New drugs

Teriflunomide

Approved indication: multiple sclerosis
Aubagio (Sanofi-aventis)
14 mg film-coated tablets
Australian Medicines Handbook section 16.5

The inflammatory demyelination of multiple sclerosis is thought to be the result of an autoimmune disorder. In recent years drugs which alter the immune system have been used to try and prevent the progression of disability. Immunomodulating drugs such as interferon beta and glatiramer have to be injected, but an oral drug, fingolimod, was marketed in 2011. Teriflunomide is another oral drug for relapsing forms of multiple sclerosis. It is the active metabolite of leflunomide, an immunosuppressant used in rheumatoid arthritis.

Teriflunomide is taken once a day. It takes approximately three months for the plasma concentration to reach a steady state. Most of the drug is excreted unchanged in faeces, but some metabolites are excreted in the urine. The median half-life of the drug is 18–19 days.

The main trial of teriflunomide involved 1088 adults, aged under 55 years, who had had relapsing multiple sclerosis for a mean of 8.7 years. They were randomised to take teriflunomide 7 mg, 14 mg or a placebo for 108 weeks (796 patients completed the study). Both doses of teriflunomide significantly reduced the relapse rate. The increase in the number and size of lesions seen with MRI was significantly less with teriflunomide.[1]

Adverse events were common in all three treatment groups. These led to treatment being stopped by 9.8% of the patients taking teriflunomide 7 mg, 10.9% of those taking 14 mg and 8.1% of the placebo group. Nausea, diarrhoea and thinning of the hair were more frequent with teriflunomide than with placebo.

Leflunomide is known to be associated with liver failure, so patients taking teriflunomide need frequent monitoring of liver function. In the clinical trial 12–14% of patients had increased concentrations of alanine aminotransferase (ALT).[1] In the USA, teriflunomide is not recommended for patients who have ALT concentrations more than twice the upper limit of normal. As it may take up to two years for teriflunomide to be eliminated, patients who develop liver problems will need to be treated with charcoal and cholestyramine to speed up elimination. This elimination procedure is also recommended for women trying to conceive. Animal studies have found that teriflunomide is teratogenic, so reliable contraception is essential.

Teriflunomide can reduce the white blood cell count which could increase the risk of infection. Patients should be screened for tuberculosis before treatment and live vaccines are not recommended. There is an interaction with warfarin which reduces the INR.

In the trial, blood pressure increased in 5–5.4% of the patients given teriflunomide, compared with 3.1% of the placebo group.[1] Hyperkalaemia, acute renal failure and peripheral neuropathy also occur.

Some of the adverse effects are predictable because of teriflunomide's relationship with leflunomide. Like leflunomide, it could potentially cause interstitial lung disease and serious skin reactions.

Most patients will have adverse events, but not all will benefit. During the trial approximately 54–57% of the patients taking teriflunomide were relapse free, compared with 46% of the placebo group. The 31% relative reduction in the rate of relapse only equates to a difference of 0.17 in the annual relapse rate (placebo 0.54 vs teriflunomide 0.37). Disability progressed in 20–27% of the patients, with no significant difference between placebo and teriflunomide 7 mg (27.3% vs 21.7%). Treatment had no significant impact on the patients' fatigue.[1]

Although it is difficult to compare studies, the annualised relapse rate with fingolimod was 0.16–0.18 (placebo 0.4), a relative reduction of 54–60%.[2] While the drugs have a modest effect on relapses, this benefit has to be balanced against the need for regular monitoring and the risk of serious adverse reactions.

T T manufacturer provided additional useful information

REFERENCES *

1. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365:1293-303.
2. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).