

# PostScript

## MATTERS ARISING

### Methotrexate is the leading DMARD in Finland

We read with interest the report by Aletaha *et al* on international questionnaires of the early treatment of rheumatoid arthritis (RA).<sup>1</sup> We would like to draw attention to the newest statistics in Finland.

In Finland the sickness insurance scheme provides reimbursement (today 75%) for prescription drugs in chronic inflammatory rheumatic diseases, principally rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, chronic reactive arthritis, juvenile idiopathic arthritis, and systemic rheumatic diseases. Eligibility entails a medical certificate written by a specialist in rheumatology and approved by the welfare authorities. All patients who are entitled to reimbursement are centrally registered by the social insurance institution. Glucocorticoids and disease modifying antirheumatic drugs (DMARDs) are medicines which can be reimbursed in this category.

As the nationwide sickness insurance scheme covers the entire Finnish population of five million, it provides a good basis for an epidemiological survey of the occurrence of all rheumatic diseases and investigation of the use of various DMARDs by these patients.

In 2001 a total of 76 552 patients had an appropriate certificate entitling them to special reimbursement for DMARDs. Of this total, only 47 967 used the drugs listed in table 1. During 2001, 4325 new certificates were granted. Table 1 shows the numbers of users of glucocorticoids and of 12 DMARDs during the past seven years. A rapid rise can be seen in the numbers using methotrexate. In 2001 the number was 16 470, a third of all users, overtaking the previously most used drug sulfasalazine. The 40 year old drug, hydroxychloroquine, has been third most used drug since 1996. The traditional sulphoxide group drugs, sodium aurothiomalate, auranofin, and penicillamine, have lost 2860 of their earlier users (29%), whereas the newest drug, leflunomide, overtook cyclosporin in 2001. Half of the patients registered used glucocorticoids.

In Finland today rheumatic patients with specially reimbursed drugs have the code 202 on their national insurance card, but this code is the same for all rheumatic diseases. In her thesis in 1997 Kaipainen-Seppänen counted that during four study years in a population of one million people, 3076 new patients had chronic inflammatory rheumatic disease and 491 connective tissue disease.<sup>2</sup> It can thus be calculated that around 16% of the patients in table 1 had connective tissue diseases.

Sulfasalazine was introduced in 1941, but the number of its users has continued to grow, albeit slowly, presumably owing to a sulphur allergy. Methotrexate has been for a decade the main drug used in RA globally, and it is also increasingly used in the spondyloarthropathies. Hydroxychloroquine is the preferred drug for systemic lupus erythematosus (SLE) and active Sjögren's syndrome. However, the preponderance of these three drugs is also based on their frequent use in combination therapies. Finnish doctors are well informed of the Fin-RACo study in early RA: treatment with methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone has proved more successful than single therapy.<sup>3</sup> The recent report by Aletaha *et al*, based on two matched questionnaires in 1997 and 2000, shows the same trend as table 1.<sup>1</sup> The most commonly used DMARDs at the onset of RA were methotrexate and sulfasalazine, with their use still increasing, and antimalarial drugs.

Table 1 shows that the use of the alkylating agents, cyclophosphamide and chlorambucil, has slightly decreased. The reason for this might be the effectiveness of methotrexate in hindering the most severe complications of arthritic diseases like AA amyloidosis.<sup>4</sup> New drugs continue to be needed, as witnessed by the rapid rise in figures for leflunomide.

