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# Benefit/risk of leflunomide in rheumatoid arthritis

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J.M. Kremer, G.W. Cannon

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Joel M. Kremer, MD, Director of Research, The Center for Rheumatology, Clinical Professor of Medicine, Albany Medical College, Albany, New York;

Grant W. Cannon, MD, Associate Chief of Staff for Academic Affairs, Veterans Affairs Salt Lake City Health Care System, Professor of Medicine, Division of Rheumatology, Department of Medicine, University of Utah, Salt Lake City, Utah, USA.

Please address correspondence to: Joel M. Kremer, MD, The Center for Rheumatology, 1367 Washington Avenue, Suite 101, Albany, New York 12206, USA.

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## Introduction

Leflunomide was first shown to have disease-modifying properties in a rat model of adjuvant-induced arthritis (1). Leflunomide has been subsequently used with success in several animal models of tissue and organ allograft (2-7) and of autoimmune disease including collagen- and adjuvant-induced arthritis (1, 7-12), interstitial nephritis (13), myasthenia gravis (14), and systemic lupus erythematosus (15-17). Based on its success as an immunosuppressive agent in these models, leflunomide was tested for the treatment of rheumatoid arthritis (RA).

## Clinical studies

The clinical trial that led to US Food and Drug Administration (FDA) approval of leflunomide in the United States was the US 301 Leflunomide Trial in Rheumatoid Arthritis (Protocol US301) – a double blind, placebo-controlled, multicenter trial involving 482 subjects (18). Patients were randomized to receive leflunomide (n=182), methotrexate (n=182), or placebo (n=118) for 52 weeks. Leflunomide was initiated with a loading dose of 100 mg daily for 3 days followed by a daily dose of 20 mg. Patients randomized to receive methotrexate received an initial dose of 7.5 mg/week and could increase the dose to 15 mg/week in week 9 of the trial if an adequate response had not yet been achieved. Sixty percent of the methotrexate patients were treated with a dose of 15 mg/week by the end of the study.

An intent to treat, last observation carried forward analysis of the results at 52 weeks showed American College of Rheumatology (ACR) 20 responses of 52% in the leflunomide group versus 26% in the placebo group and 46% in the methotrexate group ( $p < 0.001$  for both leflunomide and methotrexate versus placebo).

Radiographs of patients' hands and feet at baseline and 12 months (or at the

time of early study exit) were obtained for 352 (73%) of 482 patients. Total Sharp scores were significantly lower for patients treated with leflunomide versus placebo ( $p < 0.001$ ) and methotrexate versus placebo ( $p = 0.02$ ).

Withdrawals due to adverse events were more common in patients who received leflunomide (22%) versus placebo (8.5%) and methotrexate (10.4%). Gastrointestinal complaints were more common in patients who were treated with leflunomide. Diarrhea was observed in 33.5% of patients taking leflunomide versus 16.9% taking placebo and 19.8% taking methotrexate. Hypertension (systolic blood pressure above 160 mm Hg and diastolic blood pressure above 90 mm Hg) was observed in 11% of patients in the leflunomide group versus 5.1% and 2.7% in the placebo and methotrexate groups, respectively. Transaminase elevations were observed in 14.8% of patients taking leflunomide, 2.5% taking placebo, and 11.5% taking methotrexate. Aspartate aminotransferase (AST) elevations of more than twice the upper limit of normal but less than three times the upper limit of normal were seen in 6.0% of patients who took leflunomide and the same number of patients who took methotrexate. Elevations of AST of  $> 3$  times the upper limit of normal were observed in 8.2% and 6.5% of patients on leflunomide and methotrexate respectively, compared with 1.7% of patients on placebo. All elevations of transaminase enzymes (n=20) reverted to less than twice the upper limit of normal while treatment continued (n=10) or after treatment discontinuation (n=10).

A 24-month follow-up of the above study consisted of 235 patients (leflunomide=98; placebo n=36; methotrexate n=101) (19). The year 2 cohort comprised patients continuing into the second year of treatment with  $> 1$  dose of study medication and  $> 1$  follow-up visit after week 52. The mean maintenance dose of leflunomide was 19.6 mg

in year 2 and 12.6 mg methotrexate. Eighty-five percent and 79% of leflunomide and methotrexate patients, respectively, who entered year 2 completed 24 months of treatment. ACR 20 response rates during months 12 to 24 were sustained in leflunomide and methotrexate patients (79% and 67% respectively,  $p=0.049$ ). ACR 50 response rates were observed at 24 weeks in 56% of patients receiving leflunomide and 43% on methotrexate ( $P = 0.053$ ) with ACR 70 response rates of 26% and 20% respectively (NS). The mean change in total Sharp radiologic damage scores at year 2 compared with year 1 and baseline (leflunomide 1.6 vs. methotrexate 1.2) showed statistically equivalent sustained retardation of radiologic progression in the active treatment groups. Improvements in the Health Assessment Questionnaire (HAQ DI) were -0.60 for patients taking leflunomide and -0.37 for patients who took methotrexate at 24 months ( $P = 0.005$ ).

