Mark Freedman, MD, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, presented data from the REFLEXION trial [NCT00813709], an open-label extension of the REFLEX trial. The objective of the trial was to determine the benefits of early vs delayed treatment over 60 months in patients who experienced an FDCE.

In the REFLEX trial, patients were blindly randomized to 3 treatment groups for 24 months: (1) subcutaneous IFN-β-1a 44 μg once weekly, (2) the same dose of IFN-β-1a 3 times a week, or (3) placebo. If patients converted to CDMS, they were switched to IFN-β-1a 44 μg 3 times per week. In REFLEXION, patients previously on placebo who did not convert to CDMS were switched to IFN-β-1a 44 μg 3 times per week (delayed treatment). Those patients randomized to IFN-β-1a who did not reach CDMS continued their initial regimen for up to 60 months after randomization.

Almost 78% of the 517 REFLEX patients (n = 402) entered REFLEXION and were stratified into 3 groups: delayed treatment (placebo), IFN-β-1a 44 μg 3 times weekly, or IFN-β-1a 44 μg once weekly. Conversion to CDMS was defined as a second attack or a sustained increase in ≥ 1.5 points on the Expanded Disability Status Scale. Of note is that all 517 patients were included in the 60-month intention-to-treat analysis.

Patients in the 2 INF-β-1a groups had a longer time to conversion than those in the delayed treatment group. Further, 32.2% and 36% of patients in the IFN-β-1a 44 μg 3 times weekly and IFN-β-1a 44 μg once weekly groups converted to CDMS over 60 months, compared with 40.4% of patients in the delayed treatment group.

The cumulative probability of CDMS conversion was 38.6% (95% CI, 30.8% to 47.6%) with IFN-β-1a 44 μg 3 times weekly, 40.7% (95% CI, 32.8% to 48.6%) with IFN-β-1a 44 μg once weekly, and 44.6% (95% CI, 36.6% to 52.6%) with delayed treatment. Results were similar when the definition of CDMS was changed to a sustained 3-month increase (≥ 2.5 points) on the Expanded Disability Status Scale, with a cumulative probability of CDMS conversion of 38.6% vs 39.6% vs 43.8%, respectively, in the 3 groups.

At month 60, the annualized relapse rate was higher for patients in the delayed-treatment group and fewer patients in the delayed-treatment group were free of relapse compared with those who received IFN-β-1a.

To conclude, early treatment with IFN-β-1a appears to prolong time to CDMS over 60 months and is associated with fewer relapses. According to Prof Freedman, these data reinforce the benefits of initiating early treatment with IFN-β-1a following an FDCE.

EXPEDITION EXT: Delayed-Start Analyses of Solanezumab in Patients With Mild AD

Written by Jaye Summers

Alzheimer's disease (AD) is a progressive neurological condition characterized pathologically by beta-amyloid plaques and neuronal loss. Because the monoclonal antibody solanezumab binds to amyloid, researchers have hypothesized that it would enhance the clearance of amyloid from the brain. However, published results from 2 phase 3 trials (EXPEDITION and EXPEDITION 2) reported that solanezumab produced no significant improvement in cognitive or functional ability in patients with mild-to-moderate AD [Doody RS et al. *N Engl J Med*. 2014]. A prespecified secondary analysis showed that there is a treatment signal on cognition in the patients with mild AD.

Patients who completed either of the EXPEDITION trials were eligible to enroll in the EXPEDITION EXT [NCT01127633], an open-label extension study, presented in a poster session by Hong Liu-Seifert, PhD, Eli Lilly and Company, Indianapolis, Indiana, USA. The goal of the extension trial was to continue monitoring the efficacy and safety of solanezumab out to 104 weeks, using a delayed-start design methodology. Dr Liu-Seifert noted that researchers can use this design to distinguish a treatment's effect that alters the underlying disease pathology from an effect that only attenuates the symptoms of the disease. However, there are also methodologic challenges associated with previous applications of this design that limit its usage in clinical trials.

Dr Liu-Seifert then discussed a new modeling approach to the delayed-start design that was implemented for EXPEDITION EXT. This approach incorporated all of the randomized patients with mild AD only, from the time of initial randomization to the end of the delayed-start period, and merged them into a single model. Noninferiority was then tested using a proportional noninferiority margin that compared the treatment difference at the end of the delayed-start period with the treatment difference at the end of the placebo-controlled period.

In EXPEDITION EXT (delayed-start period), all patients received solanezumab. Patients randomized to the placebo group in the 2 EXPEDITION trials were considered the delayed-start group; those who had received solanezumab in the 2 trials were considered the early-start group.

