Leflunomide: A Manageable Safety Profile

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ABSTRACT. The safety profile of leflunomide in the treatment of rheumatoid arthritis has been well documented in clinical trials, postmarketing surveillance, and epidemiological studies. Both postmarketing surveillance and epidemiological study results are consistent with the safety profile of leflunomide reported in clinical trials, and no increased risk was observed with leflunomide, compared with other disease modifying antirheumatic drugs; these studies have allowed a more precise representation of the incidence of adverse events occurring with leflunomide under normal conditions of care. The most common leflunomide-associated adverse events include diarrhea, elevated liver enzymes, alopecia, and rash. Ninety-five percent of the Expert Panel considered the adverse events associated with leflunomide to be manageable. If an adverse event required treatment to be stopped, many of the experts would consider subsequently restarting leflunomide. For minor adverse events, it was suggested that the physician might also consider using cholestyramine or charcoal to determine if the side effect is dose-related and, if it was, reduce the leflunomide dose accordingly. In addition to informing patients about the likelihood of side effects, it is important to emphasize that their incidence appears to diminish with continued treatment. It is also important to adequately support patients who are experiencing side effects and involve them in their disease management, for example, by offering the choice of reducing the leflunomide dose and/or having symptomatic treatment. Other patient management recommendations in this review reflect the views of the majority of participants as expressed in the meeting. (J Rheumatol 2004;31 Suppl 71:21–24)

Key Indexing Terms:
LEFLUNOMIDE RHEUMATOID ARTHRITIS ADVERSE EVENTS

The primary objective of this review is to define recommendations for the optimal use of leflunomide based on the review of key studies by international experts in rheumatology at an Expert Panel Meeting held in Paris in 2003. This overview of the safety profile of leflunomide in the treatment of rheumatoid arthritis (RA), as discussed in presentations at the Expert Panel Meeting, considers data obtained in the clinical program, from postmarketing surveillance, and from specific epidemiological studies, which have allowed a more precise representation of the incidence of adverse events occurring with leflunomide under normal conditions of care. The epidemiological studies use US health management organization data from the Aetna and Protocare/PharMetrics databases.

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LEFLUNOMIDE: SAFETY PROFILE IN CLINICAL TRIALS

In total, 1693 patients were treated, for the equivalent of 2533 patient-years, in the phase II and III clinical trials performed with leflunomide. Leflunomide showed a satisfactory safety profile in all 3 phase III clinical trials. The most common differences in adverse events between patients taking leflunomide and placebo were observed for diarrhea, elevated liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and alopecia and rash (Table 1)[1-3].

LEFLUNOMIDE SAFETY PROFILE IN POSTMARKETING SURVEILLANCE

In postmarketing surveillance, spontaneous reporting rates have been analyzed for over 80,000 patient-years of treatment; in this analysis, the incidence of hepatic failure was 14 per 100,000 patient-years, no higher than that observed with other recent disease modifying antirheumatic drugs (DMARD).

Reports of other adverse drug reactions are consistent with the safety profile of leflunomide reported in the clinical trials. Serious drug-induced hepatoxicity leading to hospitalization is rare with leflunomide (0.02%)[4], and the total number of spontaneous reports of hepatic events in patients receiving leflunomide has declined, despite a marked increase in the numbers exposed, since the introduction of monthly liver function test monitoring.

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Table 1. Percentage of patients with adverse events (≥ 3%) in clinical trial[1-3].

Adverse Event	Placebo-Controlled Trials (MN301, US301) LEF, n = 315	PL, n = 210	SSZ, n = 133	MTX, n = 182	MN302 LEF, n = 501	MTX, n = 498	All Trials, n = 1339*
Gastrointestinal							
Diarrhea	26.7	11.9	9.8	19.2	22.2	10	17
Nausea	13	11	18.8	18.1	12.8	18.1	9.3
Dyspepsia	10.2	10	9	13.2	5.8	7	4.9
Hepatic							
Elevated LFT	10.2	2.4	3.8	10.4	5.8	16.9	4.9
Headache	13.3	11.4	12	20.9	9.6	7.8	6.8
Cardiovascular	8.9	4.3	3.8	2.7	9.8	4	10.3
Hypertension†	8.9	4.3	3.8	2.7	9.8	4	10.3
Respiratory infection	21	20.5	20.3	31.9	26.5	24.5	15.1
Skin							
Rash	12.4	6.7	10.5	8.8	10.8	9.6	9.9
Alopecia	8.9	1.4	6	6	16.2	9.8	9.7

* Includes all controlled and uncontrolled trials with leflunomide (duration up to 12 mo). † New-onset hypertension was low in LEF: 1% in pooled placebo controlled trials (US301 and MN301), and 2% in MN302, respectively[3]. LEF: leflunomide; PL: placebo; SSZ: Sulfasalazine; MTX: methotrexate.