Serious adverse events considered by the investigators to be related to study drug administration were reported in 3 leflunomide-treated (1.6%), 2 placebo-treated (1.6%), and 7 methotrexate-treated patients (3.7%). These included asymptomatic liver enzyme elevations (2 leflunomide, 1 placebo, 4 methotrexate), pneumonia (1 each leflunomide and methotrexate), hypertension (1 placebo), sepsis (1 each leflunomide and methotrexate) and interstitial pneumonitis (1 methotrexate). The overall incidence of infections was not different in the active and placebo treatment groups and no opportunistic infections were observed through 24 months. Diarrhea resulted in the withdrawal of 9.5% of patients receiving leflunomide, and alopecia was reported in 10.5% of leflunomide patients vs. 5.8% of patients receiving methotrexate. New onset hypertension occurred in 4.7% of leflunomide-treated patients, all of whom were receiving NSAIDs. Three liver biopsies were performed during the second and third year of drug administration including 2 in leflunomide-treated patients at weeks 106 and 135 and 1 methotrexate-treated patient at week 156. None of the biopsy specimens

showed bridging fibrosis, previously reported as a reason to discontinue methotrexate (20).

### Effects on radiographic progression

Sharp *et al.* analyzed the radiographic data from 3 phase III studies of US301 (21), and Protocol MN 301, which compared 6 months of leflunomide versus sulfasalazine versus placebo in 358 European patients, and Protocol MN 302, which compared 12 months of leflunomide versus methotrexate in 999 European patients.

Leflunomide, methotrexate and sulfasalazine were all more effective than placebo in slowing radiographic progression, and the radiographic benefit of the three drugs did not differ statistically. In all three clinical trials, radiographic progression was greater in patients who had erosions at baseline than in those who did not. Patients who met ACR 20 response criteria were more likely to show slowing of radiographic progression. Interestingly, concomitant use of corticosteroids did not have a consistent effect on treatment outcome. Overall correlations between clinical and radiographic responses were weak ( $r < 0.5$ ), and were not consistent across the protocols.

Analysis of knees at baseline and after 4 months using dynamic enhanced magnetic resonance imaging (DEMRI) with gadolinium enhancement, indicated significantly greater improvement in the patients treated with leflunomide compared with placebo ( $P < 0.05$ ) (22). The authors acknowledge that the effect of an initial loading dose of 100 mg daily for 3 days of leflunomide and the lower starting dose of methotrexate of 7.5 mg weekly would favor leflunomide after only 4 months of treatment. Nevertheless, the results are intriguing.

### Leflunomide used in combination with methotrexate

Contemporary development and assessment of therapies for RA requires that all new agents must be studied in combination with methotrexate, which has great efficacy, low toxicities, long continuation, and relatively low cost and ease of administration. Methotrexate can have effects on both the purine and

pyrimidine biosynthetic pathways, but its effects on purine metabolism predominate (23). Leflunomide inhibits pyrimidine metabolism (REF), and natural interest existed in combining these antimetabolites which have somewhat different, but potentially complementary mechanisms of action. However, both drugs have the potential to raise liver enzymes when used as monotherapy, and there was also some concern about potential effects on the liver when using the two agents in combination.

### Open study

Weinblatt *et al.* studied the effects of the combination of leflunomide and methotrexate in a small, open, two-center study involving 30 patients (24). Subjects in this 52-week study had active disease despite therapy with methotrexate at a mean weekly dose of 17 mg for  $>6$  months. Patients received a loading dose of leflunomide of 100 mg for 2 days, followed by a daily dose of 10 mg daily. After 3 months, physicians could increase the dose of leflunomide to 20 mg/day in patients with continuing active disease.

