Focus on leflunomide

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There is great interest in leflunomide (Arava), a new treatment for rheumatoid arthritis. But what is known about how to use this drug?

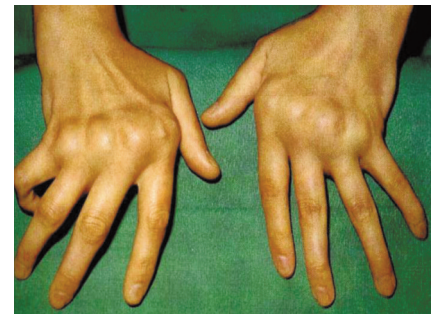

Figure. Late deforming disease.

What is leflunomide?

Leflunomide (Arava) is a new drug for treating active rheumatoid arthritis (RA), the first for more than a decade. It belongs to the DMARD (disease modifying antirheumatic drugs) class, along with methotrexate, salazopyrin, hydroxychloroquine, gold and penicillamine.

Leflunomide can reduce erosive damage and disability in RA. It is thought to work by inhibiting pyrimidine synthesis, thereby interfering with the maturation of activated lymphocytes, critical in the inflammatory process. Clinical trials have shown similar efficacy to salazopyrin and conservative doses of methotrexate in reducing pain and joint swelling in active RA, and in preventing the occurrence of new erosions on x-ray.

When should it be used?

Leflunomide is available on authority prescription for severe active RA in patients in whom methotrexate and other DMARDs are inappropriate. Leflunomide is used to treat active RA in patients who cannot take or have side effects from methotrexate, which remains the drug of choice for severe active RA. It can also be used as an adjunct in disease that is not controlled by maximal doses of methotrexate.

How is it prescribed?

Leflunomide has a long half-life (16 days). I commence therapy with a loading dose of 100 mg for three days, followed by 20 mg/day. For people less likely to tolerate three consecutive days of loading dose, I begin therapy with 100 mg on the first day of the first three weeks of therapy, with 20 mg on the remainder of the days. Leflunomide can be taken with or without food. The onset of action is four to six weeks. If there are adverse effects, reducing the dose to 10 mg/day can help. Treatment is best co-managed with a rheumatologist.

How should it be monitored?

I check the full blood count and differential, and liver function tests monthly for the first six months and periodically thereafter, depending on the clinical situation. Blood pressure should be monitored at each visit.

What about side effects?

Like all drugs strong enough to reduce joint damage, leflunomide is associated with severe adverse effects rarely, and minor effects more commonly. More than 150,000 patients have been treated with this drug in the USA.

A small number of cases of fatal pancytopenia have occurred. Recovery was associated with drug washout procedures and the use of filgrastim (Neupogen). These have usually been in combination with other agents, especially methotrexate, and occurred after a few months' therapy. Cases of Stevens–Johnson syndrome, toxic epidermal necrolysis and other rashes have occurred.

More common side effects include diarrhoea, abnormal liver function (excessive alcohol consumption is best avoided), hair fall and weight loss. These are usually mild and resolve when the dose is adjusted or therapy stopped.

New-onset hypertension and aggravation of pre-existing hypertension have been seen. Fortunately, washout with cholestyramine (8 g t.d.s. for 11 days) eliminates the drug if necessary. Serum levels are available if needed.

What are the contraindications?

There are no data on the safety of leflunomide in children, or in patients with severe renal or hepatic disease. Studies are under way to confirm safety in combination with other antirheumatic drugs and benefits in psoriatic arthritis, systemic lupus erythematosus, Wegener's, uveitis and juvenile chronic arthritis.

Leflunomide is teratogenic and must be avoided in pregnancy and lactation. When a patient (male or female) wants to conceive, I recommend washout with 11 days of cholestyramine, checking the serum level and missing one further menstrual cycle.

Drug interactions with rifampicin, tolbutamide and warfarin suggest care is needed with these drugs.

Conclusion

It has been a decade since a new treatment for RA has become available. Leflunomide is an important advance, provided it is used appropriately. MT

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