Liver toxicity is rare in rheumatoid arthritis patients using combination therapy with leflunomide and methotrexate

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ABSTRACT

Objective: Some studies have reported that adding leflunomide (LEF) to the treatment of rheumatoid arthritis (RA) in patients who do not respond to methotrexate (MTX) improved efficacy but increased the risk of liver toxicity. This study aimed at assessing the incidence of liver toxicity in patients with active RA using the LEF and MTX combination therapy in comparison with that of patients on MTX monotherapy. **Methods:** Between February and September 2009, 97 consecutive patients followed up at the University Hospital of the Universidade Federal de Santa Catarina, Brazil, were enrolled. RA patients on MTX alone or using the LEF and MTX combination had their medical records systematically reviewed. The alanine/aspartate aminotransferase enzymes were retrospectively analyzed since the beginning of treatment with MTX or MTX plus LEF. Hepatotoxicity was defined as an increase of at least two-fold the upper limits of normal of the liver enzymes. **Results:** 71 RA patients were included in the study: 36.6% were using 20-25 mg/week of MTX alone and 63.4% were using 20-25 mg/week of MTX plus 20 mg/day of LEF. Of the patients on the combination therapy, 11.1% had abnormal levels of liver enzymes *versus* 11.5% of the patients on monotherapy (P = 1.0). Abnormal aminotransferase levels have been seen with both MTX and LEF monotherapies in patients with RA. In our study, no difference was found between the percentages of aminotransferase elevations of patients being treated with MTX alone or in combination with LEF. **Conclusion:** The combination of MTX and LEF in RA patients is generally safe and well tolerated.

Keywords: arthritis rheumatoid, methotrexate, drug toxicity.

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INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic inflammation of synovial joints. In most cases this will lead to the formation of pannus tissue, ultimately leading to joint destruction. Early diagnosis coupled with aggressive use of disease-modifying antirheumatic drugs (DMARDs) has shown a favorable effect on the course of the disease.[1] Also, combinations of DMARDs have shown a higher ability to slow disease progression.[2,3]

Methotrexate (MTX) is the most effective DMARD used in RA, with low toxicity and excellent tolerance. Unfortunately, MTX alone frequently does not fully control disease activity. Given this high failure rate of RA monotherapy and the complexity of the disease pathogenesis, an increasing emphasis has been given to combinations of therapeutic agents that inhibit different pathophysiologic targets of the disease.[4]

Considering its mechanism of action, leflunomide (LEF) is useful in combination with MTX. Unlike leflunomide, MTX at the dosages used for RA therapy appears to have little effect on

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T cell proliferation, but strongly inhibits cellular synthesis of polyamines and promotes adenosine release, effects that limit inflammation and joint destruction.[5] Additionally, a recent in vitro study has suggested that methotrexate promotes apoptosis of activated T cells, an action that would be complementary to the effect of LEF to limit T cell proliferation.[6] According to some studies adding LEF to MTX non-responders improved efficacy, but increased the risk of gastrointestinal side effects and liver toxicity.[7]

The present study aimed at assessing liver safety on the addition of LEF to MTX treatment of patients with active RA, who had inadequate response to MTX alone.

MATERIAL AND METHODS

This was a cross-sectional study. Between February and September 2009, 97 consecutive patients followed up at the University Hospital of the Universidade Federal de Santa Catarina, Brazil were enrolled. The inclusion criteria were fulfillment of the American College of Rheumatology (ACR) criteria for RA[8] and use of MTX alone or in combination with LEF. Treatment with stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone at doses lower than 15 mg/day was allowed. All patients received folic acid supplementation, 5 mg once or twice a week.

The exclusion criteria comprised the concomitant use of other DMARDs, biological agents, hepatotoxic drugs, or alcohol abuse. Patients with persistent abnormal results on liver function tests were also excluded. Additional reasons for exclusion were hematopoietic disorders, human immunodeficiency virus infection, and hepatitis B or C virus infection.

The medical records of patients studied were systematically reviewed by use of a questionnaire assessing demographic data, clinical variables, and medications used.

The laboratory variables tested were alanine/aspartate aminotransferase enzymes (ALT/AST, respectively). The liver enzymes were analyzed one month after treatment start with MTX and MTX plus LEF, and every three months. Hepatotoxicity was defined as AST or ALT increased at least two-fold the upper limits of normal (ULN).

A total of 97 RA patients were enrolled, but 26 were excluded due to the following reasons: one had hepatitis B; five stopped MTX very early without adverse effects reported; three were on other combinations of DMARDs; and 17 were on biological treatment. Treatment with MTX as monotherapy or in combination with LEF was started only in patients with normal liver tests.

This study was submitted to and approved by the institutional ethics committee, and written informed consent was provided by each participant.

