Rheumatoid Arthritis Treatment with Weekly Leflunomide: An Open-Label Study

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ABSTRACT. ***Objective.*** To assess the safety and effectiveness of leflunomide (LNF) using 100 mg/week in patients with rheumatoid arthritis (RA).

Methods. Patients who were clinically active using the American College of Rheumatology criteria for RA were enrolled. They received a loading dose of 100 mg of LFN for 3 days, followed by 100 mg of LFN weekly. Efficacy and adverse events (AE) were recorded.

Results. Fifty patients were enrolled; 46 (93.6%) were women with a mean age of 45.6 years (range: 24 to 83). Disease duration was 3.7 years (range: 0.5 to 12). Twenty patients (40.8%) had previously taken disease modifying antirheumatic drugs. Outcomes achieved after 24 weeks of treatment were as follows: ACR20 (74%), ACR50 (64%), and ACR70 (28%). Five patients were withdrawn due to AE: 2 due to urticaria, 2 patients had elevated liver enzymes, and one had thrombocytopenia. Six patients (12%) were lost to followup. No severe AE were seen.

Conclusion. The results in our preliminary report indicate that using a 100 mg/week dose achieves a similar benefit to the LFN 20 mg/day treatment, and there were no severe AE. In addition, a single LFN weekly dose has better treatment compliance. A secondary important benefit is the reduction of the monthly cost of medication. Comparative and blind trials are necessary in order to confirm longterm improvement and benefits on this regimen. (J Rheumatol 2004;31:235–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TREATMENT LEFLUNOMIDE WEEKLY REGIMEN

Rheumatoid arthritis (RA) is an autoimmune and chronic disorder of unknown etiology. It is characterized by symmetric erosive synovitis and extraarticular involvement and may result in progressive joint destruction, deformity, disability, and even death[1]. Several disease modifying antirheumatic drugs (DMARD) are available for control of the progression of RA. Unfortunately, multiple drug intake, adverse gastrointestinal effects, and the cost of medication do not permit DMARD treatment of RA patients for long periods of time[2]. Leflunomide (LFN), a recent clinically used DMARD in Mexico, is an isoxazol drug with antiproliferative and immunosuppression effect, and with a half-life of up to 15 to 18 days. Leflunomide trials have shown effectiveness and safety with a 20 mg daily dose[3,4]. A weekly 100 mg regime is an attractive therapeutic option because based on the half-life and bioavailability of this drug, it can be detected for up to 15 days after its administration. A small number of cases have been reported using this regimen, in which improvements were steady during at least 6 months of treatment.

We assessed the safety and effectiveness of leflunomide 100 mg/week for 24 weeks in patients with active RA.

MATERIALS AND METHODS

This was a 24-week open label study. RA patients with clinically active disease were enrolled from October 2000 to September 2001. Diagnosis was based on the 1987 revised American College of Rheumatology (ACR) criteria for RA. Patients with previous treatment with DMARD were included, with the requirement that they be free of medication for at least one year before starting LFN. Use of nonsteroidal antiinflammatory drugs (NSAID) and corticosteroid in stable daily doses of 10 mg or less of prednisone or equivalent was allowed. They received a loading dose of 100 mg of LFN for 3 days, followed by 100 mg of LFN weekly. Efficacy was assessed with ACR 20, 50 and 70% improvement criteria, including reduction of tender and swollen joints, and at least 3 of the following: patient and physician global assessments using a Likert's scale, duration of morning stiffness, Health Assessment Questionnaire for Spanish speakers (HAQ-DI), pain score scale (visual analog scale), and laboratory assessment including Westergren erythrocyte sedimentation rate (ESR), complete blood count (CBC), liver enzymes, and glucose at 0, 2, 4, and 6 months. Liver enzymes were measured every 30 ± 5 days in all patients. Adverse effects (AE) were recorded.

RESULTS

Fifty patients were enrolled (Table 1). The mean age was 45.6 years, 93.6% were women. Thirty-eight patients had disease duration of less than 5 years, and only 20 patients (40.8%) had received DMARD previously. After 12 weeks of treatment, 76% of patients reached ACR 20 and 58%

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Submitted May 25, 2003; revision accepted July 25, 2003.

Table 1. Patient demographics.

n	50
Female (%)	44 (93.6)
Mean age, yrs (range)	45.6 (28.8–83)
Mean duration of previous RA, yrs (range)	3.7 (0.5–12)
Disease duration, yrs (%)	
< 2	18 (36)
2.1 to 5	20 (40)
> 5	12 (24)
Rheumatoid factor positive	40 (87)
Previous DMARD therapy	20 (40.8)

reached ACR 50. At the end point (24 weeks) 74% of patients reached ACR 20, 64% reached ACR 50, and 28% reached ACR 70 (Figure 1). At study onset, the median prednisone dose was 1 mg daily (range 0 to 7.5); at the end of the study, the median was still 1 mg daily but the range had significantly decreased to 0 to 2.5, ($p = 0.02$).