At study termination after 52 weeks, 12 patients (40%) continued to take 10 mg of leflunomide. The dosage was increased to 20 mg in 16 subjects (53%), and was transiently reduced to 10 mg every other day due to toxicity in 2 subjects. Twenty-seven of the 30 patients received combination therapy with methotrexate and leflunomide for at least 24 weeks, 25 for at least 40 weeks, and 23 for the full 52 weeks of the study.

The combination was generally well tolerated. The most common adverse events were mild diarrhea in 6 (20%), moderate diarrhea in 4 (13%) patients, alopecia in 7 (23%) and rash in 4 (13%) of patients. Only one patient was removed from the study because of elevation of transaminase enzymes. Asymptomatic plasma elevations of either AST or ALT were increased at least once in 19 (63%) subjects. In 70% of the cases of liver enzyme elevations, levels reversed to  $< 1.2$  times the upper limit of normal without dosage reduction of leflunomide. Three patients had recurrent elevations of liver enzymes and met the criteria for liver biopsy in pa-

tients on methotrexate (20). Two of the three biopsies showed mild, non-bridging fibrosis (Roenigk grade IIIA) and one patient had a normal biopsy. As per the published guidelines on the use of methotrexate in RA and monitoring of potential liver disease (20), all 3 patients continued treatment. One patient exhibited a 6-fold increase in transaminase enzymes and, per protocol, had cholestyramine initiated for 11 days with a quick return of transaminase enzymes to normal within 2 weeks of the initiation of treatment with the resin binder. Because of the open nature of the study, efficacy was not a primary outcome. Nevertheless, ACR 20 criteria were observed to peak at 9 months when 57% of the patients met the criteria for improvement.

### Clinical trials of leflunomide-methotrexate combination

The combination of leflunomide and methotrexate was studied in a subsequent 6 month, double-blind, placebo-controlled, multicenter study involving 20 centers in North America. Overall, 263 patients were randomly assigned to receive leflunomide and methotrexate ( $n=130$ ), or methotrexate plus placebo leflunomide ( $n=133$ ) (25). Patients assigned to leflunomide received a 100 mg loading dose for the first 2 days, followed by 10 mg/day, which was doubled to 20 mg after 8 weeks, for the duration of the 24 week investigation (Fig.). The overall ACR 20 response rate was 46.2% of the methotrexate + leflunomide group (60/130) and 19.5% of the methotrexate + placebo group ( $P < 0.001$ ); ACR 50 response rates for the leflunomide + methotrexate vs. the methotrexate only and placebo subjects were 26.2% and 6%, respectively ( $P < 0.001$ ), and ACR 70 response rates were 10.0% and 2.3% respectively in the combination versus methotrexate-placebo groups ( $P = 0.0155$ ).

The most common adverse events were diarrhea reported in 25.4% and 13.5% in the leflunomide and placebo groups, and nausea in 16.2% and 11.3% respectively. Alopecia was also seen in 6.2% of leflunomide + methotrexate patients compared with an incidence of 3.8% in those on methotrexate alone. No differ-

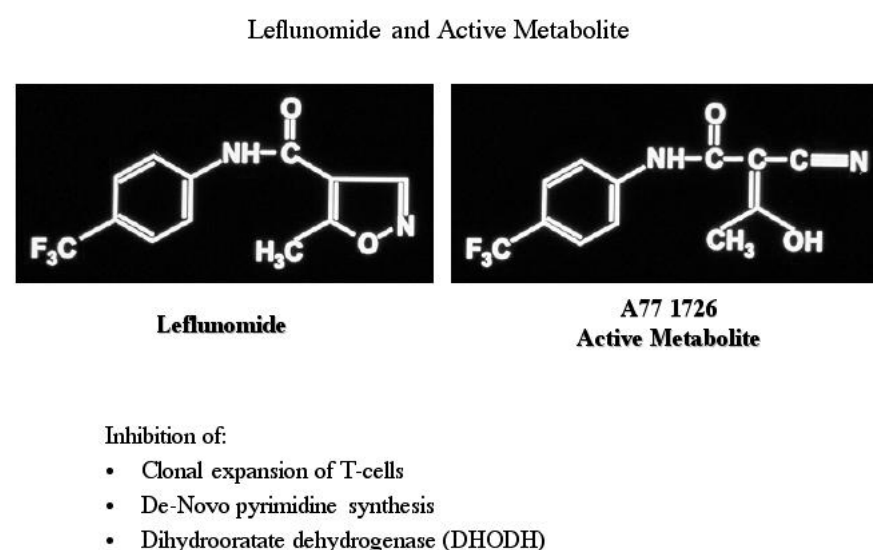


Fig. 1. Molecular structure of leflunomide and its active metabolite, A77 1726.

ences in the reported incidences of rash, upper respiratory infection or headache were observed. Infections were actually less common in the leflunomide combination-treated patients than in the methotrexate only control group (40.8% vs. 51.9% respectively).

