

Teriflunomide – A New Oral Agent for Multiple Sclerosis Treatment

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Teriflunomide is an oral immunomodulator, an active metabolite of leflunomide. Leflunomide is used in the long-term treatment of rheumatoid arthritis and is metabolized to teriflunomide *in vivo*.

The mechanism of action of teriflunomide is linked to reversibly inhibition of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in *de novo* synthesis of pyrimidine for DNA replication. The consequence of this mechanism of action is the blockade of activation and proliferation of stimulated lymphocytes (T and B cells).

The first phase II study, published in *Neurology* (2006) by O'Connor and colab., showed the efficacy and safety of teriflunomide in relapsing-remitting multiple sclerosis (RR-MS) patients. The study was a randomized, double-blind, placebo-controlled, parallel group trial and comprised of 207 screened patients, aged between 18 and 65 and EDSS score <6. The conclusions of this study were: "Teriflunomide treatment resulted in trends toward a lower annualized relapse rate and fewer relapsing patients (14 mg/day only) vs placebo. Significantly fewer patients receiving teriflunomide 14 mg/day vs placebo demonstrated disability increase. Treatment was well tolerated; numbers of adverse events and serious adverse events were similar in all treatment groups" (placebo,

teriflunomide 7 mg/day, or teriflunomide 14 mg/day for 36 weeks).

In TEMSO study, published in *New England Journal of Medicine* in 2011, the results were significantly in favor of teriflunomide for primary and secondary end points – annualized relapse rate and progression of disability. The study included 1088 patients with relapsing clinical course of MS (EDSS = 0-5.5), randomized in 1:1:1 ratio to placebo, 7 mg teriflunomide or 14 mg teriflunomide once daily for 108 weeks. The conclusion of this study was: "Teriflunomide significantly reduced relapse rates, disability progression (at the higher dose), and MRI evidence of disease activity, as compared with placebo" (with relative risk reductions of 31.2% and 31.5%, respectively).

Another study published in 2012 by Confavreux and colab. in *Multiple Sclerosis Journal* showed a long-term follow-up to 8.5 years for safety and efficacy of teriflunomide. After a placebo-controlled period, a total of 147 patients entered in an open-label extension (teriflunomide 7 mg/day or 14mg/day). The conclusions of the study for safety profile of teriflunomide were: 1) the most common treatment-emergent adverse events were mild infections, fatigue, sensory disturbances and diarrhea; 2) asymptomatic alanine aminotransferase increasing (< 3 upper limit of normal) were common; 3) mild decreasing in neutrophil counts occu-

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red; 4) incidence of malignancies was comparable to general population.

On September 12 2012, Food and Drug Administration (FDA) released an approval for Aubagio (teriflunomide) – once a day tablet – as a new oral treatment for relapsing forms of multiple sclerosis. The most common side effects are: diarrhea, abnormal liver tests, nausea, and hair loss.

On March 21st 2013, European Medicines Agency (EMA) - the Committee for Medicinal

Products for Human Use (CHMP) – published a positive opinion for marketing authorization for Aubagio (teriflunomide) 14 mg film-coated tablet for the treatment of multiple sclerosis. The approved indication is “adult patients with relapsing-remitting multiple sclerosis”.

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