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 sulphasalazine 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 not report any difference in outcomes between the two studies reflects the difference 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 Proudman’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 sulphasalazine 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 a earlier study in early RA.2 The issue of nephrotoxicity with any treatment including cyclosporin is not resolved, although the guidelines state that toxicity is acceptable when dosage rules are closely guarded.2,3 We did not advocate the combination of methotrexate and cyclosporin as first line treatment in early RA because the data on efficacy were not sufficient. On the other hand, there is no evidence that the combination cannot be used because of toxicity.

P G Conaghan, P Emery
Academic Unit of Musculoskeletal Disease, University of Leeds, UK
Correspondence to: Professor Paul Emery, Department of Rheumatology, Old Nurses Home, Great George Street, Leeds LS1 3EX, UK; p.emery@leeds.ac.uk

References

Authors’ reply

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

The Proudman study compared the combination of methotrexate, cyclosporin, and intra-articular injections with sulphasalazine monotherapy in rheumatoid arthritis (RA). Like in our study, Proudman et al noticed fewer withdrawals due to inefficacy in the combination therapy group, which underlines the importance of testing combination therapy in early disease.

Cyclosporin A in rheumatoid arthritis

We read the paper by Gerard et al with interest. 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 radiologically 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 arm. 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 aurothiomolate (Myocurin) in this respect.\textsuperscript{7} This study stratified for the use of corticosteroids, in contrast with another one published which claims that cyclosporin is better than a number of comparative disease modifying antirheumatic drugs, including chloroquine.\textsuperscript{8} 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{9}

The results, however, are 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{10} 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 cause more structural nephropathy than the disease process itself, in spite of substantial and persistent deterioration of the renal function.”\textsuperscript{11} 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{12}

A registry based study was published in 1996,\textsuperscript{13} 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{14} This view is based on the slowly progressive interstitial fibrosis and arteriolar wall thickening characteristic of cyclosporin toxicity. A review published in 1997 examines the subject of renal toxicity and long term treatment with cyclosporin of autoimmune disease.\textsuperscript{15} It concludes that even strict adherence to recommended rules carries a substantial risk for irreversible changes after long term 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 given to patients with RA who were 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 a potential increase in methotrexate effect and increased risks of adverse reactions when the drugs are combined.

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\end{thebibliography}

Authors’ reply

We thank Saxne and Wollheim for their kind remarks. Indeed, we were interested in whether the beneficial effects in the combination therapy group should be ascribed to the concerted action of the combining drugs rather than to the action of methotrexate alone. To test this hypothesis we selected a sample of 41 patients out of a cohort of 411 patients who all had participated in the methotrexate/folate supplementation study which was published recently.\textsuperscript{15} These 41 patients were matched for age, sex, disease duration, and clinical disease activity. All 41 patients had early rheumatoid arthritis (RA) and were treated with methotrexate as their first disease modifying antirheumatic drug (DMARD; median dose 15 mg/week). Of these 41 patients, 19 (47%) had an American College of Rheumatology (ACR)20 response after one year of treatment, 9 (22%) had an ACR50 response, and 3 (8%) had an ACR70 response. The patients who had responded to methotrexate mono-therapy were in the same range as the proportions of patients who had responded to cyclosporin monotherapy, and substanti-}

\begin{thebibliography}{9}
\bibitem{Ede} van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid

Is methotrexate osteopathy a form of bone idiopathy?

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 prednisone treatment. Longstanding inflammatory joint disease also affects bone. The patient had an active disease that is associated with osteoclast activation 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 scan performed between treatment 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 enthesisopathy. 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. No adverse effect of low dose MTX (<30 mg/week) on bone formation in RA has been found. 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. 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 only in 9% of patients.

On the other hand, however, this young woman developed pelvic spontaneous fracture three months after the onset of MTX treatment. Severe leg pain 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 idiopathy may also be considered. Very delayed drug induced hypersensitivity affecting fat tissue of the abdomen has been reported previously. 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. In both osteoporosis dosage groups curvy-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. We propose hypersensitivity reaction or idiopathy, 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 osteoarthritis. (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. Proposed bone hypersensitivity 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 idiocrasy 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.

A P Rozin
Bat Galim, Rambam Medical Centre, PO Box 9602, Haifa, Israel
Correspondence to: A P Rozin, B Shine Department of Rheumatology, Rambam Medical Centre, PO Box 9602, Haifa 31096, Israel; a_rozin@rambam.health.gov.il

References


Low dose methotrexate osteopathy in a patient with a particular 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, 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 2 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 cases in two centres 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 the suggested cause of the fractures. Data from paediatric cases suggest that extremely high doses of MTX (20 g/m², 80 g/m², and 135 g/m²) are associated with no significant change in markers of bone turnover. The central nervous system.

Bone formation was shown by biopsy.2 3 Minaz et al found that the proliferation and maturation of cells of the osteoblast lineage were not affected by MTX.4 In a study of 116 patients, no direct association of MTX with BMD. Parathormone marker turnovers were found, and in a small subset, no impact on bone formation was shown by biopsy.5 Thus, the evidence is sufficient to doubt the pathogenic role of MTX in this case. Further information about the treatment received by the patient in the study of Rudler et al, her BMD, parathyroid hormone levels, and long term outcome are necessary. Did she receive any treatment at all after her initial fractures? In the last paragraph the authors refer to stress fractures. Are they implying that undue stress or activity contributed to the clinical picture? We believe they should be described as insufficiency fractures. The former are fractures occurring in otherwise normal bone by an abnormally applied mechanical load and the latter are due to abnormal bone.

Currently, it is thought that the possibility of a detrimental impact of MTX on the skeleton, even with concomitant corticosteroids, is low. It is important to emphasise that MTX has had a major impact in improving the health and bones (through corticosteroid sparing) of patients with inflammatory arthritis as well as other inflammatory conditions, which greatly outweighs any possible detrimental effects.

