Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial


Objective: To compare the efficacy and toxicity of cyclosporin A (CsA) monotherapy with CsA plus methotrexate (MTX) combination therapy in patients with early rheumatoid arthritis (RA).

Patients and methods: 120 patients with active RA, rheumatoid factor positive and/or erosive, were randomly allocated to receive CsA with MTX (n=60) or CsA with placebo (n=60). Treatment with CsA was started in all patients at 2.5 mg/kg/day and increased to a maximum of 5 mg/kg/day in 16 weeks. MTX was started at 7.5 mg/week and increased to a maximal dose of 15 mg/week at week 16. Primary outcomes were clinical remission (Pinals criteria) and radiological damage (Larsen score), at week 48.

Results: Treatment was discontinued prematurely in 27 patients in the monotherapy group (21 because of inefficacy, and six because of toxicity) and in 26 patients in the combination therapy group (14 and 12, respectively). At week 48, clinical remission was achieved in four patients in the monotherapy group and in six patients in the combination therapy group (p=0.5). The median Larsen score increased to 10 (25th, 75th centiles: 3.5; 13.3) points in the monotherapy group and to 4 (1.0; 10.5) points in the combination therapy group (p=0.004). 28/60 (47%) of patients in the monotherapy group and v 34/60 (57%) of patients in the combination therapy group had reached an American college of Rheumatology 20% (ACR20) response (p=0.36) at week 48; 15/60 (25%) v 29/60 (48%) of patients had reached an ACR50 response (p=0.013); and 7 (12%) v 12 (20%) of patients had reached an ACR70 response (p=0.11). Their was a tendency towards more toxicity in the combination therapy group.

Conclusions: In patients with early RA, neither CsA plus MTX combination therapy nor CsA monotherapy is very effective in inducing clinical remission. Combination therapy is probably better at improving clinical disease activity, and definitely better at slowing radiological progression. Combination therapy should still be compared with methotrexate monotherapy.

Both early diagnosis and early treatment with disease modifying antirheumatic drugs (DMARDs) are important in patients with rheumatoid arthritis (RA) to inhibit radiological progression and to prevent long term functional loss. Methotrexate (MTX) is considered one of the most powerful conventional DMARDs which may retard radiological progression, and has an acceptable toxicity spectrum. These characteristics make MTX the anchor drug in the treatment of RA, and in a number of studies in early RA MTX was used as one part of a DMARD combination. Cyclosporin A (CsA) has proved to be effective in both advanced and early RA. The toxicity, which is particularly increased in the presence of serum creatinine and hypertension, is considered manageable if dosage guidelines are strictly maintained. In a number of studies it has been suggested that radiological progression is retarded by CsA in comparison with placebo or other DMARDs. Because both drugs have different mechanisms of action, and their toxicity patterns do not overlap, the combination of MTX with CsA may offer complementary efficacy. Patients with advanced RA and a poor response to MTX have shown significant clinical improvement after the addition of CsA, and the drug combination was tolerated well. These results were a basis for investigating the potential of CsA in combination with MTX in achieving clinical remission and in slowing radiological progression in patients with early RA. We proposed the hypothesis that patients with early RA and factors indicating a poor prognosis would gain most from early aggressive intervention by combination therapy.

The purpose of this study was to investigate whether the combination of MTX and CsA is more effective than CsA monotherapy in inducing clinical remission and slowing radiological progression in patients with early RA.

PATIENTS AND METHODS
The study was conducted in 16 centres throughout the Netherlands between November 1996 and November 1999. Patients were eligible for the study if they met the following inclusion criteria: RA according to the 1987 American Rheumatism Association criteria, age between 18 and 70 years, and a disease duration of less than three years. Patients had to have factors indicating a poor prognosis, defined as at least one

Abbreviations: ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; CsA, cyclosporin A; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomised controlled trial; VAS, visual analogue scale.
erosive lesion and/or a positive serum rheumatoid factor test (Latex test, and/or Rose-Waaler test, and/or IgM rheumatoid factor enzyme linked immunosorbent assay (ELISA)). Patients had to have active disease, defined as at least three out of four activity criteria: six swollen joints (out of 66); six tender joints (out of 68); an erythrocyte sedimentation rate (ESR) of at least 28 mm/1st h, and/or a C reactive protein (CRP) of at least 20 mg/l; a global assessor’s score of disease activity (ranging from 1=no activity to 5=severe activity) of at least 4. Only patients with a normal renal function (a creatinine clearance as calculated by the Cockroft formula of at least 80 ml/min for men and of at least 70 ml/min for women) were allowed to enter the study.