The numerical data are shown as mean and standard deviation (SD). Those variables were compared by use of the Student's *t* test for differences. The categorical variables were compared by use of the chi-square test or the Fisher's exact test. Results were evaluated according to the established normal values and were subsequently ranked as elevated or normal. Statistical significance was set at $P < 0.05$. All statistical analyses were performed by using the EpiInfo 6.04 software.

RESULTS

Patients were distributed into two groups according to current therapy: MTX (n = 26 or 36.6%) or MTX + LEF (n = 45 or 63.4%). All patients in both groups were using MTX 20 to 25 mg once a week. The dose of LEF used was 20 mg per day.

Demographic data of both RA groups revealed a similar mean age (56.4 ± 14.5 *versus* 54.2 ± 13.6, P = 0.51) and frequency of the females (88.5% *versus* 91.1%, P = 0.71). Most patients were on NSAIDs, but in the same proportion in both groups (Table 1).

Table 1
Demographic data, NSAID use, and aminotransferase elevation in both groups

	MTX (n = 26)	MTX + LEF (n = 45)	P
Age (years)*	56.4±14.5	54.2±13.6	0.51
Female sex (%)	88.5	91.1	0.72
NSAID** (%)	84.6	86.6	0.81
ALT/AST*** > 2x (%)	11.5	11.1	1.0

*Data are expressed as means and standard deviations; ** NSAID: non-steroidal anti-inflammatory drug; ***ALT/AST: alanine/aspartate aminotransferases.

Three out of the 26 (11.5%) patients treated with MTX and five out of the 45 (11.1%) patients using the combination therapy showed elevated aminotransferase levels as defined in our study (Table 1). In patients with abnormal aminotransferase levels, the MTX doses were temporally reduced.

DISCUSSION

In past years, investigators have found that some DMARDs can increase the efficacy of MTX when used in combination. Given the diverse intracellular pathways affected by both drugs, the combination of LEF and MTX has the potential for biochemical synergy. The possibility of increased benefits

should be weighed against the possible toxicities of that combination. Abnormal aminotransferase levels have been seen with both MTX[9-12] and LEF[13,14] monotherapies in RA patients.

Our study found no difference in the percentages of elevated aminotransferases between RA patients being treated with MTX alone or with the MTX and LEF combination.

A small open study has reported considerable clinical improvements and only reversible elevations in aminotransferase levels with the MTX and LEF combination.[5]

Curtis *et al.*[15] evaluated patients with RA or psoriatic arthritis initiating DMARD therapy. The authors found elevations higher than twice the ULN in 1%-2% of patients on MTX or LEF monotherapy and in 5% of patients on combination therapy. After multivariate analysis, the MTX and LEF combination was associated with a greater risk of hepatotoxicity depending on the MTX dose: MTX 10-17.5 mg/week, OR 2.91 (95% CI 1.23 to 6.90); MTX ≥ 20 mg/week, OR 3.98 (95% CI 1.72 to 9.24).

Kremer *et al.*[16] developed a 24-week multicenter, randomized, double-blind, placebo controlled trial in which LEF or matching placebo was added to existing MTX therapy. Discontinuation rates were similar in both treatment groups (23.1% in the LEF group and 24.8% in the placebo group). Elevations in AST levels greater than 1.2 times the ULN were observed in 16.9% of the LEF group (22 patients) and 4.5% of the placebo group (six patients). Also, on the basis of maximum elevation, elevated ALT and AST levels greater than three times the ULN occurred more frequently at any time during the 24-week study in the LEF group than in the placebo group. However, all elevated ALT and AST levels exceeding 1.2 times the ULN in the LEF group normalized to 1.2 times the ULN or less during the study or after 24 weeks. In this study, most patients achieved normalization with no adjustment of the LEF dose (58.5% of patients with abnormal ALT levels and 59% of patients with abnormal AST levels). Three patients in the LEF group and two patients in the placebo group had to leave the study before week 24, because ALT and AST levels were elevated beyond the protocol-defined range of acceptability on repeated testing (persistent elevations of aminotransferase levels to more than two times the ULN on repeated testing after dose adjustment or confirmation of a value higher than five times the ULN). Results of liver function tests normalized by the follow-up visit in the three LEF-treated patients. In the two patients receiving placebo, ALT and AST levels were still elevated at the follow-up visit, but normalized several months later.

Katchamart *et al.*[7] carried out a systematic review of randomized trials comparing MTX alone and in combination with other non-biological DMARDs to evaluate drug efficacy and toxicity in adults with RA. In 17 of the 19 trials (1624 patients: 824 in the combination group *vs*. 800 in the monotherapy group), combination therapy resulted in more withdrawal due to adverse reactions than monotherapy, but the differences were significant only for cyclosporine and azathioprine.

In conclusion, more trials are needed, but current evidence suggests that the MTX and LEF combination for RA patients is generally safe and well tolerated. Liver enzymes should be monitored, but serious liver toxicity is rare and similar to that of patients on MTX alone.