Three patients in the leflunomide group and 2 patients in the control group were withdrawn from the study because of transaminase enzyme values which were beyond the protocol-defined range of acceptability. In addition, some mild to moderate decreases in leukocyte and neutrophil counts were associated with leflunomide + methotrexate combination treatment, with no patient showing values below  $2,000/\text{mm}^3$ .

A follow-up open study (26) was conducted for an additional 6 months, in which patients originally assigned to receive combination leflunomide and methotrexate continued treatment with this combination, while patients who had been randomized to receive methotrexate and placebo were also treated with the combination for an additional 24 weeks. These patients in whom leflunomide was added to background methotrexate began with 10 mg daily, without a loading dose, and could have their daily dose adjusted by the investigator. All patients in the combination group also had their dose reverted to 10 mg at the onset of the open phase of the investigation, including those who had

received leflunomide at a dose of 20 mg daily.

ACR 20 responses in the subjects who received leflunomide for the first time without a loading dose were indistinguishable at week 48 from the responses seen in the combination group subjects who had received both drugs for the full one year duration of the study (27). However, ACR 50 and 70 responses were somewhat lower than those observed in the patients who received combination therapies for the entire period.

Significantly, the incidence of diarrhea, nausea and transaminitis was lower in the patients who did not receive a loading dose of leflunomide at the initiation of the open phase of the study (26). It therefore appears that considerable potential toxicities may be avoided by omitting a loading dose of leflunomide, at least when the drug is added to methotrexate.

### Leflunomide and the liver

Beginning in March 2001 with the issuance of a warning about the potential of serious liver toxicity with leflunomide from the European Regulatory Agency (EMA), there has been heightened concern over the potential for serious hepatic damage with leflunomide. A "Dear Doctor" letter to rheumatologists within the United States warning of potential liver toxicity with lefluno-

mide and recommending frequent careful monitoring of liver enzymes was sent by the manufacturer, Aventis. This situation became more complex with the filing of a "Citizen's Petition" with the Food and Drug Administration by a national consumer group claiming that the drug was responsible for 130 cases of severe hepatic events, 56 hospitalizations and 22 deaths. The group contended that the rate of hepatic events was roughly 5-fold higher with leflunomide than with methotrexate, and since methotrexate was equally efficacious, they asked that leflunomide be removed from the marketplace.

This complaint coming on the heels of the EMEA finding of 296 hepatic reactions (in 104,000 patient years of exposure), with 129 cases being considered serious, led to heightened patient concern. Advertisements in local newspapers appeared around the country from law firms seeking to represent patients who had suffered hepatic damage from leflunomide.

The Food and Drug Administration found no differences between the number of cases of hepatic impairment reported to the Medwatch database for infliximab, etanercept and leflunomide, with fewer cases reported with methotrexate (Decreased reporting of toxicity associated with a drug which has been in use for decades is expected and has been termed the "Weber effect"). Forty-three of the 50 cases (86%) reported with biological agents were found to have other proximal causes of liver damage including sepsis (29%), other drugs (14%), viral hepatitis (7%), ethanol abuse (12%) and tuberculosis and simultaneous treatment with isoniazid (19%).

The absence of an increased incidence of hepatic toxicity has been independently confirmed by information from a database of the Aetna Insurance Company covering 6.5 million lives and 40,594 patients with RA. Although the database is derived from Diagnosis Related Group (DRG) coding from hospitalizations, and therefore contains little specific clinical detail, an analysis of the cohort indicated that there was no increase in the incidence of hepatic events observed in the 11,180 patient-

years of exposure in subjects receiving leflunomide versus the 71,884 patient years of exposure in patients who received other disease-modifying, anti-rheumatic drugs (DMARDs), or the 11,259 patient years of exposure in patients who received no DMARD. As was the case after careful analysis of the overwhelming majority of the cases reported in the European (EMA) database, other factors including comorbidities, simultaneous use of other potentially hepatotoxic agents, alcohol intake and viral infection including viral hepatitis, could have contributed to the hepatic reactions. In virtually all of the cases, a careful history of previous liver disease, alcohol use and hepatitis was not available.