Patients were excluded from the study if they had received previous treatment with CsA or MTX or more than one other DMARD, and if treatment with any DMARD had been for longer than three months. Other exclusion criteria were a white blood cell count of $<3 \times 10^9$/l; platelets of $<100 \times 10^9$/l; serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), or bilirubin levels exceeding twice the upper limit of normal; a systolic blood pressure of $>160$ mm Hg and a diastolic blood pressure $>90$ mm Hg; a history of hypertension (treated or untreated) or malignancy or epilepsy; the presence of a chronic infection or gastric duodenal disease; and the use of drugs with a known interaction with CsA or with MTX.

Oral corticosteroids were not permitted and non-steroidal anti-inflammatory drugs were only permitted if the dose was stable during the two weeks before randomisation. Intra-articular injections were allowed during the study. For a period of four weeks injected joints were counted as swollen and tender.

### Study design and monitoring

The study protocol was approved by the medical ethics committees of the participating hospitals and all patients gave written informed consent.

After providing informed consent and after a four week screening period, patients were randomly assigned to one of the two study arms. Randomisation was performed by a computer generated list. Patients received the study drug for a maximum of 48 weeks.

In one study arm CsA was combined with MTX (combination therapy group) and in the other arm CsA was combined with a placebo (monotherapy group). Folic acid 1 mg/day was prescribed to all patients. CsA was provided by the patient’s regular pharmacist on prescription. The placebo was produced by the pharmacy of the VU Medical Centre and was packed and made indistinguishable from MTX at that centre. CsA was started at a dose of $2.5 \text{ mg/kg/day}$, and was increased in three steps to a maximum of $5 \text{ mg/kg/day}$ during the first 16 weeks. A period of at least four weeks between two CsA dose increments was required. MTX or placebo was started at a dose of $7.5 \text{ mg/week}$, which was kept constant during the first 16 weeks of the study and was increased in three steps to a maximum of $15 \text{ mg/week}$ at week 16. The CsA dosage was decreased by 50 mg/day if the serum creatinine level had increased by more than 30% from baseline at two consecutive visits and/or if blood pressure exceeded

### Table 1  Patient characteristics at baseline. A 48 week placebo controlled trial comparing cyclosporin A (CsA) monotherapy with CsA and methotrexate (MTX) combination therapy in patients with RA with poor prognosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CsA plus MTX (n=60)</th>
<th>CsA (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.5 (10.6)*</td>
<td>51.2 (11.6)*</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>2.9 (3.5)*</td>
<td>2.7 (5.7)*</td>
</tr>
<tr>
<td>Women</td>
<td>37 [62]†</td>
<td>42 [70]†</td>
</tr>
<tr>
<td>Erosive at start of study</td>
<td>32 [53]†</td>
<td>27 [43]†</td>
</tr>
<tr>
<td>Rheumatoid factor positive at start</td>
<td>56 [93]†</td>
<td>58 [97]†</td>
</tr>
<tr>
<td>DMARD used before study (patients)</td>
<td>11 [18]†</td>
<td>6 [10]†</td>
</tr>
</tbody>
</table>

*Mean (standard deviation); †Number of patients (percentage).

### Table 2  Total number adverse events related to study drug

<table>
<thead>
<tr>
<th>Kind of adverse event</th>
<th>CsA plus MTX</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A period with $&gt;30%$ raised serum creatinine</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>A period with hypertension</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Gastric intestinal complaints</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Raised serum potassium</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Liver enzyme disturbances</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Paraoesthesias</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>192</td>
</tr>
</tbody>
</table>
The primary end points were clinical remission according to Clinical Remission according to the Larsen modified Larsen score. Both primary end points were assessed at week 48. In brief, patients were considered to be in clinical remission if they met five of the six following criteria: duration of morning stiffness not exceeding 15 minutes; no fatigue; no joint pain (by history); no joint tenderness or pain on motion; no soft tissue swelling in joints or tendon sheaths; ESR <30 mm/1st h (female) or <20 mm/1st h (male)/or a CRP <10 mg/l. An x ray examination was made at baseline and after 48 weeks, and x rays were scored by two observers unaware of the study drug, but aware of the chronological order. The mean score of the two observers was taken as the Larsen score. If radiographs were missing for a patient, only scores of one time point were used for calculating median scores for the whole group at that time and these scores were not used for calculating progression of radiological damage.

