Combination treatment of rheumatoid arthritis with cyclosporine and methotrexate

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Supported by USPHS Grant HL04012.

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Clin Exp Rheumatol 1999; 17 (Suppl. 18): S47 - S52.

Key words:
Cyclosporine, methotrexate, combination therapy, rheumatoid arthritis.

ABSTRACT

In patients with rheumatoid arthritis (RA) not controlled on methotrexate (MTX) alone, clinical trials have shown that combination therapy with cyclosporine (CSA) and MTX is effective and relatively well tolerated over 12 months. Information regarding the long-term benefits, toxicities and tolerability of this combination therapy in clinical practice, and comparisons with alternative strategies, will determine the utility of the MTX plus CSA combination regimen in patients with RA not controlled with a single drug.

The rationale for methotrexate and cyclosporine combination treatment in rheumatoid arthritis

With the recognition that rheumatoid arthritis (RA) results in significant morbidity, decreased earnings, and increased disability and mortality (1,2), therapy for RA has evolved towards earlier and more aggressive treatment (3). Traditional therapy for RA has consisted of combinations of drugs acting through different mechanisms, often including a nonsteroidal antiinflammatory drug (NSAID), low dose prednisone, and a disease modifying antirheumatid drug (DMARD) such as gold, an antimalarial, azathioprine, or D-penicillamine. During the 1980s more widespread use of methotrexate (MTX) in the U.S. and sulfasalazine in Europe have been seen, while in the 1990s cyclosporine (CSA), leflunomide, and etanercept have been introduced (4).

In spite of efforts to obtain maximum disease control using the therapeutic strategy of combining an NSAID, a DMARD, and prednisone, the results are often unsatisfactory. Response to treatment is often only partial, and many patients are unable to continue therapy because of drug toxicity and/or loss of efficacy (5, 6).

A more aggressive approach to improving the effectiveness of RA treatment has been the use of combinations of two or more DMARDs. Such combination therapies have often been used empirically in clinical practice (more than 95% of U.S. rheumatologists use combination DMARD therapy). Uncontrolled clinical studies have suggested that some combinations of DMARDs are more effective than therapy with a single DMARD (7, 8). However, until recently, clinical trials of combination therapies have been disappointing, with most controlled studies finding increased toxicity without increased efficacy (9).

In the last decade a consensus has developed that MTX is the most effective DMARD for RA, and it has been shown that MTX is likely to be continued for significantly longer than other second-line drugs (5, 6). Consequently, for many patients, MTX is a key component of the therapy of RA. Unfortunately, MTX does not fully control RA in many patients despite dose escalation or administration by the parenteral route. In these patients with a partial response to MTX, further therapeutic decisions are difficult. The options are either to discontinue MTX and attempt to achieve better disease control with another DMARD, something which rarely happened prior to the availability of newer agents, or alternatively to use combinations of DMARDs, with MTX forming the foundation of such combination therapy. CSA in combination with MTX represents one such regimen, but others have also been shown to be effective (10, 11).

CSA as monotherapy is an effective treatment for RA, with an efficacy similar to that of more established DMARDs (12). A study in an animal arthritis model (13) and pilot studies in humans (14) have suggested that the combination of MTX and CSA is more effective than therapy with MTX alone. MTX and CSA have different mechanisms of action, which may contribute to the efficacy of the combination regimen. The mechanisms of action of MTX in RA are poorly

understood, but are thought to be mediated in part through its effects on interleukin-1 (IL-1), macrophages, monocytes and adenosine production (15, 16). CSA, by inhibiting calcineurin phosphatase activity, prevents the translocation of the cytosolic nuclear factor of activated T cells (NF-AT) to the nucleus, and thus prevents the transcription of genes for cytokines such as IL-2, with a resulting decrease in lymphocyte proliferation (17).

Evidence supporting the use of CSA and MTX combination therapy in RA derive largely from two studies. One was a randomized, placebo-controlled study which examined the effects of adding either CSA or placebo, in a double-blind fashion, to continuing therapy with a stable dose of MTX in patients who had incomplete disease control with MTX alone (18). The second was an open-label extension of this study (19).

The latter study design differs from traditional placebo-controlled RA studies in which patients randomly assigned to placebo receive no DMARD therapy, and is much more in keeping with current clinical practice, i.e., an additive therapeutic strategy that clinicians use to control disease in patients with incomplete responses to MTX. The open-label extension phase allowed patients who had been randomly assigned to receive CSA + MTX in the initial 24-week study to continue to do so for a further 24 weeks, while those patients who had been randomly assigned to placebo + MTX during weeks 0 - 24 received CSA + MTX for weeks 24 - 48.

Data from these two 24- and 48-week studies have been published (18, 19) and are summarized below. Open-label extension data beyond 48 weeks from these patients have not yet been published.

CSA + MTX combination therapy - Efficacy in clinical trials

The 24-week double-blind data (18)

The double-blind clinical trial randomly assigned 75 patients to receive MTX + CSA and 73 patients to receive MTX + placebo. Combination therapy was convincingly more effective than MTX alone according to most of the measures included in the core data set, as shown in Table I. Clinically and statistically significant improvements were noted for all outcome parameters other than the erythrocyte sedimentation rate (ESR). The lack of effect of CSA therapy on ESR, despite a significant clinical benefit, has previously been noted with CSA monotherapy (12) and may be related to the effects of CSA on factors affecting ESR, independent of changes in the degree of inflammation.

Table I. Percent improvement in RA outcomes after 6 months' treatment with CSA + MTX combination therapy compared with MTX alone.

Outcome measure	Percent improvement	P value
Tender joints	25%	0.02
Swollen joints	25%	0.005
Physician global assessment	19%	< 0.001
Patient global assessment	21%	< 0.001
Modified Health Assessment Questionnaire	26%	< 0.001
Joint pain	23%	0.04

RA: rheumatoid arthritis; CSA: cyclosporine; MTX: methotrexate.
Data from Reference 18.

The 48-week open-label extension data (19)

Forty-eight of the 56 eligible patients who had taken CSA + MTX elected to continue this treatment, and 44 of the 61 subjects who had taken placebo + MTX elected to now receive CSA + MTX. Significant improvement was noted when patients who had received placebo + MTX switched to the combination of CSA + MTX for weeks 24-48. In this group, significant improvement (comparing week 24 and week 48) was noted in 4 of 7 measures - the tender joint count, swollen joint count, physician global assessment, and joint pain - but not in the Modified Health Assessment Questionnaire (MHAQ) scores or ESR. The improvement in the patient global assessment was of borderline statistical significance (P = 0.07). At week 48, nine pa-

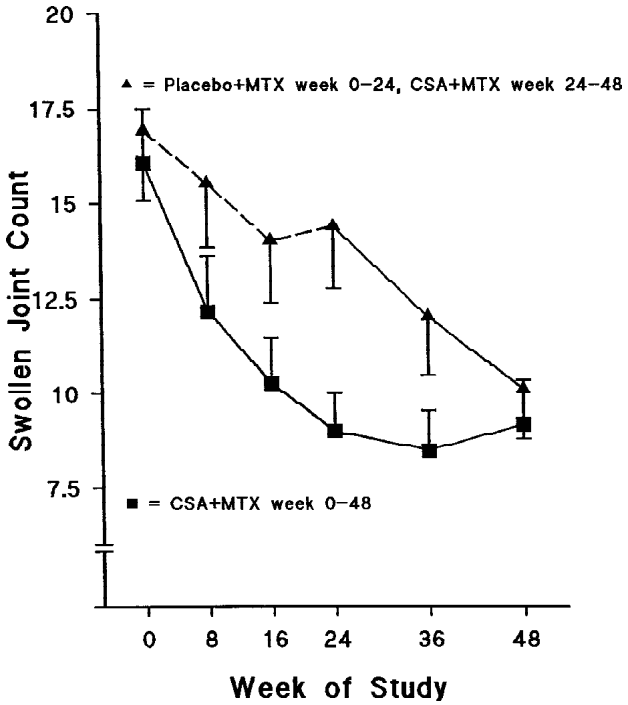

Fig. 1. Changes (mean ± SEM) in the swollen joint count in patients who received cyclosporine (CSA) and methotrexate (MTX) throughout (■), and in patients who received placebo + MTX for weeks 0 - 24 and CSA + MTX for weeks 24 - 48 (▲).

tients (26%) met the American College of Rheumatology preliminary criteria for improvement in RA (ACR20) (20). The clinical improvement in the patients who had initially received CSA + MTX (week 0 - 24) and continued to do so, was maintained through week 48. At week 48, 26 patients (54%) met the ACR 20 criteria for improvement.

