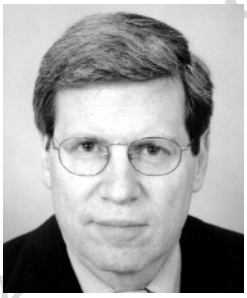
Editorial

What I Would Like to Know About Leflunomide



In a supplement accompanying this issue of *The Journal* a consensus summary and review of the safety and efficacy of leflunomide are presented. The symposium from which the statements are derived was held in May 2003, in Vienna, Austria. The reports are divided into 3 areas: efficacy of leflumomide as monotherapy[1], review of combination therapy with other disease modifying antirheumatic drugs (DMARD) and biological agents[2], and safety[3].

It is again apparent from these reviews that leflunomide is efficacious when used as monotherapy, or when compared with traditional agents such as sulfasalazine and methotrexate (MTX)[4-6]. Clinically meaningful additional efficacy is seen when used in combination with MTX[7,8]. Leflunomide appears to be efficacious in combination with infliximab as well[9-12], although some authors report a possible excess of adverse events with this combination (Emery P, manuscript in preparation).

It is also apparent, as is the case with every other drug used for the treatment of rheumatic disease, that there is potential for a variety of toxicities with the use of leflunomide including hepatic transaminase enzyme elevations, diarrhea, nausea, alopecia, rash, and hypertension. As with most of the other drugs employed to treat rheumatoid arthritis, an experienced and skilled clinician can usually manage these events using a variety of maneuvers including lowering the daily dose of drug or withholding treatment. Leflunomide is the only agent now in use that can be washed out of the body with the use of an additional drug. That is, cholestyramine, or oral charcoal, may be used to remove leflunomide from the gastrointestinal tract, where it undergoes longterm enterohepatic recirculation. This maneuver is not really akin to the reversal of MTX toxicity with the use of folate compounds, as cholestyramine does not specifically inhibit any of the biochemical activities of leflunomide, but rather allows the body to rid itself of the drug.

Because it was introduced at about the same time as new biologic agents, which were perhaps associated with greater excitement and attention at the time of launch, leflunomide may at times be viewed by rheumatologists as a second-tier choice. There is the impression among some that the drug may be more toxic, and less efficacious. The initial patient feedback to the prescribing physician may not be as immediate as that seen with the sometimes ebullient response with tumor necrosis factor (TNF) inhibitors. It is nevertheless clear that leflunomide should be welcomed in our therapeutic armamentarium, as would any agent that gives clinicians more valid treatment options, while arming us with strategies to manage possible side effects.

As with virtually all DMARD and biologic agents used to treat rheumatoid arthritis, unanswered questions regarding leflunomide abound. These areas, which could be addressed by clinical research, can be divided into those of efficacy or toxicity (Table 1). While the combination of leflunomide and MTX has been reported in both short and longterm investigations, studies of combinations of the drug with biologic agents are virtually restricted to its use with infliximab[9-12]. Kalden, *et al* describe these investigations[2]. Ideally, large multicenter studies would provide information on the use of leflunomide with biologic agents, including etanercept, adalimumab, and anakinra. Unfortunately, the conduct of large studies of this nature is unlikely in the present funding climate. Smaller investigator initiated efforts would therefore be a useful and welcome addition to our knowledge base regarding the possible use of leflunomide.

If leflunomide and MTX can be combined with increased efficacy, why not add leflunomide to triple therapy of MTX, sulfasalazine, and hydroxychloroquine? This combination would be unique in that all of the agents are given via the traditional oral route of administration, and 3 of the 4 are generic.

See Expert panel meeting: Practical management of RA patients treated with leflunomide, *Supplement 71*.

Table 1. Unanswered questions about leflunomide.