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### Authors' reply

The Finnish data presented by Drs Klaukka and Kaarela, which confirm the trend that we saw in our patient populations<sup>1</sup> as well as in the survey of rheumatologists,<sup>2</sup> are highly appreciated. They clearly show how drastically the use of disease modifying antirheumatic drugs (DMARDs) has changed over the past decade. Importantly, not only has the type of DMARDs employed most frequently undergone a change, but it appears from the table presented that the frequency of combination therapies may be quite high and that more patients receive DMARD treatment than even a few years ago. Such rapid changes are well in line with the observation we made in our matched surveys. There is another noteworthy aspect, which presumably also applies to the Finnish cohort: in our patients, median methotrexate doses increased from 10 mg (quartiles 7.5; 12.5 mg) in 1995 to 15 mg (10; 20 mg) in 2001, another indication that rheumatologists may be treating patients with rheumatoid arthritis (RA) much more efficiently today than less than a decade ago. This evolution is also supported by the effects of earlier DMARD use, as is also evident from our report.<sup>2</sup>

Together with the new DMARDs, such as leflunomide, we have the tumour necrosis factor  $\alpha$  and interleukin 1 blockers, whose appropriate dosing we also will have to learn

**Table 1** Annual number of users of antirheumatic drugs (DMARDs) in Finland 1995-2001

	1995	1996	1997	1998	1999	2000	2001
Oral glucocorticoids	19670	20700	21675	22930	24100	24830	25660
Sulfasalazine	11080	12110	12940	14050	14800	15430	15980
Methotrexate	6800	8490	9870	11530	13310	15090	16470
Azathioprine	2000	2110	2145	2280	2360	2340	2310
Aurothiomalate	6540	6440	6425	6330	6120	5730	5240
Auranofin	2460	2310	2125	2010	1885	1770	1610
Hydroxychloroquine	5780	6480	7530	8740	9760	10910	11840
Cyclosporin	530	920	1200	1450	1585	1660	1600
Penicillamine	940	810	665	550	440	290	230
Chloroquine	1260	1160	1040	960	850	760	650
Cyclophosphamide	240	250	260	260	260	230	200
Chlorambucil	90	105	100	110	115	100	70
Leflunomide	0	0	0	0	0	910	2100

over time. With more agents to come in the near future, we may soon be able to treat patients with RA in a way that previously we could only dream about.

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## Sarcoidosis: TB or not TB?

We read with interest the lesson of the month “Sarcoidosis: TB or not TB?” by Litinsky and colleagues, published in the May 2002 issue of the *Annals of the Rheumatic Diseases*.<sup>1</sup>

We, in India, face the reverse problem. With us tuberculosis (TB) is still a scourge. Sarcoidosis in India, though not unknown, is definitely rare in comparison with TB. Because non-caseating granulomas can occur in TB also, a diagnosis of TB is accepted even if acid fast bacilli are not demonstrated or grown in culture. For these reasons, many patients with sarcoidosis are initially treated for TB before the eventual diagnosis is made.<sup>2</sup>

The risk of a patient receiving corticosteroids developing TB depends on the dose and duration of the corticosteroid treatment. Our group has reported a high incidence of TB in patients with systemic lupus erythematosus receiving corticosteroid treatment.<sup>3</sup>

The patient in question undoubtedly had both sarcoidosis and TB, the latter probably the result of corticosteroid treatment. In our experience most patients develop TB in the first year of such corticosteroid treatment.<sup>3</sup> We advocate routine isoniazid prophylaxis for patients receiving long term corticosteroid treatment.<sup>3</sup>

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## Authors' reply

Gaitonde *et al* raise the interesting issue of the influence of epidemiological data on clinical decisions. The differential diagnosis between tuberculosis and sarcoidosis is not easy and every case should be considered to be tuberculosis until proved otherwise, especially in countries where tuberculosis is endemic. It is less evident in countries where tuberculosis is not common. Likewise, the decision of giving routine isoniazid prophylaxis in patients treated with corticosteroids depends on the probability of exposure to *Mycobacterium tuberculosis*. Although the incidence of tuberculosis is undoubtedly increased in patients receiving corticosteroids in India,<sup>1</sup> justifying the use of routine prophylaxis, this issue is still a matter of controversy in non-endemic areas.<sup>2</sup> However, the ease of travel around the shrinking “global village” dissolves the boundaries between endemic and non-endemic regions and demands constant surveillance.

