Cyclosporin and methotrexate therapy

We read with interest the report by Gerard et al on the efficacy of cyclosporin monotherapy compared with methotrexate and cyclosporin combination therapy in patients with early rheumatoid arthritis.1 It is pleasing to see the increasing trend of publications looking at appropriate management strategies in early disease. We have previously reported a study comparing combination methotrexate, cyclosporin A, and intra-articular corticosteroids with sulfasalazine in a similar patient group.2

In our 48 week study there was no difference in American College of Rheumatology response, remission rates, or radiographic progression between the two groups at 48 weeks. The current cohort is similar in age though with shorter disease duration and a higher proportion of rheumatoid factor positive patients. Our study did show significantly fewer withdrawals due to lack of efficacy in the combination group than in the sulfasalazine monotherapy group (1/40 vs 10/42), adding weight to the suggestion of the current study which demonstrated more effective retardation of radiographic progression in the combination treated group. These data suggest that the combination may be more effective in a larger study group.

However, combinations involving cyclosporin must be considered in the light of its significant toxicity. Both the current study and our own had significant periods of modestly raised serum creatinine and episodes of hypertension. The difference in radiographic progression in the Gerards’ study compared with our own is interesting. The mean doses of cyclosporin and methotrexate in the combination therapy group at 48 weeks were similar in both studies, and it tempting to speculate that the difference in outcomes between the two studies reflects the difference in the comparator treatment—namely, sulfasalazine versus cyclosporin monotherapy. It appears that monotherapy with sulfasalazine is more effective than cyclosporin at retardation disease progression measured by radiographic erosion progression rate. We note that the corticosteroid dose in the Gerards’ trial is not reported, although it was presumably low judged by the number of injections given. Thus it would appear reasonable to conclude that although cyclosporin (as suggested by its mode of action) is effective in early disease, the benefits are insufficient compared with its toxicity to warrant routine use as first line treatment, either as monotherapy or in combination.

Authors’ reply

With interest we read the remarks of Conaghan and Emery concerning the differences between our report and the study of Proudmant et al.1

The Proumdant study compared the combination of methotrexate, cyclosporin, and intra-articular injections with sulfasalazine monotherapy in rheumatoid arthritis (RA). We consider the comparison with our study invalid due to fewer withdrawals due to inefficacy in the combination therapy group, which underlines the importance of testing combination therapy in early disease.

Although tempting, it is difficult to compare outcome measures in Proumdant’s study and our study because of the differences in the study group and the lack of randomisation. We think that erosion scores in the two studies should not be compared when the interobserver differences are not known. We do not know if sulfasalazine or cyclosporin is better at retarding radiological progression, on the basis of the information from these two studies.

Conaghan and Emery conclude that cyclosporin cannot be used as a first line treatment in early RA, either as monotherapy or in combination therapy. We do not share that view. Cyclosporin toxicity was well controlled in our study and our own had significant periods of nephrotoxicity with any treatment including corticosteroids compared with sulfasalazine alone. Arthritis Rheum 2000;43:1809–19.

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Cyclosporin A in rheumatoid arthritis

We read the paper by Gerard et al with interest.3 The authors are to be commended for the modest claims they make about the results of their study. They show that a combination of methotrexate and cyclosporin better retards radiographically visible progression than cyclosporin alone after one year in patients with early rheumatoid arthritis (RA). It raises the question whether cyclosporin A still has a place in the early treatment of this disease. One shortcoming of this study as stated in the paper is the lack of a methotrexate only arm. Furthermore, the study did not use optimal doses of methotrexate in the combined treatment group. Therefore, the possibility that the additional beneficial effects achieved in the combined arm at least in part might have been seen with methotrexate given in monotherapy cannot be excluded. The authors cite a number of studies supporting a retarding effect of cyclosporin, but fail to cite evidence that cyclosporin is not better
than sodium aurothiomalate (Myocins) in this respect.\textsuperscript{1} This study stratified for the use of corticosteroids, in contrast with another often-cited study, which claims that cyclosporin is better than a number of comparative disease modifying antirheumatic drugs, including chloroquine.\textsuperscript{2} The three year follow up of the stratified study still showed no difference in radiographic progression between the arms. Despite strict adherence to safety rules about dosing of cyclosporin, adverse renal effects were seen, which were not completely reversible.\textsuperscript{3}

