PostScript

MATTERS ARISING

**Methotrexate is the leading DMARD in Finland**

We read with interest the report by Alethaa et al on international questionnaires of the early treatment of rheumatoid arthritis (RA). 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 reimbursement (today 75%) for prednisone, we have the tumour necrosis factor α inhibitors and interleukin 1 blockers, whose appropriate dosing we also will have to learn.

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 Kaipiainen-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. 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 sulpha 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. The recent report by Alethaa et al, based on two matched questionnaires in 1997 and 2000, shows the same trend as table 1. The most commonly used DMARDs at the onset of RA were methotrexate and sulfasalazine, with their use still increasing, and anti-malarial 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. New drugs continue to be needed, as witnessed by the rapid rise in figures for leflunomide. 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 Kaipiainen-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. It can thus be calculated that around 16% of the patients in table 1 had connective tissue diseases.

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In table 1 had connective tissue diseases.

**References**


**Authors’ reply**

The Finnish data presented by Drs Klaukka and Kaarela, which confirm the trend that we saw in our patient populations as well as in the survey of rheumatologists, 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 observations 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.

Together with the new DMARDs, such as leflunomide, we have the tumour necrosis factor α inhibitors 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Oral glucocorticoids</th>
<th>Sulfasalazine</th>
<th>Methotrexate</th>
<th>Azathioprine</th>
<th>Aurothiomalate</th>
<th>Auranofin</th>
<th>Hydroxychloroquine</th>
<th>Cyclosporin</th>
<th>Penicillamine</th>
<th>Chloroquine</th>
<th>Cyclophosphamide</th>
<th>Cladribine</th>
<th>Leflunomide</th>
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<td>6800</td>
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<td>5780</td>
<td>530</td>
<td>940</td>
<td>1260</td>
<td>240</td>
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<tr>
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<td>20700</td>
<td>12110</td>
<td>8490</td>
<td>2110</td>
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<td>12940</td>
<td>9870</td>
<td>2145</td>
<td>6425</td>
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<td>1200</td>
<td>665</td>
<td>1040</td>
<td>260</td>
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<td>2280</td>
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<td>2125</td>
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<td>15340</td>
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<td>2001</td>
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<td>650</td>
<td>200</td>
<td>70</td>
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</table>
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.

We would like to acknowledge that the reported work was performed in collaboration with the Ludwig Boltzmann Institute of Rheumatology and supported by a grant from the City of Vienna.

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References
1  Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1300 consecutive DMARD therapies. Rheumatology (Oxford) 2002;41:1367–74.

Sarcoidosis: TB or not TB?
We read with interest the letter 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.

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.

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.

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. We advocate routine isoniazid prophylaxis for patients receiving long term corticosteroid treatment.

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References

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 not always 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, justifying the use of routine prophylaxis, this issue is still a matter of controversy in non-endemic areas. 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. A finding of interest was their identification of OA (in any 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.

Occupation and levels of education have been used as surrogates of social class. Certain jobs that require repetitive movements or heavier work intensity increase the risk of developing OA, though occupation is not always linked to the development of hand OA. 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. 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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References

Principles of glucocorticoid therapy

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 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 musculoskeletal ultrasonography is a particularly good review of glucocorticoid therapy and “immune alteration” therapy, distinguishes between “replacement” and “immune alteration” therapy, which is relevant to current thinking on the possibility that some rheumatological conditions may be deficient in glucocorticoid production.


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
Fax: 416 480 6055
Email: shirley.fitzgerald@swchsc.on.ca

4th Annual European Congress of Rheumatology
18–21 June 2003; Lisbon, Portugal
Contact: Fred Wyss, Executive Secretary EULAR, Witikonerstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: euler@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 02 236 5745
Fax: +39 02 236 5790
Email: ecosrl@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: Michelena Cavalli, 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
Email: edrarcongressi@dsmedigroup.com

OARSI World Congress on Osteoarthritis
12–15 October 2003; Berlin, Germany
Tel: +1 202 367 1177
Fax: +1 202 367 2177
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
Contact: Organisation Secretariat, VP Communication, 108 boulevard G Kleyer, 4000 Liége, Belgium
Tel: +32 (4) 254 12 25
Fax: +32 (4) 254 12 90
Email: yolanda@pettecommunication.com
Website: http://nice.piettecommunication.com

IOF World Congress on Osteoporosis
14–18 May 2004; Rio de Janeiro, Brazil
Abstract deadline 14 November 2003
IOF awards are available for scientists:
IOF Claus Christiansen Research Fellowship: €45 000
IOF Servier Young Investigator Fellowship: €40 000
Contact: Congress Secretariat at info@osteofound.org
Website: www.osteofound.org

Xth International Conference on Behçet’s Disease
24–27 October 2004; Antalya, Turkey
Contact: Congress Secretariat, Figur Congress and Organization Services Ltd. STL, Ayazmaderei Cad. Karadut Sok. No: 7 80888 Dikilitas, Istanbul
Tel: +90 (212) 258 60 20
Fax: +90 (212) 258 60 78
Email: behcet2004@figur.net
Website: www.behcet2004.org

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

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