RA joint manifestations, which usually dictates the choice of treatment. Because the majority of patients had scleroderma with a mean CTD duration of 4.4 years, the general stability

Table 14.1 Mean differences in pulmonary physiology over the two time intervals in this study*. Reproduced from |7|

Variables	Time interval 1, from the first PFT before MMF initiation to MMF initiation	Time interval 2, from MMF initiation to the most recent PFT	*P*-value
Duration, days	166 (50–646)	371 (32–1299)	
FVC (litres)	0.02 (0.25)†	0.08 (0.27)†	0.45
FVC (%)	0.67 (6.55)†	2.30 (7.38)†	0.47
TLC (litres)	0.06 (0.36)‡	0.22 (0.50)‡	0.33
TLC (%)	1.6 (6.82)‡	4.01 (9.6)‡	0.42
DLCO (ml/min/mmHg)	–0.73 (2.95)§	0.81 (2.05)§	0.09
DLCO (%)	–2.12 (10.79)§	2.58 (7.24)§	0.14

*Data are presented as mean (SD) or median (range).
†$n = 21$.
‡$n = 20$.
§$n = 19$.
DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; MMF, mycophenolate mofetil; PFT, pulmonary function test; TLC, total lung capacity.
Source: Swigris *et al.* (2006).

of pulmonary physiology observed may have been attributable to the expected behaviour of scleroderma-ILD, where the greatest rate of FVC loss occurs within the first 2 years of illness. Treatment of scleroderma-ILD remains controversial. Oral cyclophosphamide has only modest and transient benefits, and significant toxicities. In contrast, MMF did appear to be very well tolerated and safe, similar to the findings of Liossis and colleagues |**8**| in a small, open-label use study of six patients. Further evaluation of MMF in larger, prospective, randomized, placebo-controlled studies is warranted.

Comparison of disease progression and mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia

Kocheril SV, Appleton BE, Somers EC, *et al. Arthritis Rheum* 2005; **53**: 549–57

Background. Kocheril and colleagues |9| compared disease progression and mortality in patients with idiopathic interstitial pneumonia (IIP) with patients having ILD due to CTDs including scleroderma, RA, systemic lupus, PM, DM, Sjögren's syndrome, and mixed CTD. A case–control study design was used with control subjects defined as individuals with IIP ($n = 51$) and cases defined as patients with CTD-ILD ($n = 46$). Kaplan–Meier survival analysis and Cox proportional hazards regression were used to estimate survival, accounting for various demographic and clinical parameters, including pulmonary function tests and HRCT diagnosis and scoring of alveolar and interstitial abnormalities.

Interpretation. Median follow-up time was 4.4 person-years. Five-year survival in the IIP group was 51.9% (95% CI 30.8–69.4) vs. 43.4% (95% CI 21.1–63.9) in the CTD-ILD group. There were no significant differences between groups in HRCT diagnostic categories, particularly UIP and NSIP. In the CTD-ILD group, there was also no significant difference in HRCT diagnosis based on the specific type of CTD. High resolution computed tomography fibrotic score was a useful discriminator with a score ≥2 associated with decreased survival among the entire group. Age at diagnosis and the most recent FVC were significant predictors of mortality when adjusted for IIP vs. CTD-ILD diagnosis, sex, and interstitial/fibrosis score. The hazard of death increased 4% for every 1 year increase in age, and increased 2% for every unit decrease in FVC (% predicted). Contrary to expectation, CTD-ILD compared with IIP appeared to have a worse prognosis after adjustment for age. A higher fibrotic score also was suggestive of decreased survival.

Comment

Both IIP and CTD-ILD were found to have a poor prognosis. For the CTD-ILD group, the poor prognosis appeared to be irrespective of the specific CTD or treatment modality. Additionally, the prognosis for CTD-ILD seemed to be worse than IIP but, as the authors acknowledge, significance testing could not be applied and the overall survival of both groups appears to be similar. The absence of clear survival benefit for CTD-ILD compared to IIP is similar to studies by Hubbard |**10**| and Tansey |**11**|, but in contrast to other studies in which CTD-ILD has been observed to have a better prognosis |**12,13**|.

Additionally, this study found that the most important factor contributing to poor survival of CTD-ILD was the severity of fibrosis on HRCT, more so than the specific type of ILD. There was a trend in each group towards decreased survival corresponding with a specific HRCT diagnosis of UIP compared with NSIP but, because of the small number of cases, there was insufficient power to reach statistical significance. It is noteworthy that a fibrotic score ≥2 was strongly associated with an HRCT diagnosis of UIP, so the relationship between fibrotic score and survival could have been confounded by HRCT diagnosis. Also, HRCT fibrotic scoring is not routinely done or available in most clinical settings. Another limitation of this study is the retrospective nature of data collection, which impacted the uniformity of data available for evaluation. However, similar to the study of Plastiras |**5**| above, where FVC measured within the first 3 years from disease onset may predict the subsequent rate of change of pulmonary function in scleroderma, this study found the most recently measured FVC to be a significant predictor of mortality in CTD-ILD in general, giving support to the usefulness of monitoring pulmonary function tests at regular intervals.

Interstitial lung disease in patients with rheumatoid arthritis: comparison with cryptogenic fibrosing alveolitis over 5 years

Rajasekaran A, Shovlin D, Saravanan V, *et al. J Rheumatol* 2006; **33**: 1250–3

BACKGROUND. Rajasekaran and colleagues |14| compared baseline clinical, physiological and radiological characteristics in 18 RA patients with ILD and 18 matched control subjects with idiopathic cryptogenic fibrosing alveolitis (CFA). Assessment was repeated in all survivors at 5 years, and data on treatment and mortality were collected.

INTERPRETATION. The median age in each group was 77 years, and 10 patients in each group were male. All-cause mortality was high, with only 10 patients in total still alive after 5 years. More of the patients with RA-ILD survived to 5 years (eight RA-ILD vs. two CFA, $P = 0.03$) (Fig. 14.6). Median survival was significantly longer for patients with RA-ILD (60 months) than for those with CFA (27 months, $P < 0.05$). Death was due to progressive lung disease and respiratory failure more often in CFA patients than in those with RA-ILD (44% vs. 11% respectively, $P = 0.028$). Death in patients with RA-ILD was more often due to other causes. Age and duration of dyspnoea predicted death. Clubbing was more prevalent among patients with CFA and, accordingly, appeared clinically to predict poorer prognosis. When present in patients with RA-ILD, clubbing was a marker for the later development of lung cancer. Baseline DLCO predicted outcome, with the mean baseline value in survivors being 57.5% predicted, compared with 47.1% in those who died ($P < 0.01$).

Comment

The authors indicate that this study is the first to prospectively address the history of ILD in RA, and to compare the outcome with matched control subjects with idiopathic CFA (UIP). Usual interstitial pneumonia is the type of ILD most often

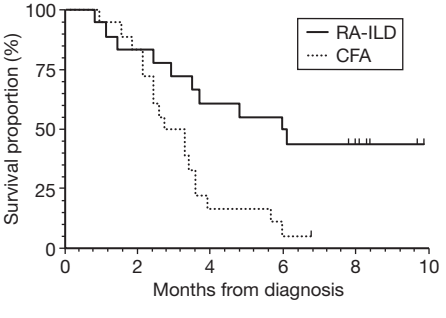

Fig. 14.6 A Kaplan–Meier plot to compare outcome in patients with rheumatoid arthritis-interstitial lung disease (RA-ILD) to those with cryptogenic fibrosing alveolitis (CFA). Source: Rajasekaran *et al.* (2006).

found in RA, as reported by Lee |**15**| (to be discussed below). This study's unique focus on RA-ILD with comparable control subjects is its strength, and is in distinction to the study by Kocheril |**9**| above, which included a number of different connective tissue diseases and was retrospective. This may help explain the difference in results, with the outcome of RA-ILD being found to be better than that idiopathic CFA in this study, similar to the findings of Flaherty |**13**|. Both studies emphasize the overall poor prognosis associated with ILD. Although prospective in nature, this study is limited by the small number and high age of patients, so the results may not be generalizable. More prospective, focused studies like this are needed to gain further understanding of individual forms of ILD in specific rheumatic diseases.

Histopathological pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease

Lee H-K, Kim DS, Yoo B, *et al. Chest* 2005; **127**: 2019–27

Background. Lee and colleagues |15| evaluated the clinical features and lung histopathological pattern of RA-ILD in a retrospective analysis. The medical records of 18 RA patients who had undergone surgical lung biopsy for symptomatic ILD were reviewed. Each biopsy was re-examined and reclassified according to the American Thoracic Society (ATS)/European Respiratory Society consensus classification of idiopathic interstitial pneumonia |1|. Clinical features and subsequent follow-up course for UIP and NSIP were compared.