Some of this risk is, however, unsettled, and the main purpose of our comment. Cyclosporin is an indispensable drug in transplantation medicine and of unquestionable value in the treatment of unresponsive patients with conditions such as vasculitis and uveitis. A prospective biopsy study in patients with psoriasis and psoriatic arthritis showed that all of around 30 patients developed interstitial fibrosis and arteriolar wall thickening characteristic of cyclosporin damage.\textsuperscript{4} A similar study in patients with RA has not been published. A study published in 1996 stated: “Long term continuous treatment of RA with low dose cyclosporin does not result in more structural nephropathy than the disease process itself, in spite of substantial and persistent deterioration of the renal function.” This study compared renal biopsy results from 11 patients with RA treated for 24 months with 22 necropsy specimens. Although no morphological differences were apparent, creatinine clearance had diminished by 26\% in the patients. The accompanying editorial pointed out the weaknesses of the study, based on small size, lack of pretreatment biopsies, and uncertainty about the control group.\textsuperscript{5}

A registry based study was published in 1996,\textsuperscript{6} consisting of 60 patients in all. It was not stated how the patients were selected for biopsy. The authors concluded that the low doses that had been given to 22 of the patients had not caused any renal damage. A more recent analysis performed in 1998 of cyclosporin induced nephrotoxicity in autoimmune diseases concluded, however, that the treatment even with doses of 5 mg/kg/day or lower was without risks, and that renal biopsies should be seriously considered in patients who develop even slight renal function impairment.\textsuperscript{7} This view is based on the slowly progressive interstitial fibrosis and arteriolar wall thickening characteristic of cyclosporin toxicity. A review published in 1996 examines the subject of renal toxicity and long term treatment with cyclosporin of autoimmune disease.\textsuperscript{8} It concludes that even strict adherence to recommended rules carries a substantial risk for irreversible changes after two years of treatment, and emphasises the need for rigorous risk-benefit analysis in each patient. In view of the lack of long term safety data based inter alia on systematic prospective biopsy results we feel that one should not use cyclosporin in patients with RA until other possible treatments have failed.

After the initial submission of this letter Fox et al published a report showing that cyclosporin was not given to patients with RA who also treated with methotrexate, inhibits the oxidation of methotrexate to an inactive metabolite and thereby potentiates the effect of methotrexate. This will thus lead to an increased risk of adverse reactions when the drugs are combined.
Is methotrexate osteopathy a form of bone idiosyncrasy?

I read the letter about low dose methotrexate (MTX) osteopathy with mixed feelings. On the one hand, it is not unusual for a woman to develop insufficiency bone fracture after 25 years of prednison treatment. Longstanding inflammatory joint disease also affects bone. The patient had an active disease that is associated with osteoclast activity mediated by tumour necrosis factor-osteoprotegerin. However, the authors underestimated other possible factors which might have had an influence on bone density. Menstrual cycle status was not discussed. Results of bone density measurement were not described despite long term steroid treatment. Risk factors such as family history, smoking, diet, and physical activity were not analysed.

Of note, besides pelvic fracture, increased technetium-99m uptake was seen in joint areas with normal standard radiographs. This may be due to active arthritis and enthesopathy. We can draw no conclusions about the duration of the bone scan findings. Data about previous scans are absent. MTX in vitro does not affect the proliferation and further maturation of osteoblasts.9 No adverse effect of low dose MTX (<30 mg/week) on bone formation in RA has been found.8 Studies have shown that low dose MTX treatment did not cause a decrease of bone density and was similar to that of the control groups.9–11 Summarising previous studies we can state that most patients have no increased risk of MTX osteopathy. Osteopathy resulting from high dose MTX treatment in children with malignancy occurs in only 9% of patients.12 On the other hand, however, this young woman developed pelvic spontaneous fracture three months after the onset of MTX treatment. Severe leg pains increased by weight bearing and relieved by rest followed after four months of treatment. Such a rapid occurrence suggests hypersensitivity of the delayed type with targeting to bones. Bone targeted drug idiosyncrasy may also be considered. Very delayed drug induced hyper-sensitivity affecting fat tissue of the abdomen has been reported previously.13 Other tissues may also be affected. Drug sensitivity tests may be helpful.

