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 v 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 retarding 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.

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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.

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 their viewpoint. Cyclosporin toxicity was well controlled and not different 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.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 doubt that the combination cannot be used because of toxicity.

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Cyclosporin A in rheumatoid arthritis

We read the paper by Gerard et al with interest.4 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 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 aurothiomalate (Myocins) in this respect.\textsuperscript{3} This study stratified for the use of corticosteroids, in contrast with another oft-cited study\textsuperscript{4} which claims that cyclosporin is better than a number of comparative disease modifying antirheumatic drugs, including chloroquine.\textsuperscript{3} 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{5}

This 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 arthropathies showed that all of around 30 patients developed interstitial fibrosis and arteriolar wall thickening characteristic of cyclosporin damage.\textsuperscript{6} 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{7} 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{8}

A registry based study was published in 1996,\textsuperscript{9} 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 not without risks, and that renal biopsies should be seriously considered in patients who develop even slight renal function impairment.\textsuperscript{10} This view is based on the slowly progressive interstitial fibrosis and arteriolar wall thickening characteristic of cyclosporin toxicity. A review published in 1999 examines the subject of renal toxicity and long term treatment with cyclosporin of autoimmune disease.\textsuperscript{11} It concludes that even strict adherence to recommended rules carries a substantial risk for irreversible changes after two years’ 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 \textit{et al} published a report showing that cyclosporin 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 potential increased methotrexate effect and increased risks of adverse reactions when the drugs are combined.

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\textbf{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{12} 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 monotherapy were in the same range as the proportions of patients who had responded to cyclosporin monotherapy, and substantially lower than the proportion who 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 safely be ascribed to methotrexate alone. Recently, Marchesoni \textit{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.\textsuperscript{13}

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.\textsuperscript{14} The study of Boers \textit{et al} showed that nephrotoxicity is reversible.\textsuperscript{15} The study of Kvien \textit{et al} is an extension of the study of Zeidler \textit{et al}.\textsuperscript{16} In the study of Zeidler dose 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 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 conclusion 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.

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Is methotrexate osteopathy a form of bone idiosyncrasy?

I read the letter about low dose methotrexate (MTX) osteopathy with mixed feelings.1 On the one hand, it is not unusual for a woman to develop pelvic spontaneous 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 biopsy 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 arthropathy and entheseopathy. We can draw no conclusions about the duration of the bone scan findings. Data about previous scans are absent. MTX in vitro may not affect the proliferation and further maturation of osteoblasts.2 No adverse effect of low dose MTX (<30 mg/week) on bone formation in RA has been found.3 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.4 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.5 On the other hand, however, this young woman developed pelvic spontaneous fractures 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 idiosyncrasy may also be considered. Very delayed drug induced hypersensitivity affecting fat tissue of the abdomen has been reported previously.6 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.4 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.7 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.8 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 idiosyncrasy 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

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.7 The authors report insufficiency fractures after low dose MTX treatment for

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Table 1: Publications on high dose and low dose MTX osteopathy since the first report in 1970

<table>
<thead>
<tr>
<th>High dose</th>
<th>Low dose</th>
<th>Onset: 4–11 months</th>
<th>Onset: 3 months–8.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabb et al, 1970</td>
<td>Preston SJ et al, 1993</td>
<td>5.6–144 g/m²</td>
<td>97.5 mg–3.5 g/m²</td>
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<tr>
<td>Newman et al, 1973</td>
<td>Shepheard D et al, 1995</td>
<td>1,200</td>
<td>1,000</td>
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<tr>
<td>Stanisavljevic et al, 1977</td>
<td>Bolognya et al, 1996</td>
<td>1–2</td>
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<td>Jaffe et al, 1987</td>
<td>Singwe M et al, 1998</td>
<td>1–2</td>
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<tr>
<td>Vassilopoulos-Sellin et al, 1992</td>
<td>Stevens et al, 2001</td>
<td>1–2</td>
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<td>Manktelow et al, 1994</td>
<td>Wijnmans et al, 2003</td>
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<tr>
<td>Exclud et al, 1997</td>
<td>Rudler et al, 2003</td>
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<td>Warner et al, 1999</td>
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