Secondary outcome variables were the disease activity scores of the World Health Organisation/International League of Associations for Rheumatology (WHO/ILAR) core set. The measures were assessed at four week intervals and included a swollen joint count (66 joints), a tender joint count (68 joints), pain (10 cm visual analogue scale (VAS) with worst imaginable pain and no pain at all as extremes), fatigue (10 cm VAS with extreme fatigue and no fatigue as extremes), patient’s and assessor’s global assessment of disease activity (five point Lickert scale ranging from no disease activity to severe disease activity), duration of early morning stiffness (in minutes), ESR (Westergren’s method), and CRP. At 0, 24, and 48 weeks functional ability was measured (the validated Dutch version of the Health Assessment Questionnaire; scores from 0 (best) to 3 (worst)). Secondary end point variables were used to calculate the number of patients meeting the American College of Rheumatology (ACR) criteria for clinical improvement (ACR20, ACR50, and ACR70) at weeks 24 and 48.

Premature discontinuation

The study protocol required patients to stop taking the study drug for the following reasons: if two consecutive dose reductions of CsA or MTX, or both, were necessary; if the patient did not meet the ACR20 criteria for clinical improvement at week 24; if the study drug was discontinued for more than two weeks; if an adverse event occurred that in the opinion of the treating rheumatologist required discontinuation of CsA or MTX; and/or if consent was withdrawn by the patient. After 48 weeks of treatment with the study drug, patients could choose to continue their drug in an open fashion. If the study drug was discontinued before week 48, the treating rheumatologists were free to make their choice of further treatment.

Sample size

The expected rise in erosion score was 5 (SD 6) during 48 weeks. The required sample size to detect a difference of 3 (6) in erosion score between the monotherapy and the combination therapy group (α=0.05, power=0.80) is 60 patients in each study arm.

In advance a clinical remission rate of approximately 10% in the monotherapy group and 30% in the combination therapy group (a difference of 20%) was assumed as clinically relevant. To detect such a difference with a power of 0.90 (two sided α=0.05), a sample size of 60 patients in each arm was necessary.

Analysis

An intention to treat analysis was performed as the primary mode of analysis. If patients had stopped treatment prematurely, the last value obtained was carried forward and used in the analysis. An analysis of those completing the study was performed as a secondary analysis. Differences in efficacy measures were analysed by comparing changes from baseline. Within-group differences were tested using t test statistics for paired observations; differences between treatment groups were statistically tested using t test statistics for unpaired observations. Parametric and non-parametric tests were used depending on distribution of data. Dichotomous outcomes (frequencies of adverse events, premature discontinuations, ACR responses) were compared using Fisher’s exact test or χ² test, if appropriate. All calculations were done using SPSS software.

RESULTS

Patients’ characteristics

A total of 120 patients were included in the study. Almost all patients were rheumatoid factor positive, and a considerable number already had erosions at the start of the study (table 1). The two groups were fairly well balanced, but the combination therapy group had a higher swollen joint count and a higher ESR at baseline.

160/95 mm Hg at two consecutive visits. Treatment with a calcium blocking agent to lower blood pressure without CsA dose reduction was allowed.

The MTX dosage was decreased by 7.5 mg if leucopenia (≤3x10⁹/l) or thrombocytopenia (≤100x10⁹/l) developed or if there was an increase of ALT or AST by more than twice the upper limit at two consecutive visits.

End points

The primary end points were clinical remission according to the Pinals criteria with a minor modification, and radiological damage according to the Larsen modified Larsen score. Both primary end points were assessed at week 48. In brief, patients were considered to be in clinical remission if they met five of the six following criteria: duration of morning stiffness not exceeding 15 minutes; no fatigue; no joint pain (by history); no joint tenderness or pain on motion; no soft tissue swelling in joints or tendon sheaths; ESR <30 mm/1st h (female) or <20 mm/1st h (male)/or a CRP <10 mg/l. An x ray examination was made at baseline and after 48 weeks, and x rays were scored by two observers unaware of the study drug, but aware of the chronological order. The mean score of the two observers was taken as the Larsen score. If radiographs were missing for a patient, only scores of one time point were used for calculating median scores for the whole group at that time and these scores were not used for calculating progression of radiological damage.