The improvement in clinical response with the combination treatment in both the double-blind and open-label studies, and the maintenance of that response over 48 weeks, is shown for the swollen joint count in Figure 1. This figure also shows that, although some improvement occurred after 8 weeks of treatment with CSA + MTX, maximum benefit occurred later and was then constant through weeks 24 - 48.

Table II. Adverse events reported during CSA + MTX combination therapy during weeks 24-48.

	Patients receiving CSA + MTX (weeks 0 - 48) (n = 48)		Patients receiving Placebo + MTX (weeks 0 - 24) and CSA + MTX (weeks 24 - 48) (n = 44)	
Adverse event	No.	%	No.	%
Nausea	2	4	13	30*
Diarrhea	3	6	6	14
Mouth ulcers	2	4	4	9
Paresthesia	2	4	4	9
Creatinine increase > 30%	18	38	7	16*
Hypertrichosis	1	2	4	9
Breast tenderness	0	0	2	5
Hypertension	8	17	10	23

Note: A single patient could report more than one side effect.
* = $P < 0.05$ comparing the frequency of each adverse effect in the two groups.
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CSA + MTX combination therapy - Adverse effects in the clinical trials

Tolerability

A concern with any combination therapy in RA is the potential for increased toxicity. CSA+MTX was generally well tolerated over 48 weeks. Two patients died, one as a passenger in a motor vehicle accident, and the other from what was thought to be a viral pneumonia. In the initial 24-week study, nine of 75 patients in the CSA + MTX group withdrew because of adverse effects compared with 5 of 73 in the placebo+MTX group. The most common cause for withdrawal in the CSA + MTX group was adverse gastrointestinal effects (5 patients).

The majority (87%) of the patients who entered the week 24-48 study completed it, and 45 of the 48 patients (94%) who had received CSA + MTX for the first 24 weeks completed weeks 24-48. The overall frequency and type of adverse reactions that occurred with CSA + MTX combination therapy was similar to that observed with CSA monotherapy in RA and are listed in Table II. Nausea was reported more frequently in the first 6 months after starting CSA, while a creatinine elevation greater than 30% of the baseline value occurred more often in the second 6 months of CSA treatment.

Renal function

CSA results in a small increase in serum creatinine in most patients, and, in the combination-therapy studies, this increase in creatinine appeared during the weeks immediately following the introduction of CSA. Thereafter, the average serum creatinine concentrations were relatively stable (Fig. 2). Over the 48-week study, only 2 patients were withdrawn from CSA + MTX combination therapy due to a > 30% increase in creatinine who did not respond to CSA dose reduction. However, a more frequent occurrence of a > 30% elevation in serum creatinine above baseline values was seen in patients who continued to receive CSA+MTX during weeks 24-48, compared with patients who received CSA for the first time during weeks 24 - 48 (Table II). This observation indicates that the long-term renal effects of MTX + CSA combination therapy require further study.

Liver function tests

The combination of CSA and MTX, two drugs that may individually result in liver

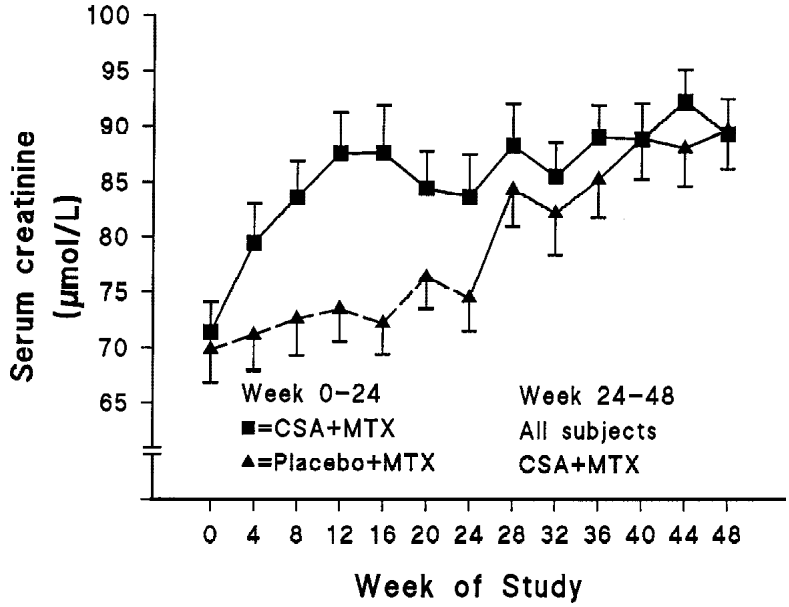

Fig. 2. Mean (± SEM) serum creatinine concentration in patients who received cyclosporine (CSA) and methotrexate (MTX) throughout (■), and in patients who received placebo + MTX for weeks 0 - 24 and CSA + MTX for weeks 24 - 48 (▲). In both groups, $P < 0.0001$ for week 0 versus week 48. Reproduced with permission from reference 19.

toxicity, raised the concern that additive hepatotoxicity might occur. Also, if the combination regimen resulted in an increased frequency of abnormal aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations, even if these elevations were clinically insignificant, it would complicate the monitoring of liver function tests for MTX and the clinical management of these patients. The addition of CSA to MTX therapy for 24 weeks did not affect the AST and ALT concentrations and did not increase the frequency of abnormal liver function tests (21). There was a clinically unimportant increase in bilirubin and alkaline phosphatase, but no evidence of additive liver toxicity over 24 weeks with CSA + MTX combination therapy (21).

CSA + MTX combination therapy - Present and future

Currently, we are at the point where CSA + MTX is one of the relatively few combination therapies that have convincingly been shown to be effective in RA. Furthermore, evidence has been presented that an aggressive therapy with CSA + MTX + intraarticular corticosteroids is more effective than monotherapy with sulfasalazine (22). However, many questions still need to be answered in order to define the clinical role of this combination therapy. Guidelines have provided consensus recommendations regarding the current clinical use of CSA in RA (23), and these will not be reviewed here. It is important for clinicians and researchers to recognize the strengths and limitations of the data available regarding the following key issues in CSA combination treatment, and to endeavor to obtain information that will guide therapy in the future.

The dose of CSA

The optimal dose of CSA in the MTX + CSA combination regimen remains to be determined. The adverse effects of CSA are dose-related; thus, identifying the lowest effective dose in patients generally (as well as in the individual patient) is important. In clinical trials, the starting dosage of CSA has most often been 2.5 mg/kg/day, with incremental increases by 0.5 mg/kg at approximately 4-week intervals if a clinical response is not observed, and with decreases if adverse effects are seen, such as an increase in creatinine > 30% of baseline. The average daily dosage of CSA after week 24 in the MTX+CSA combination study was 2.97 mg/kg, and was lower than the average dosage of 3.8 mg/kg at the completion of a CSA monotherapy study (12, 18).

In the CSA+MTX extension study, the average daily dose of CSA prescribed for patients who had previously received CSA+MTX during weeks 0-24 was 2.8 ± 0.17 mg/kg at week 24, 2.7 ± 0.14 mg/kg at week 36, and 2.5 ± 0.16 mg/kg at week 44. In some patients the clinical response was maintained despite a dosage of CSA less than 2.5 mg/kg, suggesting that the minimum effective maintenance dosage of CSA, when used in combination with MTX for RA, may in some patients be lower than the standard starting dosage of 2.5 mg/kg/day. A small study examining the effect of CSA+chloroquine (24) in RA suggested that a CSA dosage of 1.25 mg/kg was not effective in this combination regimen, whereas CSA at 2.5 mg/kg was effective. The effective dose of CSA is likely to differ among individual patients, among combination regimens, and, perhaps, also during the "induction" and the "maintenance" phases of treatment.

Renal tolerability

The potential for irreversible nephrotoxicity is a major concern with the long-term use of CSA. The risk of structural renal damage is related to the CSA dose and the maximum increase in serum creatinine (25). Strategies used in RA, such as the careful selection of patients, a low CSA dosage in the range of 2.5 - 5.0 mg/kg/day, and CSA dose reduction to limit the rise in serum creatinine to less than 30% of baseline, have effectively minimized CSA-induced nephrotoxicity (25). Patients with RA, who are often also treated with NSAIDs, may be more sensitive to the renal effects of CSA, and MTX may also cause a minor decrease in renal function (26). Therefore, the long-term effects of MTX+CSA combination therapy on renal function are of particular interest.

Substantial data regarding long-term CSA use and renal function in renal transplant recipients indicate that CSA-induced alterations in renal function in these patients appear to be stable over time (27). Many fewer data are available for RA. The small rise in serum creatinine observed in most studies is seen primarily during the first 2 - 3 months of treatment and then remains relatively stable over 12 months (19, 28). In one 12-month study performed in 102 patients, a rise in serum creatinine of > 30% occurred in 50% of the patients, with half of these responding to CSA dose reduction (28).

Emerging data indicate that long-term renal tolerability may limit therapy with CSA in patients with RA. Many patients with RA who received CSA for longer than one year, including some of those who participated in the CSA+MTX studies (and with a stable, acceptable increase in creatinine concentration while on CSA over the first year), subsequently had a creatinine rise to > 30% of baseline that was not controlled by dose reduction and had to discontinue treatment (29).

Renal biopsies in 11 patients with RA who had received CSA monotherapy (average dosage 3.3 mg/kg/day) for an average of 26 months, and who had an average increase in serum creatinine of 31%, showed no significant CSA induced-renal changes (30). The authors concluded that the continuous long-term treatment of RA with CSA did not cause any more structural nephropathy than RA itself, in spite of the persistent deterioration of renal function. Biopsy studies have limitations, however, in that there are both sampling error and inter-individual variability in the interpretation of early histologic changes. An alternative approach has been to study the reversibility of the CSA-induced decrease in renal function. Using this approach, the number of months that the serum creatinine was elevated >30% above baseline was found to be an independent predictor of a persistent decrease in renal function (31).

CSA dosing strategies

It appears that long-term, continuous CSA therapy is associated with an in-

crease in creatinine of > 30% in many patients with RA that may not allow the continuation of therapeutic doses of CSA (29, 31). In early studies, a 50% increase in creatinine was allowed, and it is possible that fastidious monitoring and strict adherence to the 30% threshold value (as currently advocated) may improve the renal tolerability of CSA over 2-4 years in RA. However, more productive strategies might include the exploration of alternative CSA therapeutic regimens and the gathering of information regarding the stability, or lack of stability, of the decrease in renal function associated with the long-term use of CSA in RA. Therapeutic strategies that might be studied include intermittent CSA therapy and concomitant therapy with agents that may diminish the renal toxicity of CSA.

Other long-term concerns

There are limited data regarding the risks of malignancy and/or infection with the use of CSA in RA, and even fewer data on the combination of MTX and CSA. While occasional serious infections have been reported in patients receiving combination therapy, similar infections have also been reported in patients receiving MTX alone (32). Rare Epstein-Barr virus-associated B cell lymphomas have been described in patients receiving MTX, CSA, and the combination of the two drugs (33-35). However, the overall data regarding malignancy in patients receiving CSA for RA are reassuring, with no increase in the frequency of malignancy (36), although the duration of CSA exposure in the patients studied to date has been relatively short.

Conclusions

Uncontrolled RA is associated with increased long-term disability and decreased life expectancy. Control of disease activity, with combination therapy if required, has the potential to modify the natural history of RA, particularly if therapy is begun early enough in the disease. The combination of CSA and MTX has been shown in clinical trials to be an effective therapeutic strategy for patients whose RA is not controlled by MTX alone. Clinical trials, while providing important information, do not necessarily predict long-term responses to therapy in RA (37, 38). The critical information regarding the long-term benefits, toxicities, tolerability, and optimization of CSA + MTX combination therapy in clinical practice are awaited.

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