Interpretation. The histopathological patterns of ILD were diverse and included UIP ($n = 10$) in the majority of patients, NSIP ($n = 6$) and inflammatory airway disease with the organizing pneumonia pattern ($n = 2$). Rheumatoid arthritis preceded ILD in most patients ($n = 12$). In three patients, ILD preceded RA, while in three other patients both conditions were diagnosed simultaneously. The majority ($n = 13$) of patients had restrictive lung deficits with or without low DLCO; two patients had only low DLCO. Patients with UIP were found to have typical HRCT abnormalities with reticular opacities and honeycombing predominantly distributed in the subpleural areas. In individuals with NSIP, HRCT revealed ground glass opacities and some reticular opacity. Patients with UIP and NSIP were significantly different in their male/female ratios (8/2 vs. 0/6 respectively, $P = 0.007$) and smoking history (current/former or non-smokers, 8/2 vs. 0/6 respectively, $P = 0.007$). Five UIP patients died, whereas there were no deaths among NSIP patients during median follow-up durations of 4.2 years and 3.7 years respectively.

Comment

There have been very few studies carefully examining the prognosis for specific types of ILD in the context of individual rheumatic diseases. The most common ILD occurring in RA in this study was UIP, confirming other reports, but contrasting with other rheumatic diseases, in which NSIP has been found most commonly |**12,16**|. Depending on the specific diagnostic criteria used, the prevalence of ILD

in RA has been reported to be as low as 5% to as high as 20% when additionally incorporating HRCT criteria |**17**|.

In this study, 8 out of 10 UIP patients were male, all of whom were current or former smokers, while all six NSIP patients were female, none of whom smoked. The authors make a very interesting postulation that smoking and/or gender may influence the development of the subtype of interstitial disease. Several risk factors for ILD in general have been previously described, including male sex, seropositive and nodular disease, longer disease duration, and early disability |**18**|. Saag *et al.* |**19**| reported that smoking was the most consistent independent predictor of radiographical and physiological abnormalities in RA-ILD. Wolfe |**20**| and Turesson *et al.* |**18**| identified smoking as a major risk factor affecting overall disease severity and development of extra-articular manifestations. However, none of these reports have suggested that smoking more specifically influences the diversity and subtype of ILD in RA. This study is limited by the small number of patients, so the author's observation will need to be further investigated.

Morphologic and quantitative assessment of CD20+ B-cell infiltrates in rheumatoid arthritis-associated non-specific interstitial pneumonia and usual interstitial pneumonia

Atkins SR, Turesson C, Myers JL, *et al. Arthritis Rheum* 2006; **54**: 635–41

Background. Atkins and colleagues |21| performed a morphological and quantitative analysis of B-lymphocytes and plasma cells in RA-associated interstitial pneumonia (RA-IP) in comparison with idiopathic IP and normal lungs. Open-lung biopsy specimens from patients with RA-IP ($n = 18$), patients with idiopathic IP ($n = 21$) and control subjects ($n = 11$) were stained with antibodies to CD20 and CD138. Morphological patterns of stained specimens were characterized and staining was quantified using computer-assisted image analysis.

Interpretation. In RA-IP, marked follicular B-cell hyperplasia was detected, which was limited almost entirely to peribronchiolar lymphoid aggregates. Plasma cells were also present in large numbers, but showed a more diffuse tissue infiltration. Quantification of B-cells demonstrated higher cellularity in RA-IP [median 2.0%, interquartile range (IQR) 1.0–5.7] compared with idiopathic IP (0.9%, IQR 0.5–2.1). Control specimens showed a significantly smaller number of B-cells compared with both diseases (0.4%, IQR 0.1–1.3). In RA patients who were smokers and in those who were male, the proportion of CD20+ tissue areas further increased to 4.3% (IQR 1.0–5.8) and 3.9% (IQR 0.7–6.9) respectively. Because of these differences, the authors noted that pathophysiological, prognostic and therapeutic insights regarding idiopathic ILD may not be readily applied to RA-associated lung disease.

Comment

This study demonstrated marked formation of peribronchiolar B-cell follicles and an increased number of CD20+ B-cells in RA-IP compared with normal lung tissue. Furthermore, the proportion of CD20+ tissue areas in RA-IP was significantly higher than in idiopathic IP. As the authors note, perhaps the most compelling evidence for a critical role of B-cells in RA, thus far, is the outcome of trials with rituximab, a chimeric anti-CD20 antibody that targets pre-B-cells and mature B-cells |**22**|. The increased cellularity found in RA-IP lung specimens, which contrasts with the predominantly fibrotic response and paucity of lymphocytic infiltrates in idiopathic IP, may have important implications for therapy in these patients, given the lack of any other proven efficacious treatment.

Interstitial pneumonitis associated with infliximab therapy

Villeneuve E, St-Pierre A, Haraoui B. *J Rheumatol* 2006; **33**: 1189–93

Background. Villeneuve |23| reported a case involving a patient with RA taking methotrexate (MTX) for more than 3 years who developed severe interstitial pneumonitis after the third infliximab infusion.

Interpretation. A 70-year-old man with long-standing erosive seropositive RA had persistent synovitis despite oral MTX 22.5 mg/week and prednisone 15 mg. Infliximab was added at 3 mg/kg because of inadequate control. Nine days after his third infusion, dyspnoea, fever and fatigue developed. He had no history of lung disease. Physical examination revealed respirations 30/min, temperature 40.2°C, and 94% O_2 saturation on room air, and clear lungs on auscultation. Chest radiography showed new bilateral interstitial infiltrates. Arterial blood gases on room air were: pH 7.46; *P*aCO_2 33 mmHg; *P*aO_2 61 mmHg; HCO_3 23 mg/dl. High-resolution computed tomography showed bilateral ground glass infiltrates in the superior two-thirds of the lung without fibrosis. No significant infection was found. MTX was discontinued and oral prednisone 100 mg/day was initiated. The patient slowly improved and was discharged 1 month later with home oxygen therapy and tapering prednisone. Infliximab was discontinued. Two months later, MTX was reintroduced. Six months later, chest radiography showed regression of the infiltrates, but HRCT was unchanged.

Comment

This case report is one of now several anecdotal reports describing the unexpected, abrupt onset of new ILD ('methotrexate pneumonitis') or significant acute worsening of previously stable ILD in RA patients shortly following the initiation of a tumour necrosis factor (TNF) agent. Reports have included not only other cases involving infliximab, but also etanercept |**24**| and adalimumab |**25**| when either added to existing MTX, leflunomide or azathioprine, or initiated as monotherapy. The mechanism is unknown. These reports should prompt continued awareness

not only for possible infectious complications, but also for more direct medication-related toxicity when new or acute respiratory symptoms arise around the time a TNF agent is initiated.

Conclusion

Interstitial lung disease has a major impact on the morbidity and mortality of rheumatic disease patients and these papers have helped to provide a better understanding of its frequency, pathogenesis, natural history, clinical relevance, prognosis and treatment.

The studies of Tashkin *et al.* |**3**| and Hoyles *et al.* |**4**| are the first prospective, randomized, double-blind, placebo-controlled trials to evaluate cyclophosphamide for scleroderma ILD. Each provides very important new information about the efficacy of cyclophosphamide, both orally and intravenously, which, unfortunately, was found to be substantially less than what had been anticipated, reflecting the continued need for further investigation to find better treatments for scleroderma. The report of Swigris *et al.* |**7**| evaluating the safety and tolerability of MMF is very encouraging, and provides support for larger, prospective, randomized, placebo-controlled studies, particularly for scleroderma-ILD of less than 4 years duration. Given the highly variable course of ILD in scleroderma, the report of Plastiras *et al.* |**5**| gives insight into the use of pulmonary function testing to help predict those patients who may have a worse prognosis and would be more ideal candidates for future prospective treatment trials. The papers by Kocheril *et al.* |**9**|, Rajasekaran *et al.* |**14**| and Lee *et al.* |**15**| contribute further to our understanding of the clinical relevance and prognosis of rheumatic disease-ILD in general and RA-ILD specifically. The Atkins *et al.* |**21**| study points out that the therapeutic and prognostic insights for RA-associated lung disease may be different than idiopathic ILD because of differences in the underlying immunohistology. While infectious pulmonary complications of the TNF agents are well known, the Villeneuve |**23**| case report calls increasing attention to an uncommon and poorly understood lung toxicity shared by TNF drugs, which may present in a clinical manner identical to infection.