LEFLUNOMIDE IN EPIDEMIOLOGICAL STUDIES

Two specific pharmacoepidemiological studies have been undertaken, an analysis of the Aetna database and a nested case-control study. The analysis of data in the Aetna database evaluated the incidence of adverse events in 40,594 patients with RA in a large US healthcare insurance database, which contains data on 6.5 million individuals. The study allowed the incidence of adverse events to be compared between leflunomide, methotrexate, sulfasalazine, and other DMARD. The incidence of hepatic dysfunction and other adverse events was similar for all DMARD[5].

The nested case-control study was a subanalysis of the ProtoCare and Pharmetrics databases. This assessed the incidence of adverse events in over 40,000 RA patients treated with DMARD, 15% of whom received leflunomide. No increased risk was observed with leflunomide compared with other treatments in the overall incidence of serious adverse events, including serious hepatic, hematological, or pancreatic adverse events[6].

Conclusion

Both postmarketing surveillance data and epidemiological study results are consistent with the safety profile of leflunomide reported in clinical trials. No increased risk was observed with leflunomide, compared with other DMARD, in the overall incidence of adverse events.

Consequently, both at the US Food and Drug Administration and the European Committee for Proprietary Medicinal Products (CPMP) leflunomide was considered to have a positive benefit:risk profile as a DMARD in the treatment of adult patients with RA.

ADVERSE EVENT MANAGEMENT

The results of a questionnaire previously sent to the experts (sample presented elsewhere in these proceedings[7]) indicate that most (95%) of the Expert Panel considered the adverse events associated with leflunomide to be manageable. If an adverse event required treatment to be stopped, many of the experts would consider subsequently restarting leflunomide. For minor adverse events it was suggested during discussions that the physician might also consider using cholestyramine or charcoal to determine if the side effect was dose-related and would, therefore, resolve after reduction in the leflunomide dose.

Another suggestion was, in addition to informing patients about the likelihood of side effects, to emphasize that their incidence appears to diminish with continued treatment. It is also important to adequately support patients who are experiencing side effects and involve them in their management, for example, by offering the choice of reducing the leflunomide dose and/or having symptomatic treatment.

Other patient management recommendations, reported below, reflect the views of the majority of participants as expressed in the interactive voting session.

SPECIFIC MEASURES FOR SAFE USE OF LEFLUNOMIDE

The following recommendations are based on questionnaire feedback and discussions by the Expert Panel.

Diarrhea. Diarrhea, when it occurs, does so generally in the first 3 months of treatment, although in 98% of cases it resolves following symptomatic treatment. One hypothesis is that diarrhea is due to the action of leflunomide on the cell cycle of the gastrointestinal (GI) epithelium. However,

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during the phase II dose-finding study, no dose-related differences in GI safety were found between leflunomide at doses of 5 mg/day, 10 mg/day, and 20 mg/day[8]. Results from the questionnaire show that about three-quarters of the experts take measures to prevent diarrhea when starting their patients on leflunomide. When diarrhea occurs, three-quarters of the Expert Panel would reduce the dose of leflunomide, about one-half would prescribe an antidiarrheal, and one-half report that, once treated, the diarrhea resolves.

Somewhat less than one-half (43%) the Expert Panel considered diarrhea to be related to the loading dose of leflunomide, one-third disagreed, and one-quarter did not comment.

Diarrhea may be associated with the loading dose, although this is not supported by current evidence. Patients should be informed that leflunomide frequently causes diarrhea, which is, in most cases, mild or moderate and resolves spontaneously under continued leflunomide therapy. Patients should change alimentary habits during the respective episodes. A symptomatic therapy, involving antidiarrheals and medication to reestablish intestinal flora, may be prescribed in the short term; diarrhea often subsides with continued leflunomide treatment.

Alopecia. Alopecia is a common side effect of leflunomide (≤ 10% of patients), although the cases seen are generally mild to moderate and transient. Alopecia is thought to be dose-dependent, although this has been reported ambiguously because of the presence of other confounding risk factors, such as RA itself and its severity. However, in studies US301 and MN301, alopecia subsided in 60% of patients treated with leflunomide (data on file, Aventis).

To resolve alopecia, 56% of the Expert Panel reduce the leflunomide dose, although 31% maintain it, and only 13% stop leflunomide treatment altogether.

The patient should be informed that alopecia might occur. A dose reduction to 10 mg can be envisaged, if this is compatible with the severity of the RA. In some cases, the use of topical lotions can afford some benefit.

Hepatic dysfunction. Elevated concentration of transaminases is a known undesirable effect of leflunomide. This usually consists of an elevation of plasma ALT levels [serum glutamate pyruvate transaminase (SGPT)], sometimes accompanied by a rise in plasma AST (serum glutamate oxaloacetate transaminase), although AST elevation alone is not a side effect of leflunomide.

The European Agency for the Evaluation of Medicinal Products requires that ALT (SGPT) be checked before initiation of leflunomide, again at the same frequency as the complete blood cell count (every 2 weeks) during the first 6 months of treatment and every 8 weeks thereafter. Most DMARD induce adverse events primarily during the first 3–4 months and rarely thereafter[9]. It is assumed that similar results will be typical for leflunomide in longterm observational studies.