Secondary outcome variables were the disease activity measures of the World Health Organisation/International League of Associations for Rheumatology (WHO/ILAR) core set. The measures were assessed at four week intervals and included a swollen joint count (66 joints), a tender joint count (68 joints), pain (10 cm visual analogue scale (VAS) with worst imaginable pain and no pain at all as extremes), fatigue (10 cm VAS with extreme fatigue and no fatigue as extremes), patient’s and assessor’s global assessment of disease activity (five point Lickert scale ranging from no disease activity to severe disease activity), duration of early morning stiffness (in minutes), ESR (Westergren’s method), and CRP. At 0, 24, and 48 weeks functional ability was measured (the validated Dutch version of the Health Assessment Questionnaire; scores from 0 (best) to 3 (worst)). Secondary end point variables were used to calculate the number of patients meeting the American College of Rheumatology (ACR) criteria for clinical improvement (ACR20, ACR50, and ACR70) at weeks 24 and 48.
the combination therapy group. Diastolic blood pressure increased from a mean of 131 mm Hg to 139 mm Hg in the combination therapy group (p<0.0001) (p=0.28 for the between-group difference). Systolic blood pressure difference between the groups). Systolic blood pressure increased from a mean of 134 mm Hg to 143 mm Hg in the monotherapy group and from 79 to 84 mm Hg in the combination therapy group. Fifteen patients in the monotherapy group and six patients in the combination therapy group received an antihypertensive drug. Sixteen serious adverse events (six in the monotherapy group and 10 in the combination therapy group) had occurred during the study period: five acute cardiovascular events, three exacerbations of the RA needing admission to hospital, two cases of malignancy, and one case each of urosepsis, Alzheimer’s disease, anaemia, sigmoid perforation, postmenopausal vaginal bleeding, and exacerbation of chronic bronchitis. None of these adverse events were thought to be related to the study drug by the judging physician.

Premature discontinuations
Twenty seven patients in the monotherapy group (21 because of lack of efficacy and six because of toxicity) and 26 patients in the combination therapy group (14 because of lack of efficacy and 12 because of toxicity) had stopped treatment during the study. In the monotherapy group, treatment was discontinued prematurely by 11 patients before week 24, 10 at week 24 because of the protocol, and six after week 24. In the combination therapy group the numbers of patients discontinuing were 15, 10, and 1, respectively. Between-group differences for the numbers discontinuing the study were not statistically significant. Hypertension or an increase in serum creatinine, or both, were more often a reason for discontinuation in the combination therapy group (nine patients vs two patients; p=0.05).

Efficacy end points
At 48 weeks, six patients (10%) in the combination therapy group and four patients (7%) in the monotherapy group (p=0.5 for the between-group difference) fulfilled the Pinals criteria for clinical remission.

Radiological damage showed significantly more progression in the monotherapy than in the combination therapy group (fig 1). Radiographs at 48 weeks were missing in three patients in the monotherapy and two patients in the combination therapy group. At the start, the median Larsen score was 2.5 (25th, 75th centile: 0.5; 5.5) points in the monotherapy group and 2.0 (0; 5.5) points in the combination therapy group. After 48 weeks, the Larsen score had increased to 10 (3.5; 13.3) points in the monotherapy group and to 4 (1.0; 10.5) points in the combination therapy group. This between-group difference was significant (p=0.004).

At baseline the total number of erosive joints was 0 (0; 1) in both groups. At week 48 the total number of erosive joints had increased to 2.5 (1; 5) in the monotherapy group and to 1.0 (0; 3) in the combination therapy group (p=0.01 for the between group difference). At baseline the total number of erosions was 0 (0; 1) in both groups. At week 48 the total number of erosions had increased with 3.5 (1; 7.5) in the monotherapy group and 1.5 (0; 4) in the combination therapy group (p=0.02 for the between-group difference).
All separate parameters of disease activity had improved significantly in both groups during the study, except the ESR in the monotherapy group. Figure 2 shows an example. Apart from the decrease in ESR, the between-group differences for improvement in disease activity measures were not statistically significant, but there was always a trend towards more improvement in the combination therapy group (table 3, intention to treat analysis). Intra-articular injections were given to 11 patients (21 injections) in the monotherapy group and 18 patients (28 injections) in the combination therapy group respectively. Figure 3 shows the numbers of patients with different levels of ACR responses. In five of the 120 patients it was not possible to calculate clinical responses because of missing values. These patients were considered non-responders. Thirty-four of the 60 patients in the combination group (57%) and 28/60 (47%) patients in the monotherapy group had achieved an ACR20 response at week 48 (p=0.36 for the between-group difference). Twenty-nine patients (48%) v 15 patients (25%) had achieved an ACR50 response (p=0.013), and 12 patients (20%) v 7 patients (12%) had achieved an ACR70 response (p=0.32).