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15

Immunosuppressant therapy in connective tissue disease

KEVIN MODER

Introduction

The past year was marked by a number of notable publications in the area of patients with connective tissue diseases (CTDs). As the title indicates, this chapter will focus on therapeutic interventions.

Ideally, therapeutic interventions would be selected using evidence-based medicine; decisions would be based on data from large prospective, randomized, controlled trials. Unfortunately, large, prospective, randomized, controlled trials are seldom conducted in patients with CTDs. This is in part due to the relative rarity of the CTDs and the heterogeneous disease manifestations.

Designing studies in patients with CTDs is challenging because not all of the patients with the same disease have the same clinical features. This makes entry criteria and outcome assessments more problematic. Therefore, some of the studies described in this article have small numbers of patients and include retrospective studies and open-label trials. Nonetheless, these studies have made a valuable contribution to the treatment of CTD patients.

Many fine articles regarding therapy for CTD patients were published in the past year. It was difficult to choose just 10. While the articles I have chosen each represent a significant contribution to the literature, there were many other articles that could not be included. The studies described here include the use of new modalities, as well as the application of previously utilized agents for new purposes. Several papers validate therapies which have been used empirically, previously based on anecdotal information.

In a landmark article by Burt and colleagues, stem cell transplantation was demonstrated to be efficacious in patients with refractory systemic lupus erythematosus (SLE). They calculate a 5-year disease-free survival of 50%.

The next three articles, by Smith, Gottenberg, and Leandro, describe the efficacy of rituximab, an anti-CD20 monoclonal antibody in SLE and other CTDs.

Previously, mycophenolate mofetil (MMF) had been shown to be efficacious in patients with diffuse proliferative lupus nephritis. The article by Karim details the benefit of MMF therapy in patients with membranous lupus nephritis. The

subsequent article by Liossis demonstrates that MMF is also beneficial in CTD patients with interstitial lung disease (ILD); this study includes patients with early scleroderma lung.

The article by Nadashkevich and colleagues describes the results of a randomized trial of cyclophosphamide versus azathioprine for patients with scleroderma. Also regarding scleroderma lung disease, Tashkin's double-blind, randomized, placebo-controlled trial published in the *New England Journal of Medicine* demonstrates a significant beneficial effect with cyclophosphamide therapy (see Chapter 14).

The final article also deals with use of cyclophosphamide. Somero and colleagues report a protocol of Lupron therapy that reduces the potential reproductive toxicity of cyclophosphamide therapy in young female SLE patients.

Non-myeloablative haematopoietic stem cell transplantation for systemic lupus erythematosus

Burt RK, Traynor A, Statkute L, *et al. JAMA* 2006; **295**: 527–35

Background. Systemic lupus erythematosus (SLE) is a disease that continues to cause significant morbidity and mortality in spite of current therapies |1|. There remain patients who are refractory to current therapies. In addition, current immunosuppressive therapies are associated with significant adverse effects. Unfortunately, even for those who are able to obtain a remission, the disease is not cured with traditional therapy as discontinuing medications leads to an increased risk of lupus flare |2|. A previous report from Jayne and colleagues demonstrated encouraging results for refractory patients with stem cell transplantation |3|. Interestingly, some patients had a long-term remission that potentially could represent cure.

Interpretation. Burt and colleagues describe the results of a single-arm trial of 50 patients with refractory SLE who underwent stem cell transplantation. Stem cells from the peripheral blood were mobilized using cyclophosphamide 2 g/m^2 and granulocyte colony stimulating factor (5 mg/kg/day). They were reinfused after treatment with cyclophosphamide 200 mg/kg and equine anti-thymocyte globulin 90 mg/kg. Treatment related mortality was 2%. Five-year survival was 84% and the predicted disease-free survival at 5 years was 50%.

Comment

This trial is important to patients with SLE for several reasons. First, it offers a potential option for patients who have been refractory to other therapy. Secondly, however, it also holds promise in that there was a predicted 5-year disease-free survival for half of those undergoing treatment. These patients were on only very modest immunosuppression with low dose prednisone and hydroxychloroquine. Of note, the levels of autoantibodies also significantly decreased with treatment

(Fig. 15.1). It is possible that stem cell transplantation could represent a true cure of the underlying disease but only time will tell.

The treatment-related mortality was not zero but was low at 2%; one patient died from an opportunistic infection. Using intent to treat analysis, the mortality was 4% as another patient died from complications of lupus after delaying the stem cell procedure. This mortality was significantly less than in previous reports |**3**|. The authors speculate that this may have been due to the fact that the prior report reported cases from multiple centres using varying protocols. All of the patients were treated at Burt's institution. The authors suggest this reduced mortality may be a centre-related effect that reflects the conditioning regimen used, supportive care guidelines, and their experience in transplanting patients with SLE.

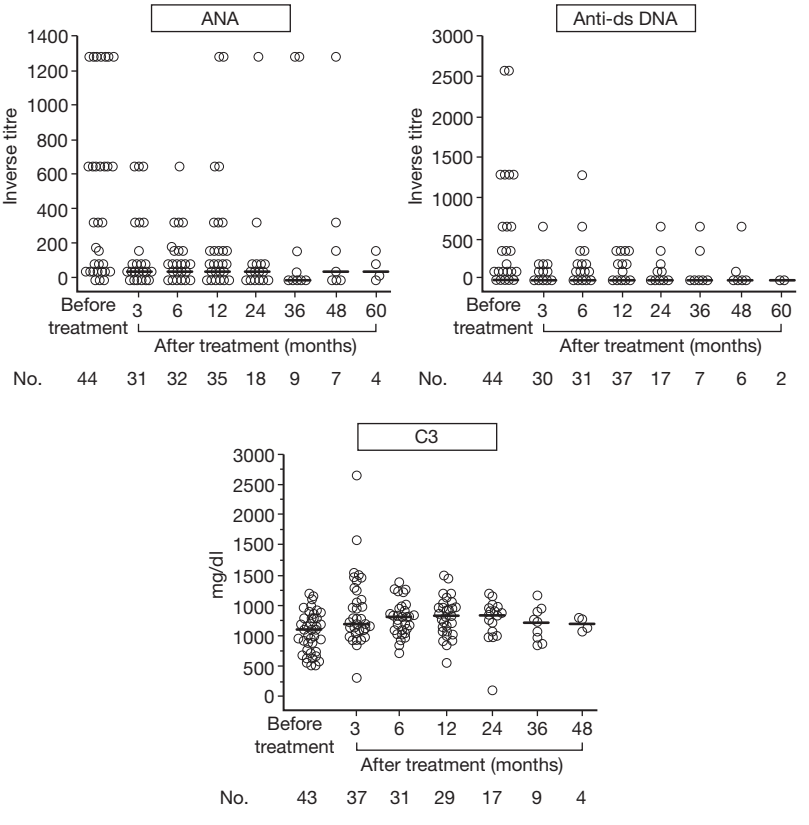

Fig. 15.1 Autoantibody results before and after treatment for anti-nuclear antibody (ANA), double-stranded DNA and the corticosteroid dose in mg/day before and after treatment. Source: Burt *et al.* (2006).

Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis

Smith KG, Jones RB, Burns SM, Jayne DR. *Arthritis Rheum* 2006; **54**: 2970–82

Background. Rituximab is a human/murine chimaeric monoclonal antibody directed against CD20 on B-lymphocytes |4,5|. Systemic lupus erythematosus is a disease marked by overproduction of autoantibodies and, therefore, B-cells probably play a major role in SLE. Several initial studies have shown that rituximab has potential efficacy for treatment of patients with SLE |6,7|. Efficacy in vasculitis has also been demonstrated |8|. This was a prospective study that used a uniform dosing regimen for all patients. The protocol included cyclophosphamide, which accompanied the initial dose of rituximab. Rituximab was given in a dose of 375 mg/m² weekly for 4 weeks. Patients with SLE and vasculitis were included in this study. Systemic lupus erythematosus patients had to have a British Isles Lupus Assessment Group (BILAG) grade A manifestation or 3 grade B manifestations for entry |9|. A grade A manifestation is usually a severe active manifestation of SLE, such as active nephritis that often requires cyclophosphamide. Indeed, 7 of 11 of the SLE patients had received cyclophosphamide therapy. All SLE patients required therapy with an immunosuppressive and corticosteroids. The lupus patients had been on a median of three immunosuppressive agents each.

