Is Leflunomide Effective in the Treatment of Psoriasis in a Patient Who Is Unable to Benefit From Standard First- and Second-Line Therapies and Needs an Affordable Treatment Option?

Andrew Graeme Affleck, BSc(Hons), MB, ChB; Hywel Williams, MSc, PhD, FRCPE

Clinical Question: Is leflunomide effective in the treatment of psoriasis in a patient who is unable to benefit from standard first- and second-line therapies and needs an affordable treatment option?

Background

A 21-year-old man was seen for a 4-year history of recalcitrant, severe psoriasis. The problem affected the patient's quality of life significantly, especially in having to miss lectures at college. Many treatments had been tried. He had been admitted to the hospital 4 times and was a regular attendee at the day treatment unit. Topical coal tar and anthralin caused irritation. Acitretin therapy (0.5 mg/kg) was ineffective. Therapy with oral or intramuscular methotrexate caused intolerable nausea. Systemic psoralen–UV-A and narrowband UV-B caused repeated erythema and were therefore stopped. Cyclosporin therapy caused acute renal impairment.

Leflunomide is a disease-modifying antirheumatic drug recently licensed for psoriatic arthritis, for which it has both short- and long-term benefit, and it has some possible benefit for psoriasis. It is a pyrimidine synthesis inhibitor and prevents lymphocyte proliferation, especially T cells. The aim of this Critically Appraised Topic is to determine from the available evidence whether oral leflunomide would be an effective and affordable treatment option for our patient's psoriasis.

Literature Search

We searched Medline and the Cochrane Controlled Trials Register for “psoriasis AND leflunomide” from inception up to October 2007.

Appraisal of the Evidence

We found 1 randomized controlled trial, 3 open trials, and 2 case reports.

Comment

In the only randomized controlled trial reporting on the use of leflunomide for psoriasis to date, 190 patients with mild to moderate psoriasis (mean Psoriasis Area and Severity Index [PASI] score, 9) and at least 3% skin involvement were studied. There was a high withdrawal rate owing to lack of efficacy—19 of 95 (20%) in the leflunomide treatment arm and 33 of 91 (36%) in the placebo arm.

The magnitude of treatment effect for leflunomide was small, with a mean decrease in PASI score of 2.1 from a baseline score of 8.7, compared with a mean decrease of 0.6 from a baseline score of 9.5 in the placebo group ($P = .003$). The mean relative reduction in PASI score was 24.1% for leflunomide compared with a reduction of 6.3% for the placebo group (reported as 22.4% for leflunomide and a deterioration of 2.2% for placebo, presumably for an analysis-adjusted analysis, which was not described in the text). Conventionally, at least a 50% improvement is desirable for a placebo-controlled study. Large standard deviations are associated with the percentage reductions in PASI score in both groups (51.6% and 70.4% for leflunomide and placebo, respectively), suggesting large variations in treatment response across individuals. There were small but significant differences in the proportion of patients achieving a 50% decrease in PASI score from baseline (PASI 50), with less than 1 in 3 in the active group responding to treatment compared with less than 1 in 5 in the placebo group. The difference in proportion of PASI 50 responders in the active vs placebo group is approximately 11%, which corresponds to a number needed to treat of 9. In other words, on average, one would have to treat an average of 9 patients with leflunomide to see 1 additional beneficial reduction for those achieving PASI 50 compared with the placebo group. At the PASI 75 level, 1 in 5 patients with mild to moderate psoriasis appeared to do well while receiving leflunomide therapy compared with approximately 8% for the placebo group, which translates to a number needed to treat of 10. No PASI 90 scores are given; this would have been useful to know because patients with severe psoriasis are often looking for substantial clearance when considering starting a potentially toxic systemic treatment.