M A Quinn, M J Green, A K S Gough
Harrague District Hospital, UK

References


Authors’ reply to Rozin and Quinn et al

We read with interest the comments by Rozin and by Quinn and colleagues about our recent publication on low dose methotrexate (MTX) osteopathy in a patient with polyarticular juvenile idiopathic arthritis. Our report was not intended to suggest that MTX osteopathy may be more common than expected, and we agree that reported cases of low dose MTX osteopathy are exceedingly rare compared with the number of patients treated with MTX. Certainly, at first glance it might not be very surprising that this patient developed serial insufficiency bone fractures after 25 years of prednisone treatment. However, the temporal association with the introduction of MTX and the multiplicity of fractures was striking.

We acknowledge that we did not provide further information about other possible factors that might have influenced the risk fracture in this patient. This 35 year old woman was not menopausal, did not smoke, and had a normal diet, and her physical activity was markedly restricted as her polyarticular joint involvement was severe. Unfortunately, family history of osteoporosis and bone mineral density were not assessed. We disagree with Rozin about his interpretation of the technetium-99m diphosphonate bone survey. The multiple areas of increased uptake are asymmetric, which would be unlikely for a flare of polyarticular juvenile idiopathic arthritis. Moreover, the enhanced uptake which was localised to the femoral condyles and right calcaneum is not compatible with joint involvement. The increased uptake is certainly too marked and too different to be related to multiple erosive pathologies, which would also be very unusual clinical features in this type of inflammatory rheumatism. In a scintigraphic study of the cruciate deficiency model of knee arthritis in dog, the uptake ratio (unstable knee/contralateral knee) did not exceed 2.0 (controls value: 1.0 to 0.10). Conversely, in a semiquantitative (“scintimetric”) technetium diphosphonate scintigraph follow up study of patients with peripheral fractures, the uptake ratio (fracture/normal reference site) was much higher (5.0 to 8.0). In our patient the uptake ratio was 5.5 and 3.7 for the left knee/ right knee and right calcaneum/left calcaneum, respectively, which is further evidence for the diagnosis of multiple fractures.

Data for the in vivo effect of MTX on osteoblasts are conflicting, but we agree with Rozin and Quinn and colleagues that the in vivo effect assessed on bone mineral density is reassuring in most studies.2 3 Moreover, better control of the inflammatory arthropathies should allow an increase of physical activity, which in turn may improve osteoporosis. The hypothesis of bone hypersensitivity or idiocrasy 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 not deter from the use of MTX in idiopathic juvenile arthritis or other inflammatory arthropathies when it is indicated.

J Pouchot, M Rudler, S Gentelle, A Grasland, P Vinceneux
Service de Médecine Interne, Hôpital Louis Mourier, Faculté Xavier Bichat, Paris VII, France

F Paycha
Médecine Nucléaire, Hôpital Louis Mourier, Faculté Xavier Bichat, Paris VII, France

References


Clinical comparisons of RA between different populations: are they feasible?

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease,
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, education, or family history of RA between the groups. None the less, there were important differences in disease activity, disability, pain, emotional mental and general health between the groups. Differences in HLA allele distribution were not observed between the groups. However, the differences in disease activity may be explained by environmental factors. Furthermore, not only may the HLA system play a part in the disease outcome and disease progression, but genetic factors may also be important. The efficacy of methotrexate, one of the most commonly used drugs for RA, may be influenced by genetic factors. For example, the HLA-DRB1*0401 allele has been found to be associated with a better response to methotrexate therapy. However, the role of genetic factors in the treatment of RA remains to be elucidated. Further studies are needed to clarify the contribution of genetic factors to the disease outcome and disease progression in RA.

**References**


**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.

T K Kvien, J Dadoniene

The Institute of Experimental and Clinical Medicine of Vilnius University, Zygimantu 9, Vilnius, Lithuania LT-2600, daddoniene@ekmii.vu.lt

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24 CME category 1 units

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Website: http://www.americanbacksoc.org

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

14–17 November 2003; Nice, France

Contact: Organisation Secrétaire, YP Communication, 108 boulevard G Kleyer, 4000 Li ge, Belgium
Tel: +32 (4) 254 12 25
Fax: +32 (4) 254 12 90
Email: yoland@pierrecomunication.com
Website: http://nice.pierrecomunication.com

**2nd International Forum on Geronto-Rheumatology**

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www.annrheumdis.com
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Tel: +31 33 434 5730
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Email: ekleinjan@marktwo.nl
Website: www.marktwo.nl

International Congress on SLE and Related Conditions
9–13 May 2004, New York, New York, USA
Contact: The Oakley Group, 2014 Broadway, Suite 250, Nashville, Tennessee 37203, USA
Tel: +1 615 322 2785
Fax: +1 615 322 2784
Email: Lupus2004@theoakleygroup.com
Website: http://www.lupus2004.org

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

International Society for the Study of the Lumbar Spine
31 May–5 June 2004; Porto, Portugal
Deadline for abstracts 15 November 2003
Contact: International Society for the Study of the Lumbar Spine, 2075 Bayview Avenue, Room MG 323, Toronto, Ontario, Canada M4N 3M5
Tel: 00 1 416 480 4833
Fax: 00 1 416 480 6055
Email: shirley.fitzgerald@sw.ca

XIIth European Lupus Meeting
3–5 March 2005; Royal College of Physicians, London, UK
Contact: Julia Kermode, Conference organiser of the British Society of Rheumatology
Email: Julia@Rheumatology.org.uk

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

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, Bruijn G A W, Goei The H S, Laan R F J M, Dijkmans B A C.