High and low dose MTX osteopathy have similar signs and symptoms, including a triad of severe low extremity pain (distal tibia), osteoporosis, and compression bone fractures occurring spontaneously or after minimal trauma. Both may develop even over a short period of time after the onset of MTX treatment.14 In both osteoporosis dosage groups scurvy-like lines may be seen on x-ray examination, which may be normal at the start. Because the multiple controls receiving the same treatment in both groups do not have signs of such severe osteoporosis, it is assumed that an as yet unknown cause may be responsible.15 We propose hypersensitivity reaction or idiosyncrasy, rapidly affecting bone tissue, may be such causes. There have been comparable reported rates of high and low dose (different by 70–100 fold) MTX osteopathy, independent of cumulative doses, pointing to the possible role of idiopathic or hypersensitivity aetiologies (table 1). Bone pain diminished within one month after stopping MTX treatment in both groups, and x-ray findings returned to normal 5–7 months later.16 Proposed bone hypersen-sitivity in MTX osteopathy may be compared with hypersensitivity lung or liver disease due to MTX treatment. These serious complications of MTX treatment may follow any cumulative dose of the drug. Recognising the phenomenon of MTX bone idiocracity or hypersensitivity may prevent the unnecessary or harmful proposal that MTX treatment is a risk factor for osteoporosis and should be relatively contraindicated in patients with multiple risk factors for osteoporosis.

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### References


### Table 1

<table>
<thead>
<tr>
<th>High dose</th>
<th>Low dose</th>
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<tbody>
<tr>
<td>Cumulative dose: 7.5–144 g/m²</td>
<td>Cumulative dose: 97.5 mg–3.5 g/m²</td>
</tr>
<tr>
<td>Onset: 4–11 months</td>
<td>Onset: 3 months–8.5 years</td>
</tr>
<tr>
<td>Warner et al, 1999</td>
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</tbody>
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Low dose methotrexate osteopathy in a patient with polyarticular juvenile idiopathic arthritis

We read with some surprise the article by Rudler and colleagues proposing a case of a 36 year old woman with methotrexate (MTX) osteopathy.' The authors report insufficiency fractures after low dose MTX treatment for...
three months and further fractures two months later.

They suggest that MTX osteopathy may be more common than expected in patients treated with low dose methotrexate, and all the evidence suggests the opposite. MTX is now the most commonly prescribed disease modifying antirheumatic drug for rheumatoid arthritis in America and parts of Europe.\(^1\) We conservatively estimate that 120 000 patients receive low dose MTX in the UK alone, with historically a greater proportion of patients in America receiving the drug. Yet cases of proposed MTX osteopathy with low dose treatment are vanishingly rare (six reported cases in adults). Moreover, recent data suggest that low dose MTX has no effect on bone turnover at all.

In this case only a low dose of MTX was used and is suggested the cause of the fractures. Data from paediatric cases suggest that extremely high doses of MTX (20 g/m\(^2\)), 80 g/m\(^2\), and 135 g/m\(^2\)) are associated with MTX osteopathy.\(^3\) Smaller cumulative doses have been implicated in adults, but in the only other published case with short duration (nine months) the patient received almost fivefold more MTX.\(^4\) It is surprising that the authors do not comment on the role of the high doses of prednisolone treatment (estimated cumulative dose of 92 g) or the presence of inflammatory disease over 27 years, both important risk factors for insufficiency fractures.

There is a growing body of evidence to refute the fact that MTX has any clinically significant effect on bone mineral density (BMD) or a significant impact on the osteoblast lineage. Patet et al carried out a prospective study of patients with psoriasis and low dose MTX treatment, and reported no significant change in markers of bone turnover or BMD after 21 months' follow up.\(^5\) Minaur et al found that the proliferation and maturation of cells of the osteoblast lineage were not affected by MTX.\(^6\) In a study of 116 patients, no direct association of MTX with BMD or lower bone turnover markers was found, and in a small subset, no impact on bone formation was shown by biopsy.\(^7\)

There appears to be sufficient evidence to doubt the pathogenic role of MTX in this case. Further information about the treatment regimens and the study of Rozin and Quinn and colleagues that the in vivo effect assessed on bone mineral density (BMD) is reassuring in most studies.\(^8\) Moreover, better control of the inflammatory arthritis should allow an increase of physical activity, which in turn may improve osteoporosis. The hypothesis of bone hypersensitivity or idiosyncrasy to MTX that is discussed by Rozin is only speculative, but appealing. Finally, we obviously concur with both comments and agree that such an exceptional observation of MTX osteopathy should certainly receive greater attention from the use of MTX in idiopathic juvenile arthritis or other inflammatory arthritides when it is indicated.

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References

affecting about 1% of the white population, particularly female patients, and has considerable physical, psychological, and social repercussions.