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## Osteoarthritis and cardiovascular death

Haara *et al* recently published a study assessing epidemiological aspects of osteoarthritis (OA) in Finland.<sup>1</sup> A finding of interest was their identification of OA (in any finger joint) as a predictor of cardiovascular death among men, with the authors suggesting an undetermined metabolic factor as a mechanism.

It may be that the disability conferred by OA in the lower limbs delays presentation of patients with ischaemic heart disease owing to a lack of exertional symptoms. Thus treatment to reduce risk is delayed. Additionally, some patients who also have generalised OA and are less physically active may be at higher risk of cardiac events.<sup>2</sup>

Occupation and levels of education have been used as surrogates of social class.<sup>3</sup> Certain jobs that require repetitive movements or heavier work intensity increase the risk of developing OA,<sup>4</sup> although occupation is not always linked to the development of hand OA.<sup>5</sup> Generally, manual workers, whose jobs demand higher physical input, are poorly paid compared with professionals.

Haara *et al* found no link between duration of education and OA of the fingers, but the association between OA and earlier death may, nevertheless, be mediated by an effect of social class. Death due to coronary disease is known to be associated with lower socioeconomic groups. Another Finnish study noted higher incidence of myocardial infarction in those of lower income, with higher pre-hospital, 28 day, and 12 month mortality rates.<sup>6</sup> These higher rates may reflect differences in prevalence and awareness of cardiac risk factors among the

different socioeconomic groups, which may also contribute to higher cardiovascular death in men with OA.

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## BOOK REVIEW

### Principles of glucocorticoid therapy

Eds A N Lin, S A Paget. (85.) London: Arnold, 2002. ISBN 0 340 75934-8.

Glucocorticoid therapy is one of the most widely used treatments in medicine, hence this volume is intended for “internists and the many subspecialists in internal medicine, as well as family physicians, paediatricians, and all who use corticosteroids in their practice”. This looks like an ambitious project, even before one sees the contents page. It draws together contributions written by the editors and 49 physicians, principally their colleagues in New York, USA and Edmonton, Canada. They fall into five sections—overview, basic science, effects in specific body systems (for example, the eye, the gastrointestinal tract), clinical usage (the largest section), and special management considerations. The editors aim to present “a systematic discussion of the use of corticosteroids in different organ systems, their side effects, and their use in special circumstances such as pregnancy and childhood.”

The arrangement of the chapters is disjointed. This follows from the different writing styles and the varied depth of explanation and evidence put forward in support of comments and assertions. But more than this, it is as if the project were started a few years ago but languished while some sections remained unfinished, only to be completed

(perhaps by new chapter authors) in a rush for publication. Thus the language and references seem a little dated in many chapters but up to date in others.

The basic science section is very good. It is current (although the field is moving rapidly) and comprehensive. The chapter on chemical action advocates "glucocorticoids" as the preferred term, a recommendation recently promulgated by a EULAR working group<sup>1</sup> and with which I concur. It was slightly irritating to have the words steroids, corticosteroids, glucocorticosteroids, and glucocorticoids used almost interchangeably throughout the book. In the reviews of the effects of glucocorticoids on various body systems, those dealing with the skeletal system and muscle inevitably came under my closest scrutiny. I thought them basically sound, but was disappointed that no references were made to the Cochrane Collaboration meta-analysis of treatment to prevent glucocorticoid induced osteoporosis... myopathy, etc.

The chapter on effects of glucocorticoids on the endocrine system is excellent, but advocates changing to hydrocortisone to manage discontinuation of glucocorticoid treatment and avoid acute withdrawal symptoms. I would need to see the hard evidence before I followed this recommendation. The review of effects on behaviour omitted any consideration of beneficial outcomes. In the large section on clinical usage, covering 13 disease areas (renal, allergic, lung, etc) the chapter on replacement therapy by Robert Lustig (a paediatric endocrinologist from San Francisco, USA) stands out as providing a particularly good review of glucocorticoid physiology and disease replacement. A useful distinction is made between "replacement" therapy and "immune alteration" therapy, which is relevant to current thinking on the possibility that some rheumatological conditions may be deficient in glucocorticoid production.

