MÆDICA - a Journal of Clinical Medicine

COMMENTS ON CLINICAL TRIALS

MAEDICA – a Journal of Clinical Medicine
2013; 8(4): 404-405

Teriflunomide – A New Oral Agent for Multiple Sclerosis Treatment

Florina ANTOCHI

Department of Neurology, Emergency University Hospital Bucharest, Romania

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 mithocondrial 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-remmittting 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 (< 3upper limit of normal) were common; 3) mild decreasing in neutrophil counts occu-

Address for correspondence:
Department of Neurology, Emergency University Hospital Bucharest, Splaiul Independentei 169, Bucharest.
E-mail: flrant@yahoo.com

Article received on the 30th of June 2013. Article accepted on the 5th of December 2013.

rred; 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-remmitting multiple sclerosis".

Conflict of interests: none declared.
Financial support: none declared.

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