Interpretation. All patients had B-cell depletion in the peripheral blood at 4 weeks. B-cell regeneration occurred in 19/22 at a median of 9 months. However, in three patients B-cells remained absent up to 30 months out from rituximab therapy. Of the SLE patients, six out of eleven achieved remission while the other five did achieve partial remission. Mean prednisone dose was decreased significantly but modestly from 10 mg/day to 5 mg/day at 12 months (Fig. 15.2). In six patients with SLE nephritis, the median 24-h proteinuria fell from 4.6 to 0.45 g after 12 months (Fig. 15.3). Nine out of 11 patients with vasculitis achieved complete remission. The relapse rate was 7 out of 11 in SLE, a median of 12 months after therapy; 6 out of 10 in the vasculitis group a median of 16 months after therapy. Adverse events were limited to infections and infusion reactions.

Comment

While both the SLE and vasculitis patients improved with rituxan therapy, the relapse rate was significant in both groups. While the rituxan therapy was generally well tolerated, there is some concern regarding the lack of repopulation of the B-cell pool in some patients. In patients in whom the B-cells have not returned more than 2 years after rituxan therapy, it is possible that they will not. The absence of B-cells could lead to potential long-term consequences, such as immunosuppression or loss

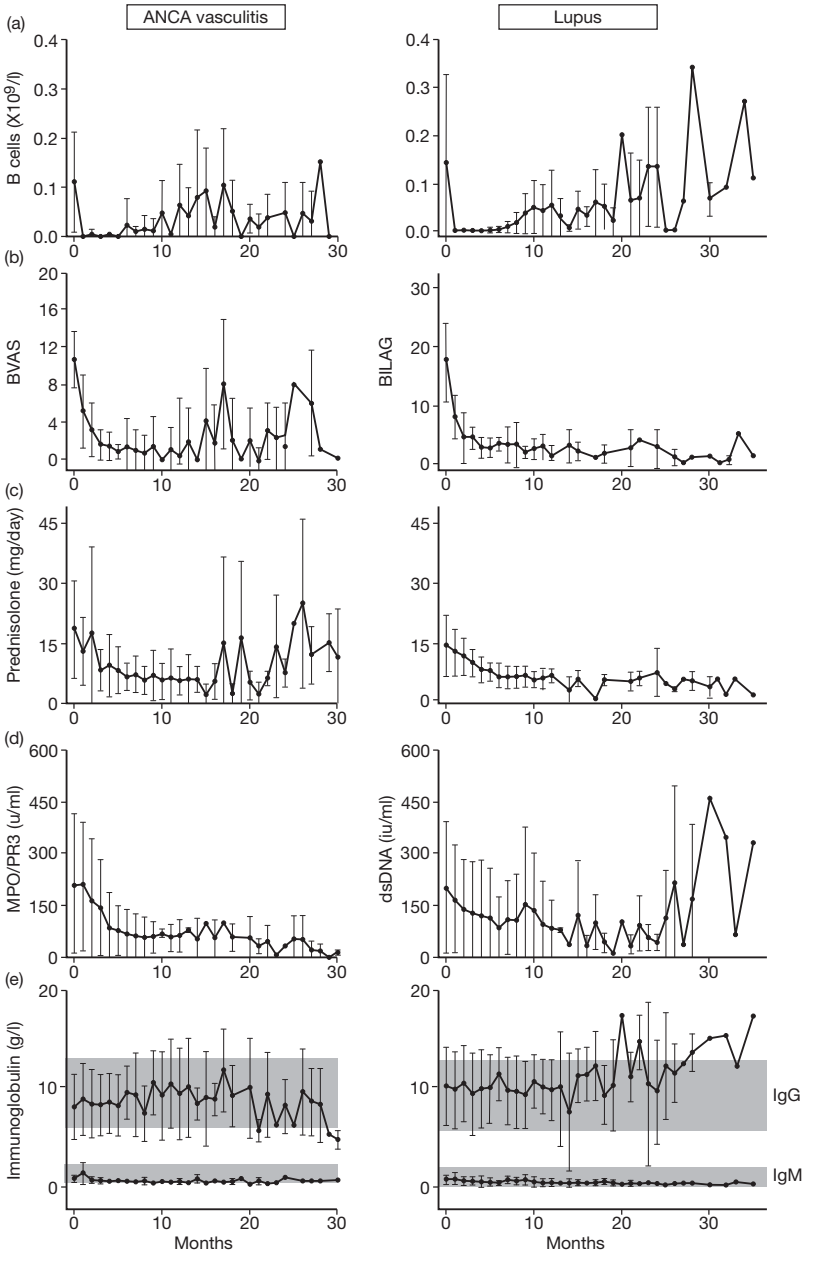

Fig. 15.2 B-cell population, the Birmingham Vasculitis Activity Score (BVAS) or British Isles Lupus Assessment Group (BILAG) score, the mean prednisolone dose, the myeloperoxidase (MPO)/proteinase 3 (PR3) value or double-stranded DNA value, and the immunoglobulin levels for patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis and lupus following treatment. Source: Smith *et al.* (2006).

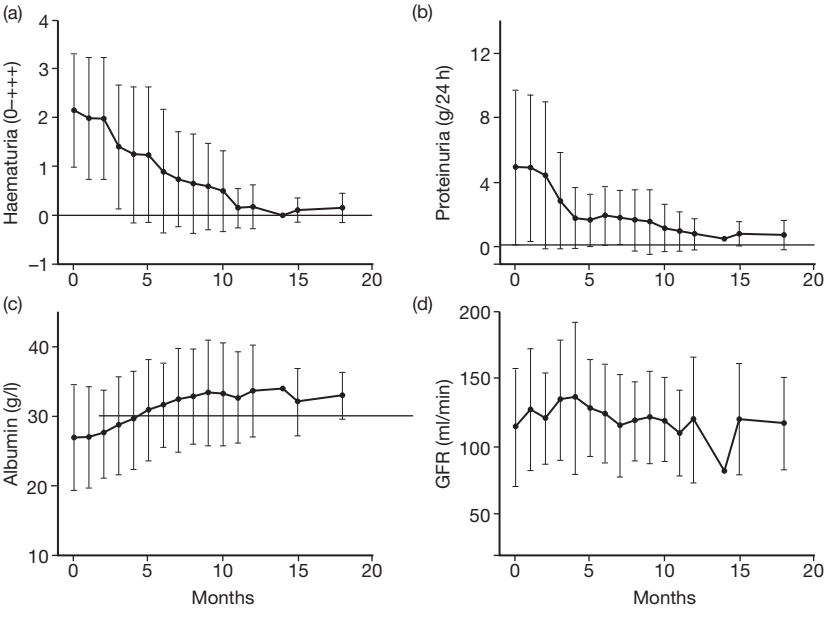

Fig. 15.3 Response to rituximab in patients with lupus nephritis. (a) Haematuria, (b) proteinuria, (c) serum albumin and (d) glomerular filtration rate (GFR). Source: Smith *et al*. (2006).

of immune surveillance. It is prudent that these patients be followed long term for increased risk of infections and possibly malignancies. It would also be desirable to try to identify some marker for patients who are at risk for the lack of repopulation of the B-cell pool.

Presumably, at a minimum the efficacy of vaccinations in this subset of patients would be reduced. The data regarding efficacy of vaccinations in patients treated with rituximab are very limited but are suggestive that vaccinations are less efficacious in patients with rheumatic diseases treated with rituximab |**10,11**|. Perhaps, it would be prudent to consider updating patients' vaccinations 4 weeks prior to receiving rituximab in those patients for whom the rituximab is being initiated in a non-emergent setting.

Tolerance and short-term efficacy of rituximab in 43 patients with systemic autoimmune diseases

Gottenberg JE, Guillevin L, Lambotte O, *et al. Ann Rheum Dis* 2005; **64**: 913–20

Background. In addition to its use in SLE, rituximab has been used in patients with other connective tissue diseases including polymyositis, dermatomyositis and Sjögren's syndrome |12–14|.

Interpretation. This study was a retrospective review of the experience of 866 internal medicine and rheumatology practitioners regarding their experience with rituximab in the treatment of rheumatic diseases (Table 15.1). They found 43 analysable cases that included 14 patients with rheumatoid arthritis (RA), 13 with SLE, six with primary Sjögren's syndrome, five with vasculitis and five with other autoimmune conditions. Two of the RA patients and two of the Sjögren's patients had coexistent lymphoma. Rituximab dose in 35 of the patients was 375 mg/m^2 weekly for 4 weeks. There were 11 adverse reactions noted in 10 patients including one episode of serum sickness in a patient with Sjögren's. Rituximab therapy was felt to be efficacious in 30 patients (70%). This included 11 with RA, nine with SLE, and five with Sjögren's.

Comment

Because this study was retrospective and involved a diverse group of patients with different rheumatic diseases, potential conclusions related to specific disease states are limited. However, the findings do suggest that rituximab may have potential applicability in a variety of CTDs.