Dermatology Life Quality Index scores were low at baseline (approximately 9) and improved only slightly during treatment, with a difference of 1.7 points between the active and placebo groups, which although statistically significant, is of questionable clinical significance.
Target lesion scores are only described briefly. In the leflunomide group, 48.4% of participants were noted to have “at least a slight response” compared with 25.6% in the placebo group, although definitions of such responses are vague. In clinical practice, patients and physicians are usually not satisfied with “a slight response.” The safety profile of leflunomide was assessed during the study and appeared similar to that for patients treated for rheumatoid arthritis. Compared with the placebo group, notably higher incidence rates were observed for diarrhea, increase in alanine aminotransferase level, and tiredness and lethargy in the leflunomide group. Serious adverse events (eg, abnormal liver function test results, bone marrow suppression requiring a reduction in the dose) occurred in 13 of 96 patients (13.5%) in the leflunomide group and 5 of 92 (5.4%) patients in the placebo group, corresponding to a number needed to harm of 12 for leflunomide compared with placebo. The most common serious adverse event was a rise in alanine aminotransferase level 2 or more times the upper limit of normal. However, there were no cases of severe liver toxic effects. White blood cell and platelet counts decreased to a greater extent in the leflunomide group than in the placebo group, a finding consistent with the anti-inflammatory action of leflunomide.

The same psoriasis data from the Treatment of Psoriatic Arthritis Study (TOPAS) were reported again in a separate article by the same authors who concluded that “leflunomide offers an efficacious, well tolerated, safe, and relatively inexpensive therapeutic option for the treatment of actively inflamed joints and psoriatic skin lesions in patients with psoriatic arthritis.”

One open study of 10 patients with psoriasis of varying severity and type (30% surface area plaque to generalized pustular psoriasis) showed no clinically remarkable improvement after 6 to 8 months of treatment with leflunomide, 20 mg/d. In another open study, 8 of 12 patients with psoriatic arthritis had moderate to marked improvement in their associated psoriasis after 2 to 3 months of treatment with leflunomide alone or in addition to another disease-modifying antirheumatic drug. However, physician’s global assessments did not reach a significant difference. The same psoriasis data from the Treatment of Psoriatic Arthritis Study (TOPAS) were reported again in a separate article by the same authors who concluded that “leflunomide offers an efficacious, well tolerated, safe, and relatively inexpensive therapeutic option for the treatment of actively inflamed joints and psoriatic skin lesions in patients with psoriatic arthritis.”

Open trial of 8 patients receiving leflunomide, 20 mg/d, over 12 weeks showed a decrease in PASI score and improvement in quality of life in 6 patients.

Both case reports stated a benefit with leflunomide therapy in severe psoriasis but are difficult to interpret because of the strong possibility of selection and reporting bias.

The potential adverse effect profile of leflunomide was examined in a study of 378 ambulatory patients with rheumatoid arthritis who received a conventional dosage regimen (100 mg/d on days 1-3 as loading doses, then 20 mg/d for 6 months). That study reported that treatment-related adverse events caused 15.9% of patients to discontinue the study prematurely. Serious adverse events possibly related to the therapy were reported in 2.4% of patients.

Limitations of the Critically Appraised Topic
The conclusions herein are based on the limited data presently available from 1 randomized controlled trial in patients who had mild to moderate psoriasis.

Clinical Bottom Line
Severe psoriasis poses a therapeutic challenge. It can be very distressing for affected individuals. Systemic treatment is often needed for severe psoriasis, but benefit is variable and adverse effects may be limiting. The use of biological therapy is increasing, but such agents are not widely available because of high costs. Dermatologists therefore turn to other nonbiological treatments such as leflunomide. Such treatment decisions should be based on high-quality evidence showing both clinical benefit and low risks of adverse effects. Presently, there is no good evidence to support the use of leflunomide in the treatment of severe plaque psoriasis. There is evidence from 1 randomized controlled trial showing a small benefit when compared with placebo in people with mild to moderate psoriasis, but it seems unlikely that such a small magnitude of benefit is likely to be useful for people with severe psoriasis.

What Happened to Our Patient?
It was decided not to treat our patient with leflunomide on the basis of existing evidence and to use fumaric acid esters instead. He has improved with fumaric acid, but not to a satisfactory level. He is now being considered for etanercept therapy.