TERIFLUNOMIDE

Andrew Chan
Dept. of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany

Teriflunomide is a selective and reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH). This enzyme is critically involved in the *de novo* pyrimidine synthesis required for the proliferation of activated lymphocytes. Although the exact mechanism of action of teriflunomide in multiple sclerosis (MS) is not fully elucidated, preclinical data suggest that by blocking the *de novo* pyrimidine synthesis pathway, teriflunomide may prevent proliferation of activated T- and B-cells in the periphery. This may lead to reduced numbers of autoreactive lymphocytes that migrate into the CNS.

Teriflunomide is approved as first-line therapy of relapsing MS. It is administered orally once daily (QD), at either 7 mg (FDA-approval) or 14 mg (FDA-, EMA-approval) dosages. In relapsing MS, teriflunomide has been studied in two large pivotal, randomized, double-blind, placebo-controlled phase 3 trials (TEMSO, n=1.088; TOWER, n=1.169) with consistent results. In both studies, teriflunomide 14 mg reduced both annualized relapse rate (ARR: TEMSO, 32% risk reduction vs. placebo [p<0.001]; TOWER, 36% risk reduction vs. placebo [p=0.0001]) and the risk of sustained disability accumulation (12-week SAD: TEMSO, 30% risk reduction vs. placebo [p=0.028]; TOWER, 32% risk reduction vs. placebo [p=0.044]). Effects of the lower dosage teriflunomide (7 mg) were less pronounced and not significant for disability progression. Consistent effects of teriflunomide were also demonstrated on MRI endpoints. In the TEMSO trial, total lesion volume (T2-hyperintense or T1-hypointense) as well as radiologic measures of active inflammatory disease (Gd-enhancing lesions, unique active lesions) were reduced with both dosages compared to placebo. No MRI examinations were performed in TOWER.

Efficacy in patients with a first clinically isolated syndrome (CIS) was investigated in the randomized, double-blind, placebo-controlled phase 3 trial TOPIC. Compared with placebo, both 14 mg and 7 mg doses of teriflunomide reduced risk of conversion to clinically definite MS (CDMS: 14 mg, 43% reduction vs. placebo [p=0.0087], 7 mg, 37% reduction [p=0.0271]). In addition, both teriflunomide doses significantly reduced the risk of a new clinical relapse or MRI lesion compared with placebo (14 mg, 35% reduction vs. placebo [p=0.0003]; 7 mg, 31% reduction vs. placebo [p=0.002]).

The safety and tolerability of teriflunomide in patients with relapsing MS has been evaluated in a pooled analysis of all randomized, double-blind, placebo-controlled studies (ie, TEMSO, TOWER and the phase 2 proof of concept study), comprising >2,500 patient-years of teriflunomide exposure. The most common AEs that were reported more frequently with teriflunomide vs. placebo were hair thinning, diarrhea, ALT elevation, nausea, and headache. AEs were mostly mild to moderate in severity and rarely led to treatment discontinuation. Many AEs resolved while patients remained on teriflunomide, without the need for therapy. There was a low incidence of serious infections, which was comparable across treatment arms (teriflunomide 14 mg, 2.5%; teriflunomide 7 mg, 2.4%; placebo, 2.5%); opportunistic infections were uncommon. No increased risk of malignancy was identified with teriflunomide treatment; the incidence of neoplasms was low (≤0.5%) in all treatment groups, and no hematologic or lymphoproliferative tumors were reported. In 9-year follow-up of the phase 3 TEMSO study, safety observations were consistent with the core 2-year study, and there were no new or unexpected AE signals during long-term exposure.

The safety and tolerability profile of teriflunomide in patients with CIS based on data of the TOPIC trial is similar to the established safety profile in relapsing MS. The most common AEs occurring at a greater frequency in the teriflunomide groups vs. placebo were ALT increase, headache, hair thinning, diarrhea, paresthesia, and upper respiratory tract infection. The incidence of serious AEs was comparable to placebo (teriflunomide 14 mg, 11.1%; teriflunomide 7 mg, 8.7%; placebo, 9.4%).

Based on animal data teriflunomide may increase the risk of teratogenic effects. Women of childbearing potential must use reliable contraception. Patients being treated with teriflunomide who are contemplating pregnancy, or those who have an unplanned pregnancy, should undergo an accelerated elimination procedure with activated charcoal or cholestyramine. This decreases teriflunomide concentrations by >97% after 11 days of administration.

In a retrospective evaluation of pregnancy outcome across the teriflunomide clinical development program, pregnancy outcomes (rate of spontaneous abortion, gestational age, and weight at birth) were within the typical range for the non-MS population, among women who received teriflunomide or partners of men who received teriflunomide.

In conclusion, consistent results from different class I evidence clinical trials, well-characterized safety and good tolerability support the use as first line therapy for patients with relapsing MS and as an effective oral treatment option for those patients who are unable to tolerate other DMTs.