Treatment With Alemtuzumab Leads to Durable Benefits in Patients With Multiple Sclerosis

Written by Maria Vinall

Treatment with alemtuzumab is associated with durable improvements in magnetic resonance imaging (MRI) disease activity in patients with active relapsing-remitting multiple sclerosis, according to Douglas L. Arnold, MD, NeuroRX Research and Montreal Neurological Institute, McGill University, Montreal, Québec, Canada, who presented the 3-year results from An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab (ClinicalTrials.gov identifier: NCT00930553), an ongoing extension study of the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) series of studies. The results showed that participants were free of gadolinium-enhancing, new or enlarging T_2, and new T lesions after 3 years of follow-up. Alemtuzumab also slowed the yearly rate of brain volume loss.

In 2 previous Phase 3 head-to-head trials with patients with active relapsing-remitting multiple sclerosis (CARE-MS I in treatment-naive patients and CARE-MS II in those who relapsed on prior therapy), 2 annual courses of alemtuzumab 12 mg proved superior to subcutaneous interferon-b1a (44 mg 3 times/wk) with respect to clinical efficacy and the reduction in MRI activity and brain volume loss over 2 years.

Patients treated with alemtuzumab in either of the CARE-MS studies continued uninterrupted follow-up in an extension study and were eligible for alemtuzumab retreatment (12 mg administered on 3 consecutive days ³12 months after their previous courses of therapy) on evidence of disease activity. MRI was performed at study entry and annually for each patient, and studies were centrally analyzed by experts masked to treatment group assignment. All patients underwent T_1-weighted pre- and post-Gd contrast, T_2-weighted and proton density precontrast, fluid-attenuated inversion recovery precontrast, and 3-dimensional gradient-echo postcontrast MRI sequences before the administration of methylprednisolone. Brain atrophy was measured by brain parenchymal fraction.

A total of 742 subjects entered the extension study (349 subjects from CARE-MS I and 393 from CARE-MS II). Durable effects on relapse rate and disability were reported at end of Year 1 of the extension study despite patients having been treated for only 2 years [Fox EJ et al. *Neurology* 2013].

The current report presents the results after 3 years of follow-up. In Year 3, 18% and 20% of the subjects in CARE-MS I and II, respectively, received retreatment with alemtuzumab; <3% of patients were treated with other disease-modifying therapies. The majority of alemtuzumab-treated patients were free of MRI activity (absence of both Gd-enhancing and new or enlarging T_2 hyperintense lesions) at both Year 2 and Year 3.

During the same period, alemtuzumab also slowed brain volume loss as measured by brain parenchymal fraction. The median yearly rate of brain atrophy decreased over time (Year 0 to 1, –0.59% and –0.48% for CARE-MS I and II, respectively; Year 1 to 2, –0.25% and –0.22%; Year 2 to 3, –0.19% and –0.10%).

These results support the efficacy of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis in both treatment-naive and previously treated patients and provide evidence of durability of benefit.

Negative Florbetaben PET Scan Excludes the Presence of Amyloid Pathology

Written by Phil Vinall

There is a strong correlation between florbetaben (an F-labeled β-amyloid-targeted tracer) uptake and amyloid pathology, according to Marwan Sabbagh, MD, Banner Sun Health Research Institute, Sun City, Arizona, USA, who presented results of the Phase III Study of Florbetaben (BAY94-9172) PET Imaging for Detection/Exclusion of Cerebral β-Amyloid Compared to Histopathology trial (ClinicalTrials.gov identifier NCT01020838). These results support the use of florbetaben as a valuable diagnostic tool for the exclusion of Alzheimer's disease (AD) or differential diagnosis of dementia as the cause of cognitive decline.

Florbetaben has recently been approved as an adjunct to other diagnostic evaluations for positron emission tomographic (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adults with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

The aim of researchers in the present analysis was to assess the diagnostic efficacy of florbetaben and its negative predictive value in a large histopathology cohort of subjects who underwent antemortem florbetaben PET imaging. The analysis was based on data from the aforementioned large Phase 3 multicenter nonrandomized trial in 205 end-of-life subjects who underwent PET imaging 90 to 110 minutes after receiving an intravenous

injection of florbetaben 300 MBq (±20%). Brain samples were obtained at autopsy and assessed for neuritic β-amyloid plaques using the Consortium for Establishing a Registry for Alzheimer's Disease criteria. PET images were assessed by 3 independent readers masked to the clinical diagnosis and all other clinical findings and quantitatively by using preestablished brain volumes of interest to obtain standardized uptake value ratios (SUVRs), taking the cerebellar cortex as the reference region.

As of the date of this analysis, 74 subjects had died. The antemortem clinical diagnoses for these subjects included AD (n=57), dementia with Lewy bodies (n=3), not demented (n=8), and other dementia (n=6). Postmortem, it was noted that the clinical diagnosis of AD was incorrect in 23% of cases (13 of 57). Histopathology confirmed the presence of β-amyloid in 47 of the 74 subjects; no β-amyloid plaques were found in 27 subjects (Table 1).

Table 1. Histopathology Results

Clinical Diagnosis	Histopathology	
	β-Amyloid Present	No β-Amyloid
Alzheimer's disease (n=57)	44	13
Dementia with Lewy bodies (n=3)	1	2
Other dementia (n=6)	1	5
Nondemented volunteers (n=8)	1	7
Total (n=74)	47	27

Of the 27 patients in whom no β-amyloid plaques were found, 4 had no neurodegenerative pathologies and were correctly read as negative on PET imaging; 23 had non-AD neurodegenerative pathologies. Twenty of these 23 non-AD neurodegenerative scans were correctly read as negative on PET imaging.

Scans from 46 of the 47 subjects with β-amyloid were correctly read as positive, yielding sensitivity of 98%. Scans from 24 of the 27 subjects without β-amyloid were correctly read, yielding specificity of 89%. Twenty-four of 25 scans read as negative were correctly assessed, yielding a negative predictive value of 96%.

For the quantitative analysis, SUVR analysis showed good discrimination of the PET signal between the presence and absence of β-amyloid. The mean composite SUVR values were 1.71±0.27 for the presence of β-amyloid and 1.24±0.18 for the absence of β-amyloid. A receiver operating characteristic curve analysis indicated that an SUVR of 1.478 was the optimal cutoff for the calculation of sensitivity (89%) and specificity (92%).

Dr. Sabbagh concluded these data support the value of florbetaben as a diagnostic marker for AD and that negative results on a florbetaben scan should encourage clinicians to search for other causes of cognitive decline.

Relapsing-Remitting Multiple Sclerosis Effectively Treated With Peginterferon Beta-1

Written by Phil Vinall

Significantly more subjects with relapsing-remitting multiple sclerosis (RRMS) achieved freedom from measured disease activity (FMDA) when treated with peginterferon beta-1a every 2 weeks (Q2W) compared with those who were treated with peginterferon beta-1a every 4 weeks (Q4W) