Baseline Features of Patients With RMS in Ocrelizumab Trials OPERA I and OPERA II

Written by Jaye Summers

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively depletes CD20+ B cells, which have been implicated in the pathogenesis of multiple sclerosis (MS) [Lehmann-Horn K et al. *Ther Adv Neurol Disor*. 2013]. Data from a phase 2 trial have suggested that patients with relapsing-remitting MS treated with ocrelizumab 600 or 2000 mg had significantly fewer gadolinium-enhancing lesions compared with placebo at 24 weeks ($P < .0001$, both comparisons) [Kappos L et al. *Lancet*. 2011].

Steven Hauser, MD, University of California San Francisco, San Francisco, California, USA, presented the demographic and baseline disease characteristics of patients from 2 international phase 3 studies of ocrelizumab—OPERA I [NCT01247324] and OPERA II [NCT01412333]—in a poster presentation.

Both multicenter randomized trials were double-blind, double-dummy, parallel-group studies investigating the efficacy and safety of ocrelizumab 600 mg administered by intravenous infusion every 24 weeks, compared with administration of subcutaneous interferon beta-1a (IFN-β-1a; escalated dose to 44 µg, 3 times per week) in patients with relapsing MS over 96 weeks. Entry criteria included a diagnosis of RMS using the 2010 revised McDonald criteria [Polman CH et al. *Ann Neurol*. 2011], an Expanded Disability Status Scale (EDSS) score of 0 to 5.5, and age of 18 to 55 years. Patients were required to have experienced ≥2 documented relapses within the last 2 years or 1 relapse in the last 1 year prior to screening (but not within 30 days prior to screening). Exclusion criteria included primary progressive MS, pregnancy, or a history of current primary or secondary immunodeficiency. Patients with a disease duration of ≥10 years and an EDSS score ≤2.0 at screening were also excluded. The primary end point was the annualized protocol-defined relapse rate at 2 years (96 weeks).

A total of 1656 patients were randomized to receive either ocrelizumab or IFN- β-1a in OPERA I (n=821) and OPERA II (n=835). The mean baseline age in both trials was 37 years; 66% of the patients were women; and approximately 90% were white. Patients had symptoms of MS for a mean duration of 6.5 years in OPERA I and 6.7 years in OPERA II; mean baseline EDSS scores were 2.77 (OPERA I) and 2.75 (OPERA II). Patients in both trials had experienced approximately 1.3 relapses in the year prior to randomization and 1.8 relapses in the 2 years prior to randomization. Magnetic resonance imaging assessments are shown in Table 1.

Table 1. Baseline MRI Characteristics in OPERA I and OPERA II

	OPERA I (n = 821)	OPERA II (n = 835)
No. of Gd+ T1 lesions, mean ± SD	1.78 ± 4.69	1.87 ± 4.88
Categorical No. of Gd+ T1 lesions, n (%)		
0	485 (59.7)	494 (59.8)
≥1	327 (40.3)	332 (40.2)
Volume of T2 lesions, median (minimum to maximum), cm^3	5.88 (0 to 83.2)	5.65 (0 to 96.0)
Normalized brain volume, cm^3		
Mean ± SD	1500.06 ± 85.86	1502.72 ± 91.55
Median (minimum to maximum)	1501.25 (1251.8 to 1736.5)	1507.92 (1202.7 to 1761.3)

Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging.
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To conclude, the results of these 2 studies are likely to provide relevant information regarding the efficacy and safety of ocrelizumab compared with IFN-β-1a in patients with relapsing multiple sclerosis.

REFLEXION Trial: Delayed Treatment of First MS Event Increases Time to CDMS

Written by Jaye Summers

Up to 85% of patients who eventually receive a diagnosis of multiple sclerosis (MS) will initially present with a first clinical demyelinating event (FCDE) [Freedman M. *Ther Adv Neurol Disord*. 2014]. If left untreated, up to 45% of patients will convert to clinically definite MS (CDMS) within 2 years [Kappos L et al. *Neurology*. 2006]. Results from the REFLEX trial [Comi G et al. *Lancet Neurol*. 2012] suggest that 2 different dosing frequencies of interferon beta-1a (IFN-β-1a) were able to significantly delay clinical relapses following an FCDE (IFN-β-1a once a week [$P=.0023$]; IFN-β-1a 3 times a week [$P=.0004$]) compared with placebo.

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.