Interestingly, an unusual adverse event, serum sickness was reported in one patient in this study with Sjögren's syndrome. A prior report also noted three out of eight patients with primary Sjögren's developed serum sickness following rituximab infusion |**12**|.

Future experience using rituximab in patients with Sjögren's may shed some light on this. Perhaps, it may be possible to identify patients who are at risk for serum sickness and pre-treat them to prevent this from occurring.

Table 15.1 Demographic and clinical features of patients with Sjögren's treated with rituxan

Case	Sex/age/ duration (year)	Previous IS	Clinical involvement at beginning of rituximab treatment	No. of infusions × dose (mg)/no. of MP pulses concomitant IS	Adverse event (Y/N)
28	F/58/15	HG	Digestive lymphoma (MALT)	$4 \times 375/m^2$/4/MP (500)/HQ	N
29	F/43/4	No	Salivary lymphoma (MALT)	$4 \times 375/m^2$	Serum sickness
30	F/71/5	HQ/CPH/ AZA	Vasculitis	$4 \times 375/m^2$	N
31	F/58/2	CPH	Vasculitis	$4 \times 375/m^2$	N
32	F/74/18	MTX/ETA/ inflix	Parotid gland enlargement, polysynovitis	$4 \times 375/m^2$/4/MP (40)	N
33	F/41/8	CPH	Parotid gland enlargement, polyarthralgia	$2 \times 375/m^2$/2/MP (40)	Infusion-related

AZA, azathioprine; CPH, cyclophosphamide; cryo, cryoglobulinaemia; ETA, etanercept; F, female; HQ, hydroxychloroquine; inflix, infliximab; IS, immunosuppressants; M, male; MALT, mucosa-associated lymphoid tissue; MP methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; pos, positive; RF, rheumatoid factor (determined by

Efficacy on extraglandular involvement (Y/N)	Initial/ final VAS	Efficacy on objective dryness (Y/N)	Time to response (weeks)/ follow-up (months)	Prednisone initial/last	RF (IU/l) initial/last ($n < 20$)	Relapse (Y/N)/ time to relapse (months)
Y	Dryness VAS: 80/50	Stable Schirmer	4/6	9/6	44/0	N
N	NA	NA	–/11	0/0	499/423	–
Y	NA	Stable Schirmer, salivary flow = 0	8/8	15/7.5	RF: 109/57 Cryo: 1%/ neg	N
Y	NA	NA	8/8	10/0	RF: 170/ neg; cryo: pos/neg	N
Y	Dryness VAS: 60/20 Fatigue VAS: 70/0	NA	4/7	6/6	RF: 130/NA	N
Y	Dryness VAS: 20/0 Fatigue VAS: 80/0	NA	4/7	4/0	NA	N

nephelometry, except RF stated as 'pos/neg', determined by latex); VAS, visual analogue scale; Y, yes; –, not relevant.
Source: Gottenberg *et al.* (2005).

B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients

Leandro MJ, Cambridge G, Edwards JC, *et al. Rheumatology* 2005; **44**: 1542–5

Background. While rituximab appears to have efficacy in SLE, at present there is not a consensus regarding the optimal treatment regimen. Some studies have used cytotoxic agents such as cyclophosphamide in combination with rituximab, while others have used it with high dose corticosteroids or both cyclophosphamide and corticosteroids. In addition some regimens have used the dosing protocol more commonly used in haematologic malignancies, 375 mg/m² weekly for four doses, while others have used more of an 'RA' protocol utilizing two doses, 2 weeks apart of 1 g each.

Interpretation. This study reports the findings of an open-label trial of SLE patients treated with rituximab and followed for at least 3 months. All patients had failed conventional therapy. The investigators used two rituximab regimens. The first six patients were treated with 500 mg×2 doses weekly with cyclophosphamide, 750 mg×2 intravenously together with oral prednisolone 60 mg daily×5 days with each infusion. The subsequent patients were treated with the same doses of cyclophosphamide but received rituximab 1000 mg×2 doses and methylprednisolone 250 mg×2 intravenously instead of oral steroids. Two patients did not receive cyclophosphamide because of allergy or refusal. Only one patient failed to achieve peripheral B-cell depletion. The period of depletion ranged from 3 to 8 months. However, there was one patient in whom the B-cells did not return even after 4 years of follow-up. Patients had improvement in BILAG scores, protein/creatine ratios, serum C3 complement, and anti-ds DNA levels (Fig.15.4). There did not seem to be a significant difference in the outcomes of the patients treated with the two different regimens.

Comment

Of note, in this trial also, there was one patient who failed to reconstitute their B-cell repertoire even several years after receiving the rituximab.

The exact dosing regimen for rituximab in patients with SLE needs to be further studied. The optimal dose, number and timing of doses, as well as the use of concomitant medications such as corticosteroids and cyclophosphamide needs to be clarified in future studies. These may be best evaluated in a randomized clinical trial that would compare several regimens head to head. In addition, we need to further identify the most appropriate SLE patients in whom rituximab should be used. Up until this time, it has been reserved for patients who have failed traditional therapy. Perhaps, introducing this agent earlier in the disease course may be of benefit, but again this can only be determined by future studies.

There were also patients in this group that were successfully re-treated with rituximab. Patients with SLE who are treated with rituximab are much more likely to develop human anti-chimaeric antibodies (HACA) than those treated with

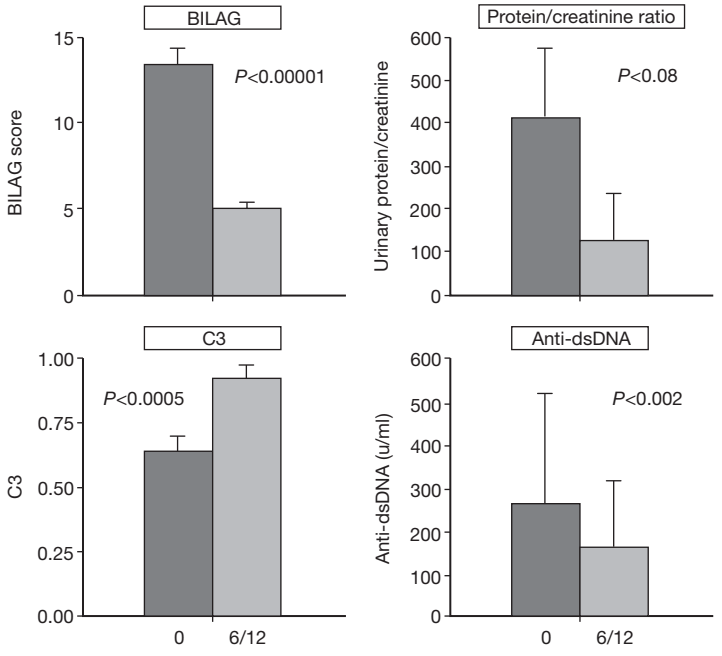

Fig. 15.4 British Isles Lupus Assessment Group (BILAG) score, protein/creatinine ratio, C3 level and anti-double-stranded DNA levels in patients before and after treatment with rituxan. Source: Leanardo *et al.* (2005).

rituximab for haematological malignancies. This study describes one patient in whom retreatment was unsuccessful, presumably because of the development of HACA.

The question that arises is what is the maximum number of successful courses of rituximab that one could receive? Additionally, is rituximab a feasible long-term therapy for SLE patients? Also, if, in fact, HACA antibodies limit the efficacy of future rituximab infusions as is suggested, then would it be imprudent to use rituximab early in disease course but instead reserve it for future need? Additional studies are needed to answer these important questions.

Reduction of proteinuria with mycophenolate mofetil in predominantly membranous lupus nephropathy

Karim MY, Pisoni CN, Ferro L, *et al. Rheumatology* 2005; **44**: 1317–21

Background. Mycophenolate mofetil is an anti-metabolite that is being used with increasing frequency in patients with CTDs |15|. It has been found to be useful for patients with vasculitis, inflammatory myopathy, non-renal lupus, and diffuse proliferative lupus nephritis |16–19|. Membranous lupus nephropathy represents a difficult clinical situation in that up until now there has not been an efficacious therapy |20|.

Interpretation. In this retrospective study, the authors evaluated the response of 10 patients with biopsy-proven membranous lupus nephritis. The patients' previous therapies included cyclophosphamide, azathioprine, cyclosporin, and corticosteroids. Patients were treated with MMF for a mean of 18.8 months. The maximum dose of MMF used varied from 1 to 2.5 g/day. Median 24-h urine protein was reduced from 2.26 to 0.66 g, which was statistically significant (Fig. 15.5). Serum albumen also increased significantly. Serum creatinine did not change. Adverse events included infections in two patients and gastrointestinal symptoms in half. Only one patient discontinued MMF therapy secondary to adverse effect from the medication.

