Results of the treatment differences on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale and the Alzheimer's Disease Cooperative Study-instrumental activities of daily living at 28 weeks in EXPEDITION EXT are shown in Figures 1 and 2. The treatment differences between early-start and delayed-start patients remained statistically significant at 28 weeks for both measures. The noninferiority criterion, defined as the lower limit of 90% CI for $\Delta_2 - 50\% \times \Delta_1 > 0$, was met for both tests.

In summary, 28-week data from EXPEDITION EXT suggest that patients with mild AD were able to sustain the cognitive effect noted in EXPEDITION and EXPEDITION 2. This effect was demonstrated in patients with mild AD and is probably consistent with a treatment effect that alters the underlying pathology of the disease.

Disease Activity in Year 1 Predicts Long-term Outcomes in Patients Taking Fingolimod

Written by Jaye Summers

The TRANSFORMS trial [Cohen JA et al. *N Engl J Med*. 2010] randomized 1292 patients with relapsing multiple sclerosis with a recent history of ≥1 relapse to oral fingolimod 1.25 or 0.5 mg or intramuscular interferon beta-1a (IFN-β-1a) 30 µg weekly. At 12 months, patients who received fingolimod had a significantly lower annualized relapse rate than the group who received IFN-β-1a ($P < .001$ for both doses of fingolimod vs IFN-β-1a).

In the TRANSFORMS extension trial [NCT00340834], 1030 patients who were randomly assigned to receive either dose of fingolimod continued on that same dose. Patients who were originally randomized to IFN-β-1a were now randomly reassigned to fingolimod 0.5 or 1.25 mg. The efficacy end points were annualized relapse rate, disability progression, and magnetic resonance imaging (MRI) outcomes [Khatri B et al. *Lancet Neurol*. 2011]. Patients who took fingolimod throughout 24 months (TRANSFORMS plus extension) showed a sustained improvement in clinical and MRI outcomes. Patients who switched from IFN-β-1a to fingolimod at 12 months experienced improvements in relapse rate and MRI findings compared with the previous 12 months.

Pavle Repovic, MD, PhD, Swedish Neuroscience Institute, Seattle, Washington, USA, presented 2 post hoc analyses in a poster using data from TRANSFORMS and the extension trial. The goal of these analyses was to determine whether year 1 MRI results and relapse rates could predict relapses or 6-month confirmed disability progression, measured by Expanded Disability Severity Scale over the following 36 months in the TRANSFORMS extension. An additional analysis explored outcomes at 24 months following the switch from IFN-β-1a to fingolimod at 12 months.

According to unadjusted logistic regression, significant predictors ($P < .01$) for either relapses or 6-month confirmed disability progression were MRI activity in year 1, relapses in year 1, and combined MRI activity and relapses in year 1.

The proportion of patients with MRI activity and relapses from baseline to month 12 was 12.9% for IFN-β-1a and 4.9% for fingolimod 0.5 mg. At months 12 to 24, the proportion remained low (3.2%) for continuous fingolimod. When patients were switched from IFN-β-1a to fingolimod, the proportion of patients with MRI activity and relapses decreased to 3.9%, which represented a 70% reduction ($P = .0014$).

In conclusion, MRI activity and relapses during year 1 were predictors of later clinical outcomes. Switching from IFN-β-1a to fingolimod after year 1 reduced the proportion of patients experiencing MRI activity and relapses, which may be associated with improved long-term outcomes.

Teriflunomide Associated With Reductions in Severe MS Relapses

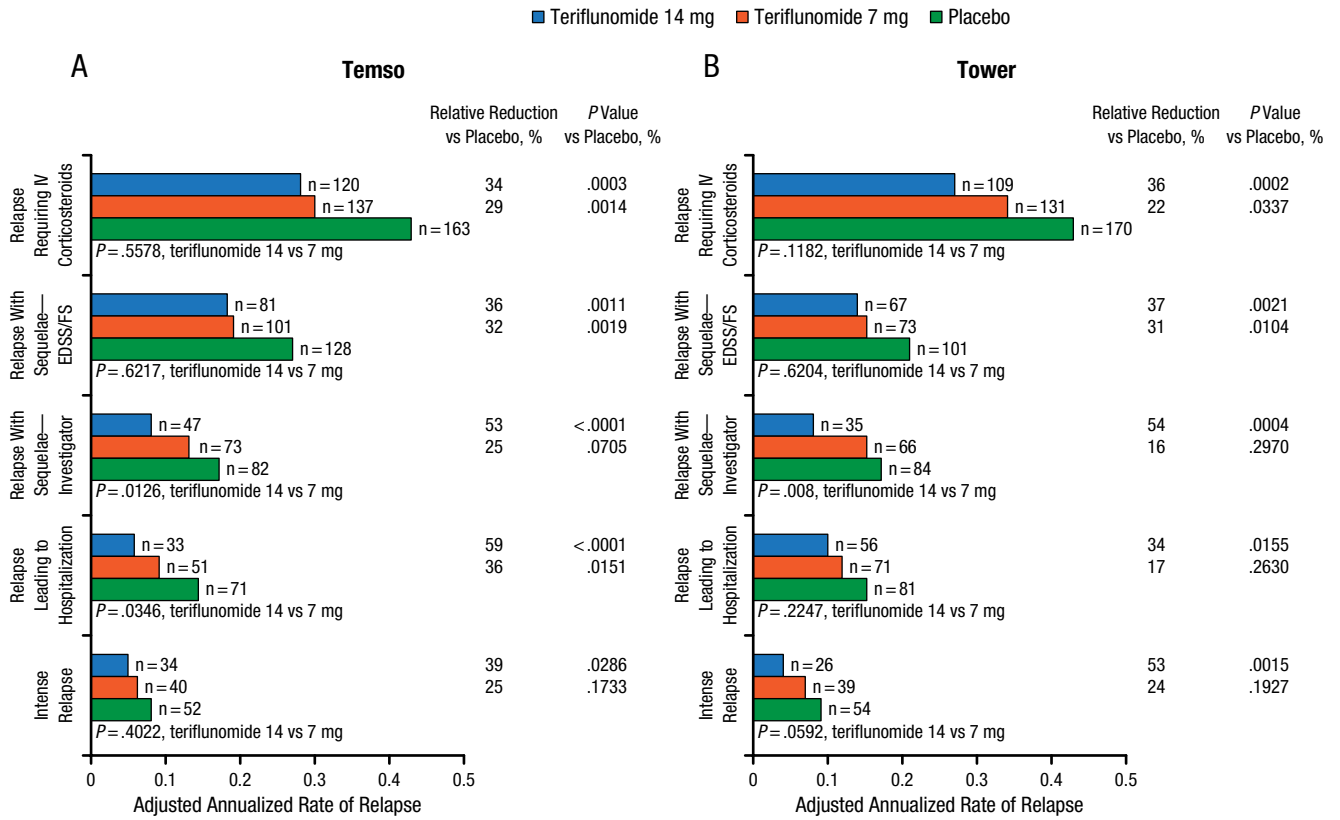
Written by Jaye Summers

Teriflunomide is a once-daily oral immunomodulating drug approved in the United States for the treatment of relapsing multiple sclerosis (RMS). Teriflunomide was tested in 2 phase 3 trials—TOWER [Confavreux C et al. *Lancet Neurol*. 2014] and TEMSO [O'Connor P et al. *N Engl J Med*. 2011]. Results from these 2 trials indicate that among people with RMS, teriflunomide 7 mg and 14 mg are both associated with significant reductions in the annualized relapse rate (ARR) compared with placebo.

Because severe MS relapses are associated with disability progression and substantial economic cost, an agent capable of reducing this type of relapse could reduce health care costs and improve patient outcomes. Richard Macdonell, MD, Austin Health, Victoria, Australia, highlighted data from post hoc analyses of TOWER and TEMSO regarding the effect of teriflunomide on severe relapses in a poster presentation.

As there is no universal definition of what constitutes a severe relapse, these analyses examined the effect of teriflunomide on 5 surrogate markers: (1) relapses with sequelae defined by increase in Expanded Disability Status Scale score/Functional System score 30 days

Figure 1. Effects of Teriflunomide on Severe Relapses in TEMSO and TOWER



EDSS, Expanded Disability Status Scale; FS, Functional System; IV, intravenous.

Sources: O'Connor PW et al. *J Neurol*. 2013 and Miller AE et al. *J Neurol*. 2014.

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postrelapse; (2) relapses with investigator-defined sequelae; (3) severe relapses by the Panitch definition, which is based on specified increases in Expanded Disability Status Scale and Functional System score used in the EVIDENCE trial in 2002; (4) relapses leading to hospitalization; and (5) relapses associated with increased use of health care resources, including those requiring intravenous corticosteroid treatment. All analyses were performed on the modified intent-to-treat population enrolled in each study (TEMSO, n = 1086; TOWER, n = 1165).

Compared with placebo, teriflunomide 14 mg significantly reduced annualized rates of all 5 indicators of severe relapse in both TEMSO and TOWER. Teriflunomide 7 mg significantly reduced the annualized relapse rates for several different indicators of relapse in both studies. The effects of teriflunomide 7 mg, 14 mg, and placebo on severe relapses in TEMSO and TOWER are shown in Figure 1.

Both teriflunomide doses showed similar and manageable safety profiles across the 2 studies. Adverse events emerging more often with teriflunomide than with placebo included elevations in alanine aminotransferase, as well as headache and diarrhea.

In summary, teriflunomide has shown consistent and significant efficacy on annualized relapse rates in both TEMSO and TOWER. Teriflunomide also reduced the rate of severe relapses, which may help reduce health care costs related to episodes of relapse, as well as improve patients' quality of life.