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 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). There 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 more 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 ≤3×10⁹/l; platelets of ≤100×10⁹/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 treated or untreated); or a 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 mg/kg/day, and was increased in three steps to a maximum of 5 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 mg/week, which was kept constant during the first 16 weeks of the study and was increased in three steps to a maximum of 5 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 mg/week, which was kept constant during the first 16 weeks of the study and was increased in three steps to a maximum of 5 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 mg/week, which was kept constant during the first 16 weeks of the study and was increased in three steps to a maximum of 5 mg/kg/day during the first 16 weeks. A period of at least four weeks between two CsA dose increments was required.

The CsA and/or MTX (placebo) study drug dosage was only increased if the patient did not meet the Pinals criteria for clinical remission, and if safety guidelines for dosing CsA and MTX were met.

At each visit (every two weeks during the first 12 weeks; every four weeks thereafter) blood pressure was measured, laboratory safety tests (biochemistry and haematology) were performed, and side effects were monitored.

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

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**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 (2.5)*</td>
<td>2.7 (2.7)*</td>
</tr>
<tr>
<td>Women</td>
<td>37 [62]†</td>
<td>42 [701†</td>
</tr>
<tr>
<td>Erosive at start of study</td>
<td>32 [53]†</td>
<td>27 [45]†</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>
<thead>
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**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>Paroarthritisias</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 End points upper limit at two consecutive visits. there was an increase of ALT or AST by more than twice the (ACR20, ACR50, and ACR70) legue of Rheumatology (ACR) criteria for clinical improvement to calculate the number of patients meeting the American College of Rheumatology (best) to 3 (worst). Secondary end point variables were used version of the Health Assessment Questionnaire; scores from 0 48 weeks functional ability was measured (the validated Dutch minutes), ESR (Westergren's method), and CRP. At 0, 24, and severe disease activity), duration of early morning stiffness (in 5 (SD 6) days, worst); 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.

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.
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 v 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 groups. 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).

### Table 3 Disease activity measures. Changes from baseline after 24 weeks’ treatment. Results are shown as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>CsA plus MTX group (n=60)</th>
<th>CsA group (n=60)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change at 24 weeks</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>21 (10)</td>
<td>−12 (10)</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>26 (13)</td>
<td>−13 (12)</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>53 (33)</td>
<td>−15 (32)</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>51 (45)</td>
<td>−15 (19)</td>
</tr>
<tr>
<td>HAQ score</td>
<td>1.43 (0.69)</td>
<td>−0.90 (0.67)</td>
</tr>
<tr>
<td>VAS for pain [cm]</td>
<td>5.0 (2.1)</td>
<td>−2.0 (2.5)</td>
</tr>
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</table>

*For the difference in change from baseline between both groups.

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**Course of the study**
The CsA dose at 24 weeks was 3.5 (1.1) (mean (SD)) mg/kg/day in the monotherapy group and 3.1 (1.2) mg/kg/day in the combination therapy group (p=0.107 for the between-group difference). The MTX dose at week 24 was 13.7 (3.0) (mean (SD)) mg/week in the combination therapy group and of 13.0 (3.5) mg/week in the monotherapy group (p=0.07). The CsA dose at 24 weeks was 3.5 (1.1) (mean (SD)) mg/kg/day in the combination therapy group and 2.7 (1.3) mg/kg/day in the combination therapy group (p=0.89). The dose of MTX was 13.0 (3.5) mg/week in the combination therapy group and of placebo 14.3 (2.2) in the monotherapy group (p=0.73 for the between-group difference) At week 24, 38 patients (63%) in the combination therapy group and 40 (67%) patients in the monotherapy group had achieved an ACR20 response and thus continued the study drug according to the protocol.

The mean CsA dosage at 48 weeks was 2.8 (1.0) mg/kg/day in the monotherapy group and 2.7 (1.3) mg/kg/day in the combination therapy group (p=0.89). The dose of MTX was 13.0 (3.5) mg/week in the combination therapy group and of placebo 14.3 (2.2) in the monotherapy group (p=0.07).

**Adverse events**
A total number of 197 adverse events in the combination therapy group and 192 adverse events in the monotherapy group were considered related to the study drug (table 2). None of the adverse events had occurred significantly more frequently in one of the groups. After 48 weeks of treatment mean serum creatinine had increased from 74 (12) µmol/l (mean (SD)) to 89 (17) µmol/l in the monotherapy group (p<0.001, and from 72 (11) µmol/l to 90 (19) µmol/l in the combination therapy group (p=0.0001) (p=0.28 for the difference between the groups). Systolic blood pressure increased from a mean of 131 mm Hg to 139 mm Hg in the monotherapy group and from 134 mm Hg to 143 mm Hg in the combination therapy group. Diastolic blood pressure increased from a mean of 80 mm Hg to 84 mm Hg in the monotherapy group and from 79 to 84 mm Hg in the combination therapy group. None of the adverse events had occurred significantly more frequently in one of the groups. After 48 weeks of treatment mean serum creatinine had increased from 74 (12) µmol/l (mean (SD)) to 89 (17) µmol/l in the monotherapy group (p<0.001, and from 72 (11) µmol/l to 90 (19) µmol/l in the combination therapy group (p=0.0001) (p=0.28 for the difference between the groups). Systolic blood pressure increased from a mean of 131 mm Hg to 139 mm Hg in the monotherapy group and from 134 mm Hg to 143 mm Hg in the combination therapy group. Diastolic blood pressure increased from a mean of 80 mm Hg to 84 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.

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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%) of 15 patients (25%) had achieved an ACR50 response (p=0.013), and 12 patients (20%) of 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.

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. 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.\(^7\) 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.\(^8\) The combination MTX/CsA should also be compared with other combination therapies in early RA. The COBRA trial (1993–97)\(^9\) 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,\(^2\) 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.

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