Teriflunomide (Aubagio) is licensed for the treatment of adults with RRMS. Here, Steve Chaplin presents the clinical data relating to its efficacy and Dr Schmrier discusses its place in therapy.

Steve Chaplin

The Association of British Neurologists (ABN) 2009 management guideline recommends beta interferon or glatiramer acetate (Copaxone) as first-line therapy for adults with active relapsing remitting multiple sclerosis (RRMS) that is not rapidly evolving. Both treatments are administered by injection, which patients may dislike. However, the ABN guideline is now out of date and current practice is for clinicians and patients to choose a drug, taking into account lifestyle, the route and schedule of administration, the side-effect profile and storage.

NICE has recommended teriflunomide (Aubagio), which is administered orally, as an option for patients with RRMS (normally defined as two clinically significant relapses in the previous two years), if they do not have highly active or rapidly evolving RRMS and the manufacturer provides teriflunomide with the discount agreed in a confidential patient access scheme.

Teriflunomide (Aubagio) is an immunomodulator and anti-inflammatory agent licensed for the treatment of adults with relapsing remitting multiple sclerosis (RRMS) at a dose of 14mg/day. It has been recommended by NICE as an alternative first-line therapy to the interferons and glatiramer acetate, both of which are injected. Compared with placebo, teriflunomide significantly reduced the annualised relapse rate and the number of brain lesions. It significantly reduced the proportion of patients with sustained disability at three months. The time to treatment failure was similar to that with interferon. Common adverse effects include raised liver enzymes (frequent monitoring is recommended) and transient alopecia. Its price is set by a confidential discount scheme.

Teriflunomide

Teriflunomide, an immunomodulator and anti-inflammatory agent, is licensed for the treatment of adults with RRMS. Its mechanism of action is not fully understood but is mediated by a reduction in lymphocyte numbers. It inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, reducing the proliferation of dividing cells that depend on de novo synthesis of pyrimidine.

The recommended dose of teriflunomide is 14mg once daily orally. No dose adjustment is required for renal impairment or mild to moderate hepatic impairment; it is contraindicated in patients undergoing dialysis and those with severe hepatic impairment. Caution is recommended in patients over 65 years old due to insufficient clinical experience. Pregnancy should be excluded before starting treatment; other contraindications include severe immunodeficiency states, blood disorders, severe active infection and severe hypoproteinaemia. Liver enzymes should be assessed before starting treatment, every two weeks during the first six months and then every eight weeks.

After stopping treatment, the plasma level of teriflunomide falls to 0.02mg/L after an average of eight months but may take two years. Elimination can be accelerated (eg in case of pregnancy) by an 11-day course of cholestyramine or activated charcoal.
Clinical trials

Three Phase 3 trials provide the key evidence for teriflunomide: TEMSO, TOWER and TENERE. All recruited patients with RRMS with at least two relapses within the previous two years and an Expanded Disability Status Scale (EDSS) score of 5.5 or less. About 9 per cent of patients in TEMSO had secondary progressive or progressive relapsing MS. All trials included a treatment arm with the unlicensed dose of 7mg/day; these data are not reported here.

TEMSO (n=1088) and TOWER (n=1169) were placebo-controlled trials in patients aged 18–55 with a primary end-point of annualised relapse rate (ARR) and a key secondary endpoint of sustained accumulation of disability of at least 12 weeks (SAD) of ≥12 weeks. TEMSO and TOWER included a treatment arm with the unlicensed dose of 7mg/day; these data are not reported here.

In TEMSO, 27–29 per cent of patients did not complete the trial, most frequently due to adverse effects, perceived lack of efficacy or withdrawal of consent. In TOWER, the corresponding figures were 32 per cent with placebo and 34 per cent with teriflunomide. In TENERE, 20 per cent of patients discontinued teriflunomide compared with 30 per cent who discontinued interferon beta-1a.

In TEMSO and TOWER, teriflunomide significantly reduced the ARR compared with placebo and the risk of sustained disability of at least 12 weeks was reduced by about 30 per cent (see Table 1). In TOWER, the proportion of patients free of sustained disability progression was numerically but not statistically significantly lower with teriflunomide (84 vs 80 per cent with placebo at 108 weeks).

Patients treated with teriflunomide had smaller changes in total lesion volume and fewer gadolinium-enhancing lesions on MRI scan. Teriflunomide did not consistently improve fatigue. In TOWER, teriflunomide was associated with a significantly smaller decline than placebo in the quality of life summary score for mental health but not physical health.

In TENERE, 29 per cent of patients assigned to interferon beta-1a and 20 per cent of those taking teriflunomide discontinued treatment, primarily due to adverse effects. Treatment failure occurred after 48 weeks in 37 per cent of patients assigned to interferon beta-1a and 33 per cent with teriflunomide (p=0.60); there was also no difference between the rates of treatment failure after 96 weeks. There was no significant difference in ARR (0.22 vs 0.26 respectively).

Adverse events

The adverse events most frequently reported in clinical trials were: influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia. Blood pressure may be increased.

Diarrhoea, nausea and alopecia were considered mild to moderate and transient. Alopecia was described as

<table>
<thead>
<tr>
<th>TEMSO (108 weeks)</th>
<th>TOWER (median 556–588 days)</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Teriflunomide</strong></td>
</tr>
<tr>
<td>ARR</td>
<td>0.54</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>32%</td>
</tr>
<tr>
<td>SAD ≥12 weeks</td>
<td>27.3%</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>30%</td>
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ARR Annualised relapse rate
SAD Proportion of patients with sustained accumulation of disability of at least 12 weeks
*p<0.001, *p=0.03, *p<0.001

Table 1. Summary of main endpoints in TEMSO and TOWER

*Teriflunomide*
Of all licensed and NICE-approved drugs to treat people with relapsing MS, teriflunomide currently has the least clearly defined role among disease-modifying agents (DMAs). The uncertainty when considering teriflunomide has several sources and can be summarised in its lack of an unequivocally favourable benefit-risk profile. Having only a similar – i.e. not superior – effect on relapses compared to the well-established injectable drugs (beta interferons and glatiramer acetate) is not sufficient as an explanation; given teriflunomide is administered orally would still have a significant bonus in terms of convenience, avoiding flu-like symptoms and the – at the very least cosmetically unpleasant – injection-site reactions of beta interferons (and to a lesser degree glatiramer acetate). However, teriflunomide’s adverse effect profile includes severe liver toxicity, leading to high frequency lab monitoring over the first six months, and – again cosmetically unfavourable – effects such as hair thinning. In a disease that most often affects young women such adverse effects are simply not a great prospect, even if they are relatively uncommon (though alopecia was reported in 15 per cent within the first six months) and transient.

Apart from the above, a central issue for many young women, and men, with MS is teratogenicity and other pregnancy related risks of a DMA. Animal experiments have shown birth defects on teriflunomide, and women are therefore strongly advised not to become pregnant while on the drug. Given the available alternatives and the current competition of DMAs for people with relapsing MS, it is unlikely for teriflunomide to become a blockbuster similar to the way dimethyl fumarate (Tecfidera) has been adopted by neurologists and people with MS alike. When gastric side effects and flushing, common with dimethyl fumarate during the early phase of treatment, are persistent (i.e. in about 10 per cent) teriflunomide might be a valuable alternative.

**References**


**Declaration of interest**

Steve Chaplin has none to declare.