The questionnaire results showed that the experts regard hepatic monitoring during the first 6 months of leflunomide therapy as very important. They report that 15% of patients have a 2–3-fold increase in liver enzymes, but 58% of the experts consider this is reversible during treatment. Although only 4% of patients have a > 3-fold increase in liver enzymes, 94% of the Expert Panel stated that this is reversible only on stopping leflunomide therapy.

Strict compliance with the monitoring, as described in the summary of product characteristics, is recommended.

Cutaneous reactions. In clinical trials, allergic cutaneous reactions (rash, purpura) were common (< 10%) side effects of leflunomide, but were of mild to moderate severity and, in 90% of cases, resolved with continued treatment. Stevens-Johnson or Lyell syndrome, or toxic epidermal necrolysis, have been reported very rarely. Isolated pruritis is rarely seen with leflunomide treatment, but mucosal ulcers have been presented.

The experts reported that a minority (< 10%) of patients develop a rash while on leflunomide treatment; this is always either mild (72%) or moderate (28%). Most experts (95%) reported that the rash appears within the first 1–3 months. Although 53% stated that it resolves only when leflunomide is stopped, 56% would reduce the dose in patients with a mild/moderate rash. The physician should consider informing the patient of potential cutaneous adverse reactions. If mild reactions occur, leflunomide can be continued with symptomatic anti-allergic medication if needed. Patients with isolated pruritis require H_1 antagonist treatment. Leflunomide treatment may be continued or stopped, at the physician's discretion. Patients with mouth ulcers can continue taking leflunomide but must be closely monitored. Treatment should be stopped if ulcers persist or worsen.

Hypertension. Current labelling requires blood pressure to be measured before the start of treatment and periodically thereafter. The entire Expert Panel would use leflunomide in patients with preexisting hypertension, although 94% have seen either aggravated or new-onset hypertension in patients receiving leflunomide. New-onset hypertension usually occurs within the first 3 months of therapy. Most of the experts (94%) consider hypertension to be manageable during leflunomide treatment, with either a maintained (56%) or reduced (39%) dose, and by giving symptomatic antihypertensive treatment.

The patient should be informed that leflunomide may cause hypertension, and blood pressure should always be measured before starting, and regularly throughout, treatment; more frequent monitoring is needed in patients with preexisting hypertension. Newly emerging hypertension requires treatment; if necessary the physician may consider the possibility of reducing dose or discontinuing leflunomide treatment.

Infection. Most (79%) of the Expert Panel considered the

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incidence of infection to be similar in patients treated with leflunomide and with other DMARD (with the exception of biological agents). Respiratory infections were the most commonly reported. Over two-thirds reported the infections as mild, and 95% stated that they resolve during leflunomide treatment. Nearly one-half (47%) the Expert Panel would maintain the dose, although 37% would stop leflunomide, in patients with infections.

Cytopenia. Current labelling for leflunomide in the European Union requires a complete blood cell count, including differential white blood cell count and platelets, before the start of leflunomide treatment, every 2 weeks for the first 6 months of treatment, and every 8 weeks subsequently.

The entire Expert Panel would stop leflunomide treatment if the patient's neutrophil count decreased to < 1000 mm^3. All the expert participants would stop leflunomide in these patients; 64% would also do so in those with neutrophil counts of 1000–1500/mm^3, although a further 29% would reduce the dose instead. All reported that neutropenia is reversible, either during therapy or after treatment is stopped. Eosinophilia, anemia, and lymphopenia were not a concern according to the experts.

There is a need to monitor blood counts in patients taking leflunomide, according to the summary of product characteristics; however, it should be noted that all the experts stated that the frequency of this monitoring is similar to other DMARD such as sulfasalazine or methotrexate. Should cytopenia occur, a search for confounding medications or other causes should be undertaken. Should leflunomide be associated with significant cytopenia, appropriate measures should be taken; for example, stopping leflunomide and, if necessary, initiating a washout procedure.

Washout procedure. Indications of a severe reaction (inflammation of the buccal or genital mucosa, fever, extensive body rash, including bullous reactions or other signs suggestive of Stevens-Johnson or similar syndromes) or signs of anaphylaxis (e.g., angioedema) or severe, poorly tolerated, alopecia, warrant immediate withdrawal of leflunomide and initiation of the washout procedure. Following cessation of leflunomide, an 11-day washout period commences, during which cholestyramine (8 g tid) is administered. Alternatively, activated charcoal (50 g qds) is administered over the same period. It should be noted that the duration of washout may be modified depending on clinical and laboratory variables.

When leflunomide, administered at a daily maintenance dose of 20 mg, is withdrawn, it is estimated that levels of the active metabolite will remain above the limit of detection of 0.02 mg/l in approximately one-half of all patients for at least 22 weeks, although most will have undetectable levels 1 year after stopping treatment[10]. Cholestyramine can facilitate the rapid elimination of leflunomide. One day's treatment with cholestyramine (4 g tid) has been shown to shorten the half-life of leflunomide dramatically so that 90% of patients have undetectable levels after 3 weeks[10].

CONCLUSION

Most of the Expert Panel consider adverse events to be manageable when the practical recommendations listed above are followed. At the same time, patients should be supported and involved in the management of their side effects; this will require support from nurses and other healthcare professionals.

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