Comment

While this was a retrospective study, it does provide compelling evidence for the efficacy of MMF in the treatment of membranous lupus nephritis. In the author's experience, many clinicians are now using MMF for membranous lupus nephritis.

While MMF did reduce proteinuria and improve albumen, it is not surprising that the serum creatinine did not change with therapy. Unfortunately, the authors do not include 'normal' values for the serum creatinine in their lab. However, as is the case in many patients with membranous nephropathy, the serum creatinine in the patients included in this study appears to be normal or near normal initially.

Erythrocyte sedimentation rate, which has been linked to lupus activity and damage accrual, did not change either with MMF therapy |**21**|. Levels of dsDNA antibodies also did not decrease nor did European Consensus Lupus Activity Measurement Index |**22**|. Mean daily prednisolone dose did not change with MMF therapy either. It is possible that because of small patient numbers, improvement in these measures may not have been noted. The mean oral prednisolone dose, for example approached statistical significance with a *P*-value of 0.054.

Somewhat unexpectedly, the mean lipid levels also did not improve with therapy of the proteinuria. This might be explained by the fact they were measured in only seven patients, and the median level of proteinuria seen in these patients was modest (< 3 g/24 h).

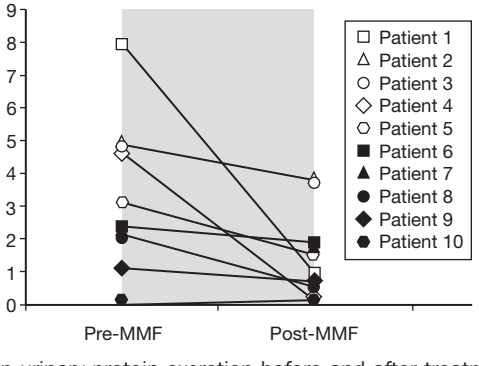

Fig. 15.5 Changes in urinary protein excretion before and after treatment with mycophenolate mofetil. Source: Karim *et al.* (2005).

To confirm its efficacy, a larger prospective trial of MMF in the treatment of membranous lupus nephropathy is justified. A future trial could also hopefully address the question of the optimal dose and duration of therapy. As this study was retrospective, the doses of MMF used and the duration of therapy were varied.

Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease

Liossis SN, Bounas A, Andonopoulos AP. *Rheumatology* 2006; **45**: 1005–8

Background. Clinically significant ILD is seen in about 40% of patients with systemic sclerosis and it is a leading cause of morbidity and mortality in these patients |23,24|. In fact, the mortality rate among patients with severe restrictive lung disease, as measured by a forced vital capacity (FVC) of < 50% of predicted is 42% at 10 years |25|. This underscores the need for an effective therapy for this entity. There has been some data regarding the efficacy of cyclophosphamide in the treatment of scleroderma lung disease. However, cyclophosphamide is associated with significant toxicity. MMF is well tolerated and generally tends to have fewer adverse events in association with treatment than cyclophosphamide |26|.

Interpretation. This study was a prospective, single-centre, open-label trial. Five consecutive patients with systemic scleroderma and alveolitis were entered initially; a sixth patient, with longstanding scleroderma lung disease, was later added. Patients were treated initially with MMF 500 mg, BID with dose escalation to 2 g/day after the first month of therapy. Patients were also given prednisolone 7.5–10 mg daily. Patients were assessed for response after 4–6 months of therapy. DLCO improved significantly compared with pretreatment values (75% vs. 64% of predicted, $P = 0.033$). Values of FVC also improved and approached statistical significance (mean FVC 76% vs. 66% of predicted, $P = 0.057$). Ground glass opacities on computed tomography (CT) of the lungs improved in four patients (Fig. 15.6). Five out of six patients had clinical, functional, and radiographic improvement. One patient did withdraw from the study secondary to treatment failure. No serious adverse events were noted with the MMF therapy.

Comment

T-cells appear to play a role in the pathogenesis of scleroderma so it is not unexpected that MMF may be beneficial in this disease. Mycophenolate mofetil inhibits T-cell proliferation and effects intracellular adhesion to endothelial cells.

The authors point out that while they did not formally measure skin scores, they noted improvement in the patients' skin also. Once again, it was found that MMF was well tolerated in patients with a CTD.

This study suggests that additional larger studies of MMF are justified in patients with scleroderma. Initial studies might be done first in patients with early disease but the response of the patient in this study who had disease of 10 years duration is also encouraging, in that MMF might be a therapy that will be beneficial to patients even later in their disease course.

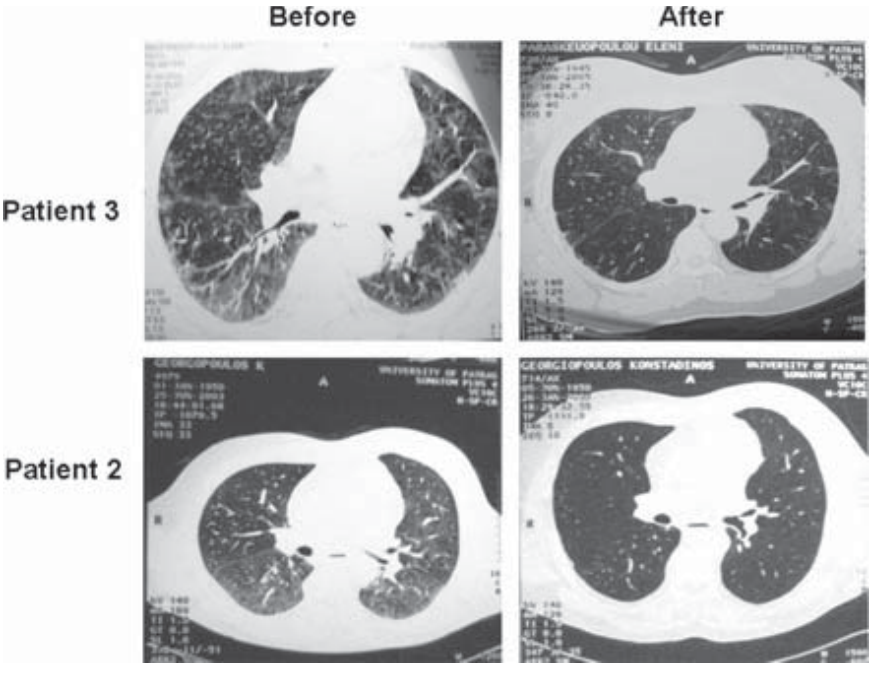

Fig. 15.6 High-resolution computed tomography scan showing appearance of the lung before and after treatment with mycophenolate mofetil. Source: Liossis *et al.* (2006).

A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis

Nadashkevich O, Davis P, Fritzler M *et al. Clin Rheumatol* 2006; **25**: 205–12

Background. Some older studies have suggested scleroderma has a 5-year survival rate of about 30% |27|. While the survival rate probably has significantly improved, unfortunately, there are no established efficacious therapies for scleroderma. D penicillamine has been used but a controlled trial did not show significant benefit |28|. Results with minocycline in an open-label study were initially encouraging but subsequently a larger trial did not show significant benefit |29,30|. Methotrexate showed only minimal benefit compared with placebo in a randomized controlled trial |31|. It is questionable as to whether the difference really was clinically significant. A more recent small study suggested that azathioprine (AZA) may at least have a stabilizing effect on interstitial lung disease in scleroderma |32|. Not surprisingly, given the lack of efficacious agents for treatment of scleroderma, there have been very few controlled trials comparing agents.

Interpretation. This study was an international collaborative project done in the Ukraine and Canada. It was a prospective, randomized trial comparing the efficacy of azathioprine versus cyclophosphamide in patients with early diffuse scleroderma (Table 15.2). Sixty consecutive patients were enrolled: 30 were assigned to receive cyclophosphamide orally 2 mg/kg daily for 12 months, then 1 mg/kg daily; and 30 were given oral azathioprine 2.5 mg/kg daily for 12 months and then 2 mg/kg daily thereafter. Both groups also received oral prednisolone 15 mg daily initially which was tapered by 2.5 mg monthly; patients were off prednisolone by the end of month 6. Outcomes for the trial had all been previously validated and included modified Rodnan skin score, attack frequency of Raynaud's phenomenon, DLCO, FVC, and erythrocyte sedimentation rate (ESR). The cyclophosphamide-treated group showed statistically significant improvements in modified Rodnan skin score, frequency of Raynaud's, and ESR at 12 months; these differences became more pronounced at 18 months. There was no statistically significant change in the FVC or DLCO, although there was a tendency for improvement in the DLCO. In the azathioprine-treated group, there was statistically significant worsening in the DLCO and FVC. When the cyclophosphamide-treated group was compared with the azathioprine-treated group, all studied outcome measures favoured the cyclophosphamide group. Adverse events in both groups were relatively uncommon. There were several patients with hair loss in the cyclophosphamide group; leukopenia and nausea were noted in both groups.