#### **Recommendations for monitoring liver toxicity**

Recommendations for monitoring for the potential development of liver toxicity with leflunomide are empiric, as no prospective studies with baseline and follow-up liver biopsies have been performed. The recommendations are therefore derived from the experience with methotrexate, in which these studies were performed over prolonged treatment intervals (27). From the experience with methotrexate, it was apparent that hepatic histology remains normal when patients are managed so that serum values of AST, ALT and serum albumin remain within the normal range. A relationship is seen between hepatic enzyme elevations and hepatic histologic damage with methotrexate (27, 28). To our knowledge, the studies of baseline and annual liver biopsies along with simultaneous and frequent, regular monitoring of hepatic enzymes, is the only study of chronic exposure of a physician-prescribed, potential hepatotoxin in which all of these elements have been examined. It would also be costly, cumbersome and legally difficult in today's regulatory climate to duplicate the studies of hepatic safety reported with methotrexate.

It therefore appears both logical and reasonable to apply the experience gained with methotrexate to another drug with potential hepatic toxicity, leflunomide. Rheumatologists have al-

ready been trained to monitor methotrexate, and their experience can and should be readily applied to the use of leflunomide. As is the case with the manufacturer's recommendations, we suggest that transaminase enzymes and serum albumin be obtained at baseline and then monthly for the first 6 months in a patient receiving leflunomide. If the drug is being added to methotrexate, a strong case can be made for obtaining the first monitoring hepatic blood samples after only 2 weeks of the combination. If the transaminase enzymes and serum albumin remain within the normal range for the first 6 months of treatment (keeping in mind that the upper limit of normal in commercial laboratories is already 2 standard deviations from the statistical norm), then monitoring frequencies of 4 to 8 weeks could be employed, as is the case with methotrexate.

It seems prudent to suggest that patients limit or abstain from alcohol consumption while taking leflunomide, as with methotrexate, although no studies of the effects of the interaction of leflunomide with alcohol intake have been performed. If the rapid elimination of leflunomide is clinically indicated, cholestyramine may be administered in a recommended dose of 8g TID for periods of 7-10 days, resulting in the elimination of A77 1728 and the return of elevated transaminase enzymes to the normal range (Fig. 2).

#### **Infections**

Specific infections that occurred more frequently in leflunomide-treated subjects than in subjects receiving placebo in Phase III placebo-controlled trials included bronchitis and pneumonia (29), including upper respiratory infections in 21% of the leflunomide-treated subjects in these trials. However, this incidence was not higher than that seen in placebo-treated subjects in the same trials (20.5%), and presumably reflects the fact that such infections are more common among subjects with RA in general. In the same trials, the incidence of upper respiratory infections was 20.3% and 31.9% in sulfasalazine- and methotrexate-treated subjects, respectively. The incidence of bronchitis



during leflunomide treatment in Phase III trials (5.1%) was higher than in placebo-treated subjects (1.9%), but an increased incidence of bronchitis was also seen in other actively treated subjects in these studies (3.8% and 6.6% in sulfasalazine- and methotrexate-treated subjects, respectively).

Ten subjects (3.2%) treated with leflunomide in Phase III placebo-controlled trials developed pneumonia as opposed to no cases in the placebo group (29). All of the leflunomide-treated subjects who developed pneumonia were older than 65 years of age and were receiving concomitant glucocorticoids. Further analysis of this complication in observations in long-term therapy will be of value.

### Central nervous system

The most common CNS-related adverse event associated with leflunomide treatment was headache, which occurred in 13.3% of the subjects receiving leflunomide in Phase III placebo-controlled trials. However, this incidence was only slightly higher than that seen in placebo-treated subjects (11.4%) (30) and may be of limited clinical significance.

