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# Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis

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## Key words:

Rheumatoid arthritis, methotrexate, leflunomide, combination therapy.

## ABSTRACT

An open-label, one-year study was conducted to evaluate the safety and clinical response to leflunomide and methotrexate combination therapy for rheumatoid arthritis. Study results revealed tolerable safety, no significant pharmacokinetic interactions between methotrexate and leflunomide, and suggested improved clinical response with combination therapy.

## Introduction

Methotrexate (MTX) is one of the most frequently prescribed primary disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA). MTX used in combination with other DMARDs increases the clinical response relative to monotherapy. Rational use of combination DMARD therapy for the treatment of RA is being increasingly directed towards the use of DMARDs that have complementary mechanisms of action. DMARDs that inhibit different immunopathologic processes in RA could potentially have an additive or synergistic effect on therapeutic efficacy without significantly increasing toxicity.

Leflunomide is a new DMARD that has been shown in phase II (1) and phase III (2, 3) trials to be a safe and effective therapy for the treatment of RA. Leflunomide, a synthetic isoxazol derivative, is a prodrug that is actively converted in the gastrointestinal tract to the active metabolite A77 1726. This metabolite inhibits dihydroorotate dehydrogenase (DHODH) and *de novo* pyrimidine biosynthesis (4-7). During T cell proliferation, the pyrimidine pool within lymphocytes must expand. The inhibition of lymphocyte pyrimidine nucleotide synthesis by A77 1726 arrests T cell proliferation and thereby might decrease the autoimmune response in patients with RA.

Leflunomide might preferentially induce

the arrest of autoimmune lymphocytes by the inhibition of DHODH and the resultant decrease in rUMP levels. Lowered rUMP levels may cause translocation of p53 from the cytoplasm to the nucleus as activated lymphocytes pass through the G1 phase, leading to cell arrest (8, 9).

In contrast, MTX is thought to act through a p53-independent pathway. The therapeutic effects of MTX in RA are not believed to be due to the inhibition of lymphocyte proliferation. MTX inhibits purine biosynthesis, inhibits cytokine production, and in an animal model causes release of the potent antiinflammatory molecule adenosine (10, 11). Therefore, the proposed complementary mechanisms of action of MTX and leflunomide in theory support their use in combination for the treatment of RA. An open-label, 52-week two-center study was conducted to evaluate the clinical response, safety, and pharmacokinetics of the addition of leflunomide to MTX treatment for patients with RA (12, 13).

## Patients and protocol

Thirty patients with active RA despite 6 or more months of treatment with MTX at dosages of greater than 15 mg/week (or 10 - 12.5 mg/week if higher dosages were not tolerated) were enrolled and continued on their stable weekly dose of MTX and folic acid. Stable dosages of NSAIDs and prednisone (< 10 mg/day) were allowed. Patients met 3 of the 4 following criteria for active disease: swollen joint count (SJC) > 8 (based on a 28-joint count); tender joint count (TJC) > 10 (based on a 28-joint count); erythrocyte sedimentation rate (ESR) > 28; and morning stiffness > 45 minutes. Clinical response was defined by the American College of Rheumatology (ACR) criteria (14) as follows: a greater than 20% improvement in the SJC and TJC, and more than 20% improvement

in 3 of the following 5 parameters: Modified Health Assessment Questionnaire score (functional disability), patient's global assessment (visual analog scale), physician's global assessment (visual analogue scale), pain intensity assessment (visual analog scale), and ESR.

Drugs were evaluated for safety and efficacy every 2 weeks over the first 8 weeks, and then every 4 weeks. Blood samples from 11 patients were analyzed for plasma concentrations of leflunomide and MTX at baseline, and at weeks 6, 12, and 24.

Leflunomide therapy was initiated with a loading dosage of 100 mg/day for 2 days, then a maintenance dosage of 10 mg/day. Given the lack of safety data regarding leflunomide used in combination with MTX, a 2-day rather than the normal 3-day leflunomide loading dose was used. The leflunomide dosage was increased to 20 mg/day after 3 months if the patients had an inadequate clinical benefit, or was decreased to 10 mg every other day if toxicity was seen, or the drug could be discontinued if necessary.

The standard leflunomide dosing adjustments based on elevated liver enzymes were followed. The leflunomide dose was halved if plasma liver enzymes were 2-5 times the upper limit of normal, and this result was confirmed in repeat testing within 72 hours. Levels were again determined after 7-14 days and the patient was withdrawn from the study if the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were > 3 times the upper limit of normal. If the AST or ALT were 5 times the upper limit of normal and the level was confirmed on retesting, leflunomide was discontinued and the patient was treated with cholestyramine.

Thirty subjects with a mean disease duration of  $13.6 \pm 8.7$  years were enrolled in the study. Patients at baseline had a mean of  $16.9 \pm 7.8$  TJC and a mean SJC of  $16.3 \pm 6.1$  despite being on MTX ( $17.2 \pm 3.9$  mg/week).

## Results

Twelve subjects remained on the 10 mg/day leflunomide starting dosage for the 52 weeks of the study. The leflunomide dose was increased to 20 mg/day in 16 patients (53%) for lack of adequate re-

sponse to 10 mg/day leflunomide. Two subjects (7%) required a decrease in the dosage to 10 mg/every other day, due to toxicity.

Twenty-seven subjects received at least 24 weeks of combination therapy with MTX and leflunomide; 25 subjects at least 40 weeks; and 23 subjects completed the 52-week study.