The chapter on rheumatic and autoimmune disorders describes the current use of glucocorticoids. A table offers general descriptions of typical treatment regimens in various rheumatic conditions. I felt a little uncomfortable that they might be used indiscriminately by inexperienced non-rheumatologists. The authors offer little evaluation of the evidence supporting the different uses. This probably reflects the way in which many of the chapters in this section are presented, but I found it interesting to gain a general overview of the approaches used by our physician colleagues. Singh and Tyrell's chapter on treating infection is incisive, analytical, and full of evidence. It contrasts with that on the risk of infection in the special management section. Here many potential dangers are mentioned, but nowhere is the risk quantified. The chapter on "pulse" therapy suffers from not including the newer understanding about the mechanisms of action of glucocorticoids.

This book contains delights and disappointments, roughly in equal measure. Half way through I wondered if it was worthwhile continuing—but by the end I was glad I had done so. It will not provide the reader with detailed arguments for particular therapeutic approaches, but it gives a fair picture of current practice.

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<sup>1</sup> **Buttgereit F**, da Silva JAP, Boers M, Burmester G-R, Cutolo M, Jacobs J, *et al*. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61:718-22.

## FORTHCOMING EVENTS

### 30th Annual Meeting of the International Society for the Study of the Lumbar Spine

13-17 May; Vancouver, Canada

Contact: Dr S Boden, Sunnybrook and Women's Health Science Center, Room MG 323, 2075 Bayview Avenue, Toronto, Canada M4N 3M5

Tel: 416 480 4833

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### 4th Annual European Congress of Rheumatology

18-21 June 2003; Lisbon, Portugal

Contact: Fred Wyss, Executive Secretary EULAR, Witikonstrasse 15, CH-8032, Zurich, Switzerland

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Fax: +41 1 383 9810

Email: eular@bluewin.ch

Website: www.eular.org

### 25th Annual Meeting of the American Society for Bone and Mineral Research (ASBMR)

19-23 September 2003; Minneapolis, Minnesota, USA

Tel: +1 202 367 1161

Fax: +1 202 367 2161

Email: asbmr@dc.sba.com

Website: www.asbmr.org

### 10th European Pediatric Rheumatology Congress

2-5 October 2003; Stresa, Italy

Contact: Organising Secretariat, ECON srl, Via della Moscova 16, 20121 Milan, Italy

Tel: +39 022 900 5745

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Email: econsrl@tin.it

Website: www.pres.org.uk

### 7th EULAR Sonography Course

9-12 October, 2003; Rome, Italy

An introductory and practical course on musculoskeletal ultrasonography

Scientific secretariat: Professor Guido Valesini

Email: annamaria.iagrocco@uniroma1.it

Contact: Organising Secretariat: Michela Civelli, EDRA Spa, Medical Publishing and News Media, Viale Monza, 133 - 20125, Milan, Italy

Tel: +39 (0)2 281 72300

Fax: +39 (0)2 281 72399

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### OARSI World Congress on Osteoarthritis

12-15 October 2003; Berlin, Germany

Tel: +1 202 367 1177

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Email: oarsi@oarsi.org

Website: www.oarsi.org

### Fourth International Symposium on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

14-17 November 2003; Nice, France

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Abstract deadline 14 November 2003

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### Future EULAR congresses

9-12 June 2004; EULAR 2004; Berlin, Germany

8-11 June 2005; EULAR 2005; Vienna, Austria

21-24 June 2006; EULAR 2006; Amsterdam, The Netherlands

### Future ACR meetings

24-28 October 2003; 67th Annual Scientific Meeting; Orlando, Florida

16-21 October 2004; 68th Annual Scientific Meeting; San Antonio, Texas