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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 smaller and a higher proportion of rheumatoid arthritis groups at 48 weeks. The current cohort is smaller and a higher proportion of rheumatoid arthritis patients has been included in the current study compared with Proudman’s study. However, combinations involving cyclosporin are still advocated in this study as stated in the paper is earlier study in early RA.

The Proudman study compared the combination of methotrexate, cyclosporin, and intra-articular injections with sulfasalazine monotherapy in rheumatoid arthritis (RA). The authors compared the combination therapy group with interobserver differences were 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. However, 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.

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 erosive 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 a earlier study in early RA.4 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. 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.

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.

The Proudman study compared the combination of methotrexate, cyclosporin, and intra-articular injections with sulfasalazine 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. 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 sulfasalazine or cyclosporin is better at retarding radiological progression, on the basis of the information from these two studies.

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Cyclosporin A in rheumatoid arthritis

We read the paper by Gerard et al with interest.7 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 short-coming 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

PostScript

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References


Cyclosporin A in rheumatoid arthritis

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than sodium aurothiomalate (Myochrysine) in this respect. This study stratified for the use of corticosteroids, in contrast with another observation which claims that cyclosporin is better than a number of comparative disease modifying antirheumatic drugs, including chloroquine. The three year follow up of the stratified study showed no deterioration 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. This issue, 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. 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 elicit 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 nephropy 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. A registry based study was published in 1996, 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 nephrotoxicity in autoimmune diseases concluded, however, that the treatment even with doses of 5 mg/kg/day or lower was not without risks, and that renal biopsies should be seriously considered in patients who develop even slight renal function impairment. 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. 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 when given to patients with RA 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 potentiation of the methotrexate effect and increased risks of adverse reactions when the drugs are combined.

**References**


**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. 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 proportion of patients who had responded to methotrexate monotherapy were in the same range as the proportions of patients who had responded to cyclosporin monotherapy, and substantially lower than the proportion who had responded to cyclosporin plus methotrexate combination therapy in our study.

These results give an indication that the effects seen in the combination therapy arm cannot be ascribed to methotrexate alone.

Recently, Marcheson et al published the results of a study showing that the combination of cyclosporin and methotrexate is more effective in retarding radiological progression than methotrexate alone.6

The subject of nephrotoxicity of cyclosporin remains highly controversial. We agree with Saxne and Wollheim that structural damage to the kidney is not clearly demonstrated in patients with RA treated with cyclosporin. Reports in other autoimmune diseases cannot be extrapolated to RA but warrant a careful approach. Most reports on cyclosporin in RA state that impairment of the renal function is reversible if dosage guidelines are strictly followed.7,8 The study of Boers et al showed that nephrotoxicity is reversible.9 The study of Kvien et al is an extension of the study of Zeidler et al.10 In the study of Zeidler the reduction of cyclosporin was required if serum creatinine rose to >50% above the baseline, while guidelines recommend 30%. In the study of Kvien it is clear that it was mainly patients who had a rise in creatinine >50% during cyclosporin treatment who were at risk of creatinine remaining high after discontinuation of cyclosporin. This again underlines the importance of the guidelines. We advocate the use of creatinine clearance measurement or calculation before starting cyclosporin treatment, to select patients at risk.

Data on renal function should be viewed from the point of view that renal function loss is common in patients with RA. It is not clear whether the patients in the study of Zeidler and Kvien who were treated on the basis of the cyclosporin guidelines (a rise in creatinine no more than 30% is acceptable) were subjected to a greater risk of renal function loss than other patients with RA. Unfortunately, studies from Zachariae (on psoriasis and with higher cyclosporin dosages) and Vercauteren (not concerning patients with RA) do not shed light on this topic. Our concern is that on the basis of current knowledge on toxicity there is no reason to withhold cyclosporin from all patients with RA. However, questions about efficacy still have to be answered.
Is methotrexate osteopathy a form of bone idiocrasy?

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 predosine 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 mineral 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. 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 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 idiocrasy may also be considered. Very delayed drug induced hyper-sensitivity 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 and osteo-sarcoma-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 idiocrasy, it is assumed that an as yet unknown cause may be responsible. We propose hypersensitivity reaction or idiocrasy, 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 actiologies (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.

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Table 1

<table>
<thead>
<tr>
<th>High dose</th>
<th>Low dose</th>
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<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>
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Ragab et al, 1970
Newman et al, 1973
O’Regan et al, 1973
Kooller, 1976
Stainiavlicevic et al, 1977
Jaffe et al, 1987
Vassilopoulou-Sellin et al, 1992
Munder, 1994
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Stevens et al, 2001
Wrennings et al, 2001
Rudler et al, 2003

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, although 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. 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 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 MTX osteopathy. Smaller cumulative doses have been implicated in adults, but in the only other published case with short duration (nine months) of high dose MTX the patient received almost fivefold more MTX. 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 of 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. Patel 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 Minnaur 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 of patients in the study of Ruzicka 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 other possible factors. 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 bones 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.

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 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 fractures in 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 menstruating. She 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 more marked and too diffuse to be related to multiple enthesopathies, 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 4.0 (controls value: 1.0 to 1.0). Consequently, in a semiquantitative (“scintimetric”) 99mTc diphosphonate scintigraph follow up study of patients with peripheral fractures, the uptake ratio (fracture/nonreference 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. 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 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 deserve more from the use of MTX in idiopathic juvenile arthritis or other inflammatory arthropathies when it is indicated.

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References


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

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease,
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, education, or family history of RA between the two groups. None of the fewer patients available for consultation were patients in the Vilnius group, the worst scores. Furthermore, the number of patients who had used disease modifying anti-rheumatic drug (DMARD) was similar in both groups. Vilnius patients had more commonly used methotrexate, gold salts, and antimalarial drugs, whereas Oslo patients had used methotrexate, gold salts, cyclosporin, and n-penicillamine. 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 hypothesized the differences between these 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 populations. 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 70QKRRA74 in DRB1*04 alleles had the strongest association with RA. However, we did not find any significant association between HLA and RA in African Colombians, emphasising the importance of genetic differences even among populations living within the same country.

There have been different findings from one area to another. In Latin America, the differences are important. In Chilean patients the HLA-DRB1*0401 alleles were DRB1*0404 and *0408 and the SE influenced the radiographic evolution of hands erosions. 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 all showed a lack of association between DRB1*0401 and RA in the Latin American population. 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 without inclusion 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, DMARDs, 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

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27–29 November 2003; Amsterdam, The Netherlands
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3–7 November, 2004; Budapest, Hungary
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Fax: +41 22 732 2850
Email: autoim04@kenes.com
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Figure 1 Clinical characteristics of children with JIA.