**DISCUSSION**

It can be concluded from this study that a DMARD combination of CsA and MTX is better than CsA monotherapy in slowing down radiological progression. Whether the combination is more effective than CsA monotherapy in improving disease activity can be disputed. Clearly, trends in all clinical measurements support the superiority of combination therapy, but proportions of ACR20 responses are not significantly different between combination and monotherapy.

The primary end point of this study was clinical remission at 48 weeks of treatment, and it is obvious that both monotherapy and combination therapy failed to induce clinical remission in a substantial proportion of patients. However, the Pinals criteria are difficult to meet, and other studies with conventional DMARD combinations have also reported low numbers of clinical remissions.7

Despite the absence of contrast in proportions of patients with clinical remission, we found a highly significant difference in radiological progression in favour of the combination therapy group. An early deceleration of radiological progression is relevant for long-term outcome. Radiological progression has been shown to be related to long-term functional outcome.1

Radiological progression is considered to be a consequence of inflammatory processes, and the between-group difference in radiological progression in the absence of statistically significant differences in clinical disease activity was somewhat unexpected. A possible explanation may be that a type II error is operative. There are strong indications that patients in the combination therapy group had better clinical improvement than patients in the monotherapy group, but that the study was insufficiently powered to detect small differences. The inability to detect small differences is not a shortcoming of the study. Our randomised controlled trial (RCT) was powered to detect relevant differences in the proportion of patients with clinical remission, not in the proportion of patients with an ACR20 response. Higher response rates in the control group (CsA monotherapy in our study) deflate the power of an RCT to detect treatment effects in dichotomous outcomes, as demonstrated here. Our study can therefore neither prove nor exclude differences in clinical efficacy between the groups. As a consequence, significant deceleration of radiological progression may very well be due to non-significant but clinically relevant differences in disease activity between both groups. The results suggest that the quality rather than the quantity of clinical responses differs between the groups.

An obstacle in positioning the efficacy of the combination of CsA and MTX is the absence of a control arm with MTX monotherapy. We tried to find additional reported evidence for the effects of MTX alone in patients with RA. Despite the fact that a number of RCTs have included a MTX monotherapy arm, differences in patient population, MTX dose, and dose strategy, study duration, and type of assessments made it impossible to compare the results appropriately. Therefore we cannot conclude that the combination of MTX and CsA is better than MTX monotherapy. Limited evidence that CsA plus MTX combination therapy adds to the effect provided by MTX alone is found in a study by Marchesoni et al.17 In that randomised trial in early RA, CsA/MTX combination therapy was compared with MTX monotherapy. The data in that study showed a higher ACR20 response and significantly lower radiological progression in the combination therapy group than in the group receiving MTX alone.17 The combination MTX/CsA should also be compared with other combination therapies in early RA. The COBRA trial (1993–97)18 focused on patients with RA with similar disease duration, similar prognostic factors, and similar disease activity. In the COBRA study patients were treated either with sulfasalazine monotherapy or with a step down combination regimen with temporary high dose prednisolone, low dose MTX, and maintenance sulfasalazine. The ACR20 criteria were met by 72% of the patients in the COBRA combination therapy group and the ACR50 improvement criteria were met by 49% of the patients at week 28. In our study ACR20 improvement criteria were met by 63% of the patients in the combination therapy group and 40% had met the ACR50 criteria at week 24. These results suggest that the clinical effectiveness of the MTX/CsA combination may be compared with the COBRA combination therapy in patients with early RA.

A second obstacle in positioning the combination of MTX and CsA in clinical practice may be increased toxicity. All adverse events, either serious or not, were similarly divided among both groups, but there was an obvious trend towards more premature discontinuations for toxicity in the combination therapy group. It is relevant to mention the significantly higher proportion of patients withdrawing because of renal function loss and hypertension in the combination therapy group, emphasising that some increased toxicity cannot entirely be excluded.

