Brain Volume Loss and Cognition in Teriflunomide-Treated Patients in TEMSO

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Objective:
To evaluate the relative contribution of relapses, MRI lesions, and percent brain volume change [PBVC] as surrogates mediating the effect of teriflunomide on cognition.

Background:
In the Phase 3 TEMSO core study (NCT00134563), teriflunomide demonstrated efficacy vs placebo on relapses, MRI lesions, and cognitive function, assessed using PASAT-3. Teriflunomide also reduced brain volume loss (BVL), which has been associated with reduced cognitive function. Prentice criteria are used to evaluate the relative contribution of surrogates as potential mediators of the effect of teriflunomide on cognition.

Design/Methods:
Patients from the core TEMSO study were included in this post-hoc analysis. Prentice criteria were used to assess the utility of three potential treatment mediators for cognition (PASAT-3 z-score): number of new/enlarging T2-weighted (T2w) lesions at Week 108, total number of relapses over 2 years, and BVL assessed as PBVC at Year 2. The proportion of teriflunomide's effect on cognition that could be explained by each surrogate was evaluated by assessing the attenuation of the association between treatment and cognition when each surrogate was added to the ANCOVA model.

Results:
Teriflunomide 14 mg reduced the decline in cognition (LS mean difference [SE] compared with placebo = 0.113 [0.046];  P=0.0146). Teriflunomide 14 mg reduced the number of active T2w lesions by 52% (P<0.0001), total number of relapses by 62% (P=0.0004), and PBVC by 0.461% (P=0.0008) compared with placebo. PBVC demonstrated the strongest utility as a surrogate, accounting for 44.3% of teriflunomide's effect on cognitive impairment, followed by active T2w lesions (16.8%) and relapses (7.1%). Combined, the three surrogates explained no more of the treatment effect on cognition than PBVC alone.

Conclusions:
Teriflunomide's effect on cognition (PASAT-3 performance) may be mediated, in part, by its effects on PBVC, suggesting that teriflunomide impacts neurodegenerative aspects of MS.