Adverse effects. AE are shown in Table 2. Headache was the main complaint of the group (16%), followed by hair loss (10%), and myalgias (10%). Four patients developed urticarian rash mainly on the trunk and arms. Two of these patients had moderate rash, itching, and facial edema. Both were excluded. There were only 2 patients with diarrhea that resolved spontaneously in both cases. Liver enzyme abnormalities were seen in 5 patients (Figure 2). A maximum alkaline phosphatase level of 210 u/l was reached in one patient at week 16 (normal range: 27-130 u/l). The highest measurements of glutamic piruvic transaminase (ALT) and glutamic oxaloacetic transaminase (AST) enzymes were 76 and 66 u/l, respectively, (normal ranges: 0-41 u/l and 0-37 u/l) in the same patient. None of these patients developed more than 2.5 times the normal upper limit of liver enzymes. One patient developed severe thrombocytopenia (< 70,000 mm^3), but this resolved when medication was stopped. There were no serious AE. One patient withdrew because of lack of efficacy at 16 weeks and 6 patients were lost to followup during the study.

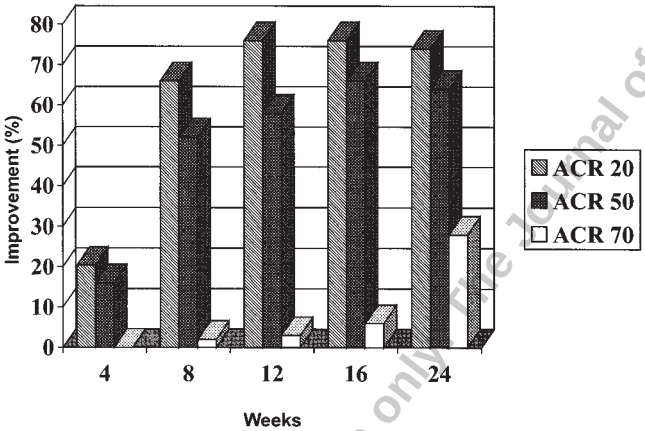

Figure 1. Percent improvement in ACR 20, 50, and 70 assessments at 4, 8, 12, 16, and 24 weeks of treatment with LFN.

Table 2. Adverse events.

Adverse Event	Minor (%)	Moderate (%)
Headache	8 (16)	
Hair loss	5 (10)	
Myalgias	5 (10)	
Urticaria	4 (8)	2 (4)
Diarrhea	2 (4)	
Upper airway infection	1 (2)	1 (2)
Melena	2 (4)	
Elevated liver enzymes	5 (10)	
Thrombocytopenia		1 (2)

DISCUSSION

Effective treatment of RA is a goal for internal medicine and rheumatology clinical practitioners[5]; however, several factors contribute to a lack of successful disease control. Use of multiple drugs, gastric complaints, AE, and high cost can interfere with patient compliance. Jakez-Ocampo[6] reported 6 patients who did not respond to conventional treatment. They were given LFN 100 mg/week for 6 months. All patients reached ACR 20 at the third month and ACR 50 at the sixth month of treatment, according to the ACR improvement criteria for RA. No AE were reported. A second brief report from the same investigators showed outcomes from 30 patients divided into 3 groups in an open label study[7]. One group received LFN 20 mg/day, the second group received LFN 100 mg/day, and the third group received methotrexate (MTX) 7.5-15 mg/week during 6 months of treatment. The first group (LFN20) showed more improvement than the other 2 groups at 4 months of treatment ($p < 0.05$). However, at the end point of study, the ACR 20, 50, and 70 were similar in all 3 groups. AE were minor in the LFN 100 group compared with the other groups. In both studies there was evidence that the regimen

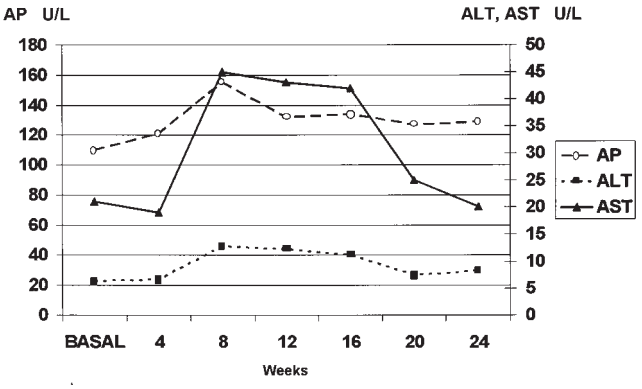

Figure 2. Change in mean liver enzyme levels in 5 patients who experienced change over 24 weeks of treatment with LFN. AP: alkaline phosphatase; ALT: glutamic piruvic transaminase; AST: glutamic oxaloacetic transaminase.

of LFN 100 mg/week might be a good option in the treatment of RA.

To date, our study includes the largest group of patients with RA treated with 100 mg/week LFN. The improvement attained with this treatment schedule showed benefit at the end point of the study, but results (according to ACR 50 and 70) were superior even when compared to the studies with the 20 mg/day LFN regimen. This is probably because it was an open label study. With regard to AE, it is possible that the less frequent AE seen in our patients when compared with the previous LFN 20 mg/day studies may be due to the less accumulative weekly dose (100 mg vs 140 mg). A weekly dose of medication appears to be an easier way for patients to adhere to treatment. An added benefit is a cost saving of almost 35% of the real cost of medication in the non-insured population found in our country. Even though the results were favorable, we do not yet know if the treatment will be effective for long periods of time. Double blind and comparative studies are still needed to show an improvement over long periods of time.

These preliminary outcomes demonstrate the improvement achieved with LFN 100 mg weekly, similar to that achieved with the traditional 20 mg/day regimen. Patients feel comfortable and have better compliance with the prescribed weekly treatment. Furthermore the monthly cost of medication is reduced. Fewer adverse effects were seen with the 20 mg/day dose, but longterm blind and comparative trials should be undertaken to confirm the therapeutic benefits achieved with 100 mg weekly LFN in patients with RA.

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