A glance at table 2 shows that more than 50% of all reported adverse events are CsA related (creatinine rise, hypertension, hypertrichosis, gingivitis), whereas only a minority are MTX related (liver enzyme disturbances) and one might expect a more advantageous toxicity spectrum in patients treated with MTX alone. Various studies have looked at the relevance of CsA related renal function disturbances, hypertension, and so called CsA nephropathy. The common conclusions, which have led to recommendations, are that clinically relevant CsA nephropathy can be prevented by avoiding higher doses of CsA,7 and by not only monitoring serum creatinine but also by taking proper action when there is renal function loss. The effects of adding MTX to CsA on the renal function and blood pressure, however, have never been thoroughly investigated beyond the RCT. Any additional type of CsA related toxicity which may be due to the addition of MTX should be weighed against the benefits of this DMARD combination in efficacy.

In summary, this study of the efficacy of CsA plus MTX combination therapy in comparison with CsA monotherapy suggests they are equivalent in their induction of clinical remission. Post hoc analyses indicate that the study was probably underpowered to determine differences in induction of clinical remission. The results showed slight superiority of the drug combination in improving clinical disease activity, and definite superiority of the combination in retarding radiological progression.

**ACKNOWLEDGEMENT**

This study was supported by a grant from Novartis Pharma, The Netherlands.
REFERENCES


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 a 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.2 Like in our study, Proudman et al noticed fewer withdrawals due to ineffectivity 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 that view. Cyclosporin toxicity was well controlled in a earlier study in early RA.3 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.4 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.

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Cyclosporin A in rheumatoid arthritis

We read the paper by Gerard et al with interest.5 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 combination 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

References


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than sodium aurothiomalate (Myocin) in this respect.7 This study stratified for the use of corticosteroids, in contrast with another offspring study 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 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.8 This is reassuring, but 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.9 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.”10 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.11

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 nephropathy 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.12 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.13 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 given to 41 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 additive combination toxicity effect and increased risks 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 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 at the time of fracture 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 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 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. 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 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. 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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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. 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>
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<tr>
<td>Cumulative dose: 7.5–144 g/m²</td>
<td>Cumulative dose: 97.5–35 g/m²</td>
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<tr>
<td>Onset: 4–11 months</td>
<td>Onset: 3 months–8.5 years</td>
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<td>Koller, 1976</td>
<td>Zonneveld et al, 1996</td>
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<td>Warner et al, 1999</td>
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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. However, in 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) 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 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. Minaur et al found that the proliferation and maturation of cells of the osteoblast lineage were not affected by MTX.

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. 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 Rozin and colleagues that the increase in bone mineral density of patients with psoriatic arthritis was much higher (5.0 to 8.0). It is important to emphasise that the authors do not comment on the role of the multiple areas of uptake ratio (fracture/normal reference site) of 2.7, which is further compatible with joint involvement.

We disagree with Rozin about his interpretation of the technetium-99m diphosphonate scintigraphic 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/hip and left calcaneum respectively, which is further evidence for the diagnosis of multiple fractures.

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. Indeed, 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 that the uptake ratio was 5.5 and 3.7 for the left knee/hip and left calcaneum respectively, which is further evidence for the diagnosis of multiple fractures.

References


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

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease,
focusing 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 histocompati-

bility complex genes.17 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 sus-
ceptibility and progression, and this may suggest a relatively stronger importance of environmen
tal factors.3

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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IOF World Congress on Osteoporosis
14–18 May 2004; Rio de Janeiro, Brazil
Abstract deadline 14 November 2003
IOF awards are available for scientists:
IOF Claus Christiansen Research Fellowship: 45 000
IOF Servier Young Investigator Fellowship: 40 000
Contact: Congress Secretariat at info@osteofound.org
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International Society for the Study of the Lumbar Spine
31 May–5 June 2004; Porto, Portugal
Deadline for abstracts 15 November 2003
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XIth International Conference on Behcet’s Disease
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4th International Congress on Autoimmunity
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VIIIth European Lupus Meeting
3–5 March 2005; Royal College of Physicians, London, UK

Corrections
Corrections printed in the journal also appear on the Annals website www.annrheumdis.com and are linked to the original publication.


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.