Comment

This study is important for several reasons. First, it is a large, long-term study. Secondly, it is one of few studies in patients with scleroderma comparing two agents. The results of this study, especially when viewed with the findings from the next article by Tashkin, firmly establish the efficacy of cyclophosphamide as a treatment for scleroderma. Questions, however, remain regarding the optimal use of cyclophosphamide in scleroderma. Perhaps, cyclophosphamide could be utilized as initial therapy in scleroderma patients and then maintenance be initiated with MMF considering the studies done by Liossis and Swigris covered earlier in this chapter.

Table 15.2 Comparison of the mean ± SD changes in the outcome measures between the two groups after 18 months of treatment

Variables	CYC group ($n = 30$)	AZ group ($n = 30$)	P
MRSS (0–51)	–9.47 ± 0.84	0.2 ± 0.21	< 0.001
Attack frequency of RP (no. per day)	–1.59 ± 0.11	0.41 ± 0.08	< 0.001
ESR (mm/h)	–14.6 ± 1.4	1.3 ± 0.5	< 0.001
FVC (% predicted)	3.3 ± 0.7	–11.1 ± 1.0	< 0.001
DLCO (% predicted)	0 ± 1.6	–11.6 ± 1.3	< 0.001

AZ, azathioprine; CYC, cyclophosphamide; DLCO, carbon monoxide diffusing capacity; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; MRSS, modified Rodnan skin score; RP, Raynaud's phenomenon.
Source: Nadashkevich *et al.* (2006).

The continued improvement out to 18 months with cyclophosphamide suggests that perhaps this therapy should be utilized for that length of time, but then it is possible that another agent could be substituted. Perhaps cyclophosphamide could be used for induction therapy. Mycophenolate mofetil would be a potential agent that could be considered for maintenance therapy, based on these recent reports. However, future trials will be needed to answer this question.

Cyclophosphamide versus placebo in scleroderma lung disease

Tashkin DP, Elashoff R, Clements PJ, *et al. New Engl J Med* 2006; **354**: 2655–66

Background. About 40% of patients with systemic sclerosis have clinically significant interstitial lung disease. It is a leading cause of morbidity and mortality in patients with diffuse scleroderma |23,24|. In scleroderma patients with severe restrictive lung disease, as measured by an FVC of < 50% of predicted, the 10-year survival is just 42% |28|. Obviously, this is a significant clinical problem. In previous papers covered in this chapter by Liossis and Swigris, there is evidence that MMF is beneficial in this subset of patients. In the prior article by Nadashkevich, cyclophosphamide is shown to be beneficial in patients with scleroderma. This article goes even further in exploring the efficacy of cyclophosphamide use, specifically for scleroderma patients with interstitial lung disease.

Interpretation. This study was a double-blind, randomized placebo-controlled trial in patients with scleroderma and lung disease (either active alveolitis or interstitial lung disease). One hundred and fifty-eight patients were recruited at 13 different centres and 145 patients completed at least 6 months of therapy. Patients were treated initially with 1 mg/kg/day of cyclophosphamide orally; this dose was gradually increased to a maximum of 2 mg/kg daily. There was a statistically significant difference in the mean FVC favouring the cyclophosphamide-treated group versus placebo at both 12 and 24 months. The mean predicted FVC difference was 2.5%. Beneficial effects were also demonstrated in dyspnea, skin thickening, and health-related quality of life assessment scores. Adverse events were more frequent in the cyclophosphamide-treated group but there was no significant difference in the number of serious adverse events.

Comment

This study is a significant contribution to the literature in that it demonstrates that cyclophosphamide has benefit to patients with scleroderma and associated interstitial lung disease. While the benefit in lung function was modest, it was sustained at 24 months of follow-up.

The question that is raised, however, is whether or not all patients with scleroderma should be treated at the time of diagnosis with cyclophosphamide.

Possibly one should initiate therapy with cyclophosphamide and then switch to another medication such as MMF for maintenance. Alternatively, one could argue that perhaps initial therapy should be with MMF and cyclophosphamide added only later in patients that fail to respond or who develop interstitial lung disease. Future studies will be necessary to determine the optimal use of this agent in patients with scleroderma.

Future long-term studies, may be necessary to document the effect of cyclophosphamide on survival in scleroderma patients.

Use of gonadotropin-releasing hormone analogue for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus

Somers EC, Mardez W, Christman GM, *et al. Arthritis Rheum* 2005; **52**: 2761–7

Background. In addition to the morbidity and mortality from the underlying disease, many patients with CTDs suffer adverse events from the medications used to treat them. In particular, many young women with SLE who are treated with cyclophosphamide suffer from premature ovarian failure. Somers and colleagues suggest an effective way to protect against this untoward effect of cyclophosphamide.

Interpretation. Young females were recruited who were receiving intravenous cyclophosphamide for SLE. This study was nested in a larger intravenous cyclophosphamide protocol that has been ongoing since 1985. Twenty patients were treated with 3.75 mg monthly injection of leuprolide acetate during their cyclophosphamide therapy. These patients were compared with 20 age-matched control subjects, who were also matched for cumulative cyclophosphamide dose. Reproductive status was determined after a minimum of 3 years of follow-up. The primary outcome was time to premature ovarian failure (POF). Premature ovarian failure developed in 1 out of 20 leuprolide-treated patients compared with 6 out of 20 control subjects ($P < 0.050$). Kaplan–Meier survival estimates to time of POF are shown in Fig. 15.7. There was no statistically significant difference in adverse events comparing the treated patients with control subjects.

Comment

This study is important in that it suggests a preventative measure that can be taken to forestall a common but serious side-effect of cyclophosphamide. The incidence of POF in rheumatic disease and cancer populations treated with cyclophosphamide varies from 12% to 83%, depending on factors including patient age, mode of administration and cumulative dose of cyclophosphamide |**33,34**|.

This therapy has potential for use not only in SLE patients but also for patients with other rheumatic diseases that require cyclophosphamide treatment. In

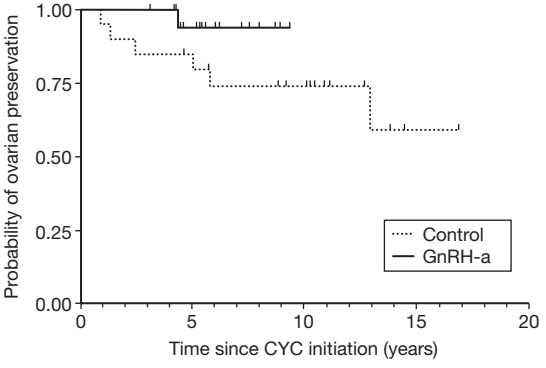

Fig. 15.7 Kaplan–Meier survival estimates to the time of premature ovarian failure in those treated with leuprolide versus control subjects. Source: Somers *et al.* (2005).

addition, it may have application to cyclophosphamide-treated cancer patients too. Its use in cancer patients may be limited by the potential effects of the agent on the underlying malignancy, however. Nonetheless, this study may have implications beyond the realm of rheumatology alone.

Conclusion

In summary, the past year was marked by a number of significant additions to the literature. Stem cell transplantation has been established as a viable therapy for some patients with SLE. Rituximab has shown utility in SLE and a number of other CTDs. Mycophenolate mofetil has been found to be helpful for membranous lupus nephritis. Mycophenolate mofetil and cyclophosphamide have both been beneficial to patients with scleroderma, especially those with associated ILD. The use of leuprolide acetate was able to ameliorate premature ovarian failure in SLE patients treated with cyclophosphamide.

With the exception of the fine articles by Tashkin and Nadashkevich, the papers presented here are not large, prospective, randomized controlled trials. As explained in the introduction, trials of this sort are uncommon in patients with CTDs. However, the contributions of the authors underscore the importance of retrospective studies, and open-label trials to the expansion of evidence-based medicine.

In addition, these studies raise further questions that must be addressed in future investigations. We need to determine what types of patients are appropriate candidates for these different therapies. For example, in regard to SLE patients, which ones are best treated with stem cell transplant? When during the disease course is rituximab best introduced? The answers to these and other important questions must await the efforts of future investigators who build on the knowledge base developed over the past years.