Throughout EXPEDITION EXT, the study staff and patients remained blinded as to whether patients had received solanezumab or placebo in the previous trials.

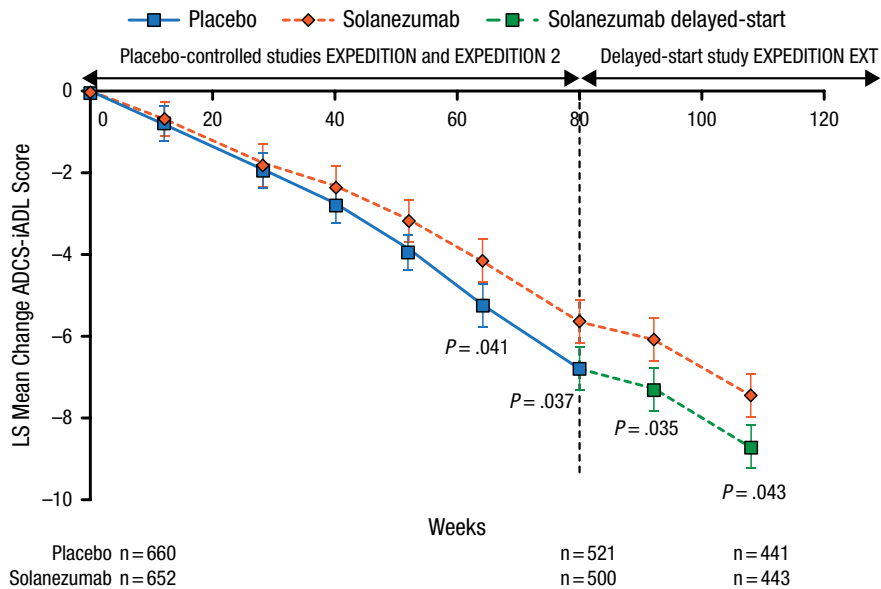Figure 1. Results of ADAS-Cog14 in Patients With Mild AD at 28 Weeks[a]
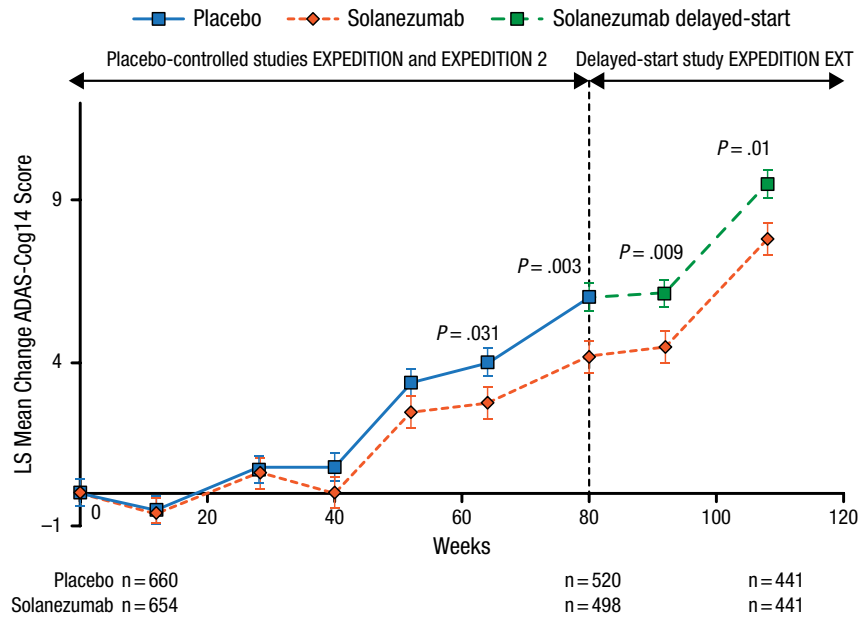
AD, Alzheimer disease; ADAS-Cog14, 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; LS, least squares.

[a]Lower limit of 90% CI for $\Delta_2 - 50\% \times \Delta_1 = 0.15$.

Reproduced with permission from H Liu-Seifert, PhD.

Figure 2. Results of ADCS-iADL in Patients With Mild AD at 28 Weeks[a]

AD, Alzheimer disease; ADCS-iADL, Alzheimer's Disease Cooperative Study-instrumental activities of daily living; LS, least squares.

[a]Lower limit of 90% CI for $\Delta_2 - 50\% \times \Delta_1 = 0.08$.

Reproduced with permission from H Liu-Seifert, PhD.

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