In a paper published previously in the *Annals*, Dadoniene et al described and compared two cohorts of patients with RA from Vilnius (Lithuania) and Oslo (Norway). There were no significant differences in sex, age, extra-articular manifestations, location, or family history of RA between the groups. None the less, there were important differences in disease activity, disability, pain, employment status and general health in patients in the Vilnius group having the worse scores. The number of patients who had never used a disease modifying anti-rheumatic drug (DMARD) was similar in both groups. Vilnius patients had more commonly used azathoprine, sulfasalazine, and antimalarial drugs, whereas Oslo patients had used methotrexate, gold salts, cyclosporin, and t-penicillin. Surgery was more common in the Oslo patients. That study was developed to compare the evolution and outcomes of two different populations with RA and was the first to include health related quality of life. The authors highlighted the differences between these two groups to differences in economic status, medical care, drugs used and, to a lesser extent, genetic differences.

During the past years the HLA system has been gaining an increasingly important role in the pathogenesis of autoimmune diseases. HLA polymorphism has multiple effects on the immune system. HLA-DRB1 alleles have been associated with RA in a number of publications. In the third hypervariable region of their DRβ1 chain, they share a sequence of amino acids named “the shared epitope” (SE).

In a mestizo Colombian population we found that the SE 5′QKRAA located in DRB1*0404 and *0408 and the SE influenced the radiographic evolution of hands erosions.” In the Argentinian population the DRB1*0404 was also important but only DRB1*1001 was related to RA severity. In the Peruvian population an association between RA and the SE was not found. There was a lack of uniformity in the development of these trials, but they all showed a lack of association between DRB1*0404 and RA in the Latin American populations. These findings suggest that SE inheritance and genetic influence may vary depending on the genetic background of the studied population even in apparently closely located countries. The previous study comparing the Norwegian and Lithuanian populations with exclusion of genetic typing may be misleading. Furthermore, not only may the HLA system play a part in the disease outcome and disease progression of these patients but pharmacogenetics may also be at least as important. The efficacy of methotrexate and other DMARDs in reducing the radiological progression of RA erosions has been proved; however, their efficacy and tolerability may be influenced by mutations in their metabolic pathways or in their cellular targets. Epidemiology of autoimmune diseases is becoming more complex as our knowledge of HLA and genetics becomes more complete. The time is coming when diseases will be defined not only by their symptomatology but also by the genetic background of their hosts.

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Authors’ reply
We thank Drs Cadena and Anaya for their important and interesting comments on our paper reporting differences in disease activity and health status between matched patients in Norway and Lithuania. Cadena and Anaya focus on the difference in the genetics of the HLA system or pharmacogenetic differences as a potential explanation for our findings. They refer to several studies, mainly from their own region of the world, where genetic markers have been associated with disease severity and progression. We agree that rheumatoid arthritis is associated with genes, mainly in the region encoding the major histocompatibility complex genes. However, the relative importance of genes is controversial also because low disease concordance has been found in monozygotic twins. Some of the genetic studies indicate only a limited influence of genetic factors on disease susceptibility and progression, and this may suggest a relatively stronger importance of environmental factors.

However, we completely agree with the comments of the authors that genetic factors, ideally, should have been examined in both populations. However, blood samples were not available for such analyses, but our results would have been stronger if data on the genetic background of the populations had also been available.

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References

Forthcoming Events
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Fax: +1 510 536 1812
Email: info@americanbacksoc.org
Website: http://www.americanbacksoc.org

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14–17 November 2003; Nice, France
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Website: http://www.lupus2004.org

**IOF World Congress on Osteoporosis**
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**Contact:** Congress Secretariat at info@osteofound.org
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**International Society for the Study of the Lumbar Spine**
31 May–5 June 2004; Porto, Portugal

**Contact:** International Society for the Study of the Lumbar Spine, 2075 Bayview Avenue, Room MG 323, Toronto, Ontario, Canada M4N 3M5
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Fax: 00 1 416 480 6055
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**XVth European Lupus Meeting**
3–5 March 2005; Royal College of Physicians, London, UK

**Future EULAR congresses**
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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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**Corrections**


In fig 1 of this article the numbers of patients were corrected but the size of the boxes was not corrected at the same time. The correct figure is shown below.


One of the authors names was supplied incorrectly. The correct authors are as follows: Gerards A H, Landewe R B M, Prins A P A, Bruyn G A W, Goei Thé H S, Laan R F J M, Dijkmans B A C.
Cyclosporin A in rheumatoid arthritis

T Saxne and F A Wollheim

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