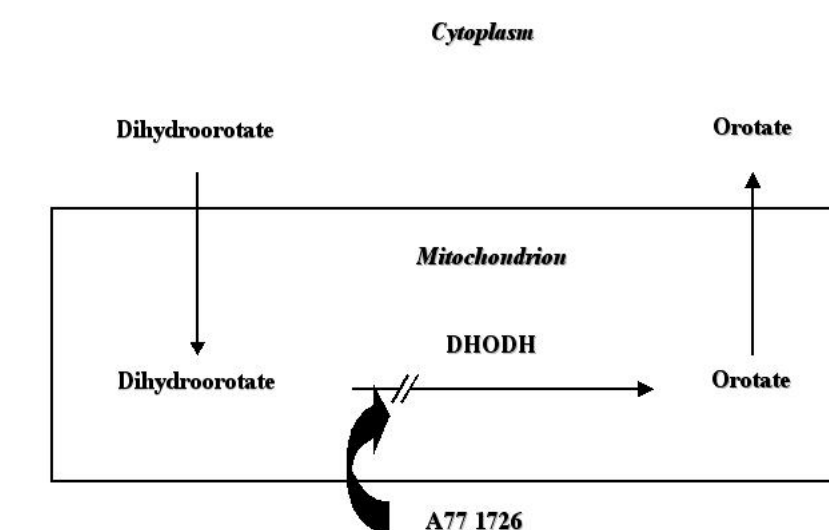
Paresthesia and other neurologic-related events were noted in 4.8% of the leflunomide-treated subjects in Phase III placebo-controlled trials and in 2.4% of the subjects receiving placebo. A similar incidence rate was seen in methotrexate-treated subjects in the same trials (4.9%).

### Alopecia

Treatment with leflunomide was associated with a 9% incidence of mild hair loss (alopecia), compared to 1.4% in the placebo group (29). Alopecia was reversible if leflunomide treatment was discontinued. Only one subject receiving leflunomide withdrew from Phase III, placebo-controlled trials because of alopecia.

### Rare adverse events

Treatment of large populations of RA subjects with DMARDs also results in adverse events that, while infrequent (incidence of <1%), are of potential clinical importance. Several such events



**Fig. 2.** The metabolic pathway for the production of nucleic acids showing where A77 1726 acts to inhibit pyrimidine synthesis.

were noted in the active treatment groups during Phase II and III studies of leflunomide and are discussed here.

**Lymphoproliferative disorders:** Subjects with RA have been reported to have a 3- to 4-fold greater risk for lymphoma/myeloma (30). The observation that some RA subjects treated with methotrexate experienced spontaneous remission of lymphoma after withdrawal of methotrexate has led to the suggestion that immunosuppressive therapies *per se* may be a risk factor for this disease (30, 31).

In Phase II and III clinical trials of leflunomide, 5 cases of lymphoproliferative disorders were reported. Of these, 3 occurred in subjects treated with leflunomide and 1 each in methotrexate- and sulfasalazine-treated subjects. Of the 3 leflunomide-treated subjects, 1 was diagnosed with chronic lymphocytic leukemia that was thought to be unrelated to the treatment. In the second case, the morphology of the neoplastic cells was not that typically seen in lymphomas associated with a significantly altered immune system. Thus, it was felt that the lymphoma was coincidental to, rather than the result of, leflunomide therapy for RA. Histopathological examination of neoplastic cells taken from the third subject indicated a large cell lymphoma that expressed CD30, suggestive of a lymphoma developing in the setting of an altered

immune state.

**Hematologic:** During Phase III clinical trials of leflunomide, 2 cases of agranulocytosis were reported in subjects treated with sulfasalazine and one case of neutropenia was reported in a subject receiving leflunomide (29). Neutropenia in the leflunomide-treated subject had a very gradual onset and persisted for 6 months after discontinuation of the drug treatment. Although leflunomide administration cannot be excluded as the cause of the neutropenia, a direct relationship between the use of leflunomide and the neutropenia was not definitively established.

**Interstitial pneumonitis and reversible renal impairment:** Interstitial pneumonitis and reversible decline in renal function are associated with methotrexate therapy for RA (32, 33). Neither of these adverse events was noted in any of the subjects treated with leflunomide in Phase II and III clinical trials. In the same trials, 4 cases of interstitial pneumonia, 1 case of interstitial fibrosis, and 3 cases of reversible renal failure were reported in methotrexate-treated subjects.

### Conclusion

Leflunomide is clearly efficacious in the treatment of RA, used as monotherapy or in combination with methotrexate. The administration of the drug has been associated with a variety of toxic-

ities, although almost all of them are manageable, and avoidable if recognized early by an experienced, alert and astute clinician. It appears that there is lower risk of toxicity when the drug is used without a loading dose, at least when prescribed in combination with methotrexate. Relatively few cases of serious or opportunistic infection have been reported. It may be reasonable to favor leflunomide over TNF inhibitors in patients with a history of pneumonia, recurrent sinusitis, serious or opportunistic infections. Leflunomide may also be considered before biologic agents in debilitated individuals, in whom monitoring transaminase levels may prove to present less risk than possible unpredictable potential infectious complications associated with TNF inhibition. The use of leflunomide with biological agents has not been adequately explored and represents a prime area for future clinical research.

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