Efficacy
1. Use in combination with biologic agents including etanercept, anakinra (no data on either), and infliximab (some data)
2. Use with triple therapy (methotrexate, sulfasalazine, hydroxychloroquine)
3. Use with azathioprine
4. Utility and tolerability of a variety of alternative dosing regimens

Toxicity
1. Mechanism of hypertension, and best way to treat:
   a. Add hypertensive. Define which category of antihypertensive agent is most effective
   b. Discontinue NSAID or Coxib. Do COX-2 inhibitors present more of a risk when used together?
   c. Discontinue leflunomide and add biologic agent
   d. Which of approaches a–c above is most cost effective?
2. Mechanism of rash, and danger of continued treatment
3. Mechanism of diarrhea, and best way to treat
4. Mechanism of weight loss, and best approach if it occurs
5. Ideal interval for monitoring blood tests, once stabilized on medication

As leflunomide primarily inhibits pyrimidine metabolism, the rationale for combining the drug with MTX, which primarily inhibits purine metabolic pathways, is evident. The same may be said of possible combinations with azathioprine, another purine antimetabolite. It goes without saying that pilot studies of these and other combinations must monitor potential toxicities with added care.

The etiology of most of the toxicities associated with the use of leflunomide remain somewhat mysterious. Why does the drug cause hypertension in some patients, and what is the best way to treat it? Is it better to add an antihypertensive drug to a patient with a good response to leflunomide who has developed or exacerbated preexisting hypertension, or discontinue leflunomide and add a biologic agent? Which maneuver is most cost effective and really serves the patient better? Should nonsteroidal antiinflammatory drugs be discontinued in a patient with hypertension who is treated with leflunomide? Are coxibs more likely to contribute to this problem?

The rash associated with leflunomide has a distinctive appearance. As with the common rash that occurs with the use of gold salts, it is immediately recognizable and looks like almost nothing else associated with the drugs we use. It may involve larger, even confluent areas on the lower extremities, with deep, almost dusky erythema, without scaling. When full blown, it has a disturbing appearance. Some clinicians have permanently discontinued the drug in individuals with this reaction, but there is no evidence that patients may be at risk for a direct progression to a more fulminant reaction. Perhaps biopsies would help, but histological descriptions are also lacking in the literature.

Diarrhea is probably the most common side effect of leflunomide and is significantly more common with the use of a loading dose than without[13]. It would be potentially useful to know the mechanism of this effect. It is unclear why some patients seem almost immune to this phenomenon, while others remain sensitive.

Some patients receiving leflunomide may experience what can be substantial weight loss. This effect of the drug could actually be welcomed in a patient who is overweight, but is nevertheless bothersome when neither the patient nor physician understand why the individual receiving the drug is shrinking. Commentary in the literature regarding this phenomenon is rare to nonexistent. Anecdotally, many patients may inexplicably stabilize their weight after considerable loss. Interestingly, patients with diarrhea are not necessarily the ones who are affected by weight loss and the 2 problems usually do not occur in the same individual. Therefore it appears that it is not an issue associated with malabsorption. Patients may describe an easy satiety, or simply diminished appetite, but not true anorexia. It is a very poorly understood phenomenon, which could be partially centrally mediated. Because it may often stabilize after several months, weight loss may not be a reason to discontinue the drug in the majority of patients who experience this phenomenon, although sporadic verbal reports of resolution of the problem with lowering of the daily dose are sometimes heard.

Finally, the daily dosing of leflumomide has recently been redesigned in creative ways[14]. There are undoubtedly other innovative regimens that could be used to dose this agent, which has a 15 day half-life; these might prove to be better tolerated in certain individuals, while remaining efficacious[15].

It is probably true that an equal number of unanswered questions could be generated without too much effort for the majority of the other DMARD now in use, including MTX, which has been employed for considerably longer than other drugs. The issues regarding leflunomide should therefore be considered in the proper perspective. As we struggle with treatment decisions regarding what to do with patients who have not responded adequately to, or who are not candidates for, TNF antagonists, it is important to remember that other treatment alternatives exist that have not yet been adequately explored.

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