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List of abbreviations

AASV	anti-neutrophil cytoplasmic antibody-associated vasculitis
ABMS	American Board of Medical Specialists
ACR	American College of Rheumatology
ADAMTS	a disintegrin and metalloprotease with thrombospondin-like repeat
ADEPT	Adalimumab Effectiveness in Psoriatic Arthritis Trial
ADM	amyopathic dermatomyositis
ADR	adverse drug reaction
AIP	acute interstitial pneumonia
AMI	acute myocardial infarction
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
Apo A	apolipoprotein A
Apo B	apolipoprotein B
AR	adjusted risk
ARC	Arthritis Research Campaign
AS	ankylosing spondylitis
ASAS	Assessment in Ankylosing Spondylitis (International Working Group criteria)
ASSERT	Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy
ATS	American Thoracic Society
AZA	azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BILAG	British Isles Lupus Assessment Group
BoNT/A	*Botulinum* toxin type A
BOOP	bronchiolitis obliterans with organizing pneumonia
BSR	British Society of Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
BVAS	Birmingham Vasculitis Activity Score
C ANCA	cytoplasmic anti-neutrophil cytoplasm antibody
CAD	coronary artery disease
CADM	clinically amyopathic dermatomyositis

CASPAR	classification criteria for psoriatic arthritis
CCST	Certificate of Completion of Specialist Training
CEP	circulating endothelial cell precursor
CFA	cryptogenic fibrosing alveolitis
CHD	coronary heart disease
CI	confidence interval
COMP	cartilage oligomatrix protein
COP	cryptogenic organizing pneumonia
COX-2	cyclo-oxygenase-2
CPPD	calcium pyrophosphate dihydrate
CrCl	creatinine clearance
CRP	C-reactive protein
CSS	Churg–Strauss syndrome
CTD	connective tissue disease
CTX-II	C-terminal cross-linking telopeptide of collagen type II
CVD	cardiovascular disease
CVS	cardiovascular system
DAS	Disease Activity Score
dcSSc	diffuse cutaneous systemic sclerosis
DESS	double echo steady state
dGEMRIC	delayed gadolinium-enhanced MRI of cartilage
D-HAQ	Dutch version of the Health Assessment Questionnaire
DIP	desquamative interstitial pneumonia
DLCO	diffusing capacity of the lung for carbon monoxide
DLQI	Dermatology Life Quality Index
DM	dermatomyositis
DMARD	disease-modifying anti-rheumatic drug
EM	electromyogram
EMEA	European Agency for the Evaluation of Medicine Products
EMQ	extending matching question
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study group
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAST	Fibrosing Alveolitis in Scleroderma Trial
FDA	Food and Drug Administration
FLASH	fast low-angle shot
FSE	fast spin echo
FVC	forced vital capacity
GAG	glycosaminoglycan
GAIT	Glucosamine/chondroitin Arthritis Intervention Trial
GALS	gait, arms, legs and spine system
GI	gastrointestinal
GIS	gastrointestinal system
GMC	General Medical Council
GPM	gradient peak method
HF	heart failure
HA	hyaluronic acid

HACA	human anti-chimeric antibodies
HAQ DI	Health Assessment Questionnaire Disability Index
HAQ	Health Assessment Questionnaire
HDL	high-density lipoprotein
HDM	hypomyopathic dermatomyositis
HGM-CoA	hydroxymethylglutaryl-coenzyme A
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IBM	inclusion body myositis
IBP	inflammatory back pain
ICAM-1	intercellular adhesion molecule-1
ICC	intraclass correlation coefficient
ICER	increment cost-effectiveness ratio
ICFDH	International Classification of Functioning, Disability, and Health
IIM	idiopathic inflammatory myopathy
IIP	idiopathic interstitial pneumonia
IL-1R	interleukin-1β receptor
IL-8	interleukin 8
ILAR	International League Against Rheumatism
ILD	interstitial lung disease
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
IMT	intima–media thickness
IPF	idiopathic pulmonary fibrosis
IQR	interquartile range
IRR	incidence rate ratio
ISN/RPS	International Society of Nephrology/Renal Pathology Society
JCHMT	Joint Committee for Higher Medical Training
JDM	juvenile dermatomyositis
JHO	junior house officer
JKOM	Japanese Knee Osteoarthritis Measure
JSW	joint space width
LAD	left anterior descending
lcSSc	limited cutaneous systemic sclerosis
LFA-3	lymphocyte function associated antigen 3
LIP	lymphocytic interstitial pneumonia
Lp(a)	lipoprotein(a)
LUMINA	Lupus in Minorities: Nature vs. nurture trial
MAA	myositis-associated autoantibodies
MC3-R	melanocortin type 3 receptor
MCP-1	monocyte chemoattractant protein-1
MCS	mental component summary
MCTD	mixed connective tissue disease

MDCT	multidetector computed tomography
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-term (programme)
MEQ	modified essay question
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MLN	membranous lupus nephritis
MMF	mycophenolate mofetil
MMP	matrix metalloproteinase
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MRFIT	Multiple Risk Factor Intervention Trial
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSS	modified Rodnan skin score
MS	mass spectrometry
MSA	myositis-specific antibody
MSS	musculoskeletal system
MSU	monosodium urate
MTX	methotrexate
NCEP/ATP III	National Cholesterol Education Program/Adult Treatment Panel III
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NO	nitric oxide
NOAR	Norfolk Arthritis Register
NSAID	non-steroidal anti-inflammatory drug
NSIP	non-specific interstitial pneumonia
OA	osteoarthritis
OM	overlap myositis
OR	odds ratio
OSCE	objective structured clinical examination
P ANCA	perinuclear anti-neutrophil cytoplasm antibody
PAH	pulmonary arterial hypertension
PAL	peer-assisted learning
PAN	polyarteritis nodosa
PASI	Psoriasis Area and Severity Index
PBL	problem-based learning
PCr	plasma creatinine
PCS	physical component summary
PRHO	pre-registration house officer
PM	polymyositis
POF	premature ovarian failure
PPI	proton pump inhibitor
PR3	proteinase 3
PsA	psoriatic arthritis
PsARC	PsA response criteria
pUAc	plasma uric acid concentration
QALY	quality-adjusted life-year
QI	quality indicator
QWMI	Q-wave myocardial infarction
RA	rheumatoid arthritis
RA-ILD	rheumatoid arthritis-intersitial lung disease

RA-IP	rheumatoid arthritis-associated interstitial pneumonia
RANTES	regulated upon activation, normal T-cell expressed and secreted (protein)
RB-ILD	respiratory bronchiolitis-associated interstitial lung disease
REFLEX	Randomized Evaluation of Long-Term Efficacy of Rituximab (trial)
REMS	regional examination of the musculoskeletal system
ROS	reactive oxygen species
RR	relative risk
RS	respiratory system
SASP	sulphasalazine
SDI	Systemic Lupus International Collaborating Clinics Damage Index
SELENA	Safety of Estrogens in Lupus Erythematosus, National Assessment trial
SF	synovial fluid
SF-36	Short-Form 36 (Health Survey)
SHBG	sex hormone-binding globulin
SHO	senior house officer
SLAM	Systemic Lupus Activity Measure
SLE	systemic lupus erythematosus
SLEDAI	systemic lupus erythematosus disease activity index
SLS	Scleroderma Lung Study
SMR	standardized morbidity ratio
SNR	signal-to-noise ratio
sOB-R	soluble leptin receptor
SPGR	spoiled gradient recalled echo
SpR	specialist registrar
SRP	signal recognition particle
SSC	student-selected component
SSc	systemic sclerosis
STIR	short TI inversion recovery
StR	specialist training registrar
SUCCESS-I	Successive Celecoxib Efficacy and Safety Study I
TGF	transforming growth factor
TIMP	tissue inhibitor of metalloproteinase
TIR	Toll/interleukin-1 receptor
TLC	total lung capacity
TLR	Toll-like receptor
TNF	tumour necrosis factor
uCTX-II	urinary C-terminal cross-linking telopeptide of collagen type II
UIP	usual interstitial pneumonia
UK GPRD	United Kingdom General Practice Research Database
ULT	urate-lowering therapy
UMER	Undergraduate Medical Education in Rheumatology

uSpA	undifferentiated spondyloarthritis
VAS	visual analogue scale
vdH–S	van der Heijde–Sharp (score)
VDI	Vasculitis Damage Index
VS	vocational studies
VTR	velocity of tricuspid regurgitation
WG	Wegener's granulomatosis
WGET	Wegener's Granulomatosis Etanercept Trial
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities
WORMS	whole-organ magnetic resonance imaging score

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