Seven subjects did not complete the 52 weeks of therapy. Three subjects withdrew because of adverse events, two due to lack of efficacy. The most common mild-to-moderate side effects were nausea, diarrhea, cough, and respiratory infection. No significant leukopenia or myelosuppression was noted. There were no significant changes in renal function. Elevation of plasma transaminases (AST, ALT) were noted in 19 patients. In 70% of these patients, transaminase levels decreased to < 1.2 times the upper limit of normal without a change in the leflunomide dose. Three patients were withdrawn from the study because of persistent elevated liver enzymes, which normalized with the discontinuation of leflunomide.

The three patients with repeatedly elevated transaminase levels during the study underwent liver biopsies. Liver histopathology showed no evidence of marked fibrosis or cirrhosis. Two biopsies were scored as Roenigk grade III A

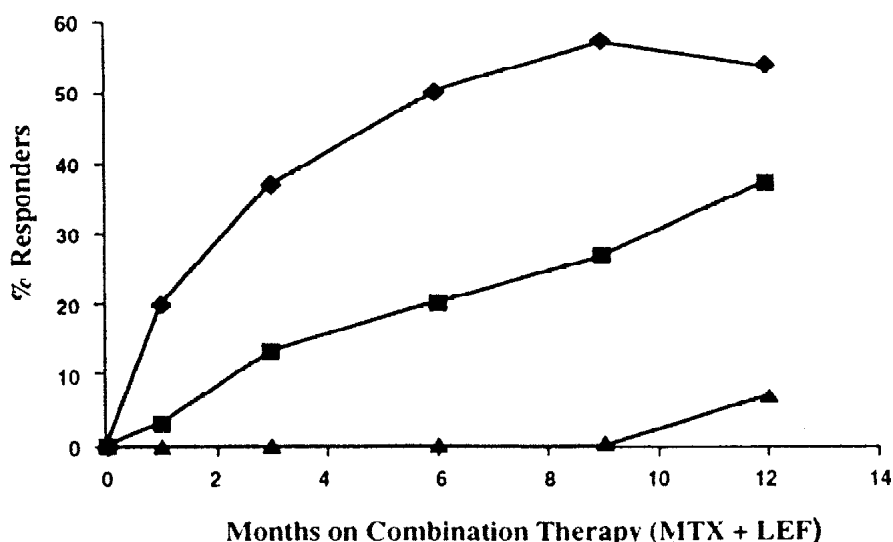
(mild fibrosis) and one as grade I (normal). These patients remained on combination therapy with both MTX and leflunomide.

There were no significant changes in the pharmacokinetics of methotrexate from baseline after the administration of leflunomide. Plasma concentrations of the active A77 1726 metabolite of leflunomide remained stable throughout the 24 weeks of the pharmacokinetic study.

After 9 months of combination therapy with methotrexate and leflunomide, 57% of the subjects met the ACR 20% response criteria, while at one year 37% met the ACR 50% clinical response criteria (14) (Fig. 1). All subjects showed a decrease in their TJC and SJC, with mean reductions of 67% and 44%, respectively. Two patients met the ACR criteria for remission.

## Conclusion

The clinical responses noted in this study after the addition of leflunomide to MTX therapy in patients with active RA suggest increased clinical efficacy with MTX and leflunomide combination therapy. However, assessment of the clinical response was limited by the open-label study design. Therefore, a placebo-controlled, double-blind multicenter trial is currently being conducted to further evaluate the clinical response and safety



**Fig. 1.** Percentage of patients with rheumatoid arthritis who met the American College of Rheumatology criteria for 20% response (◆) and 50% response (■) and for remission (▲), as a function of the number of months receiving methotrexate and leflunomide (MTX + LEF) combination therapy. The percentage of 20% responders peaked after 9 months and remained constant thereafter, while the percentage of 50% responders continued to increase throughout the study period (reproduced with permission from Reference 13).

of MTX and leflunomide combination therapy.

The absence of significant myelosuppression seen with MTX and leflunomide combination therapy supports the theory that the leflunomide inhibition of rUMP leads to immunomodulation rather than immunosuppression, and that non-activated lymphocytes can meet nucleotide requirements through salvage pathways (8, 9).

Leflunomide and MTX do not appear to affect the metabolism of one another when used in combination. No significant changes were seen in the metabolism of either A77 1726, the active metabolite of leflunomide, or of MTX in this study (14).

The most common adverse event observed in patients who took both MTX and leflunomide in combination was an elevation of plasma transaminases. However, transaminase levels were decreased to < 1.2 times the upper limit of normal without a dosage reduction in 70% of the patients who developed elevated transaminase levels with the addition of leflunomide. The three patients who were withdrawn from the study because of persistently elevated plasma transaminases normalized their liver enzymes with discontinuation of leflunomide.

The three patients who underwent liver biopsies for repeatedly elevated transaminase levels subsequently had normalization of their liver enzyme levels despite continued treatments with leflunomide and MTX. Two of the patients had a liver biopsy histopathology that

was scored as Roenigk grade III A. Combination therapy with MTX and leflunomide was continued in these two patients because Roenigk grade III A liver biopsy results are consistent with mild fibrosis which does not require discontinuation of MTX (15).

This open-label, one-year study evaluating the safety and clinical response to leflunomide and MTX combination therapy for RA revealed tolerable safety, no pharmacokinetic changes, and encouraging clinical response results. Further studies will be required to determine the long-term safety of leflunomide and MTX combination therapy, particularly with respect to potential hepatotoxicity, as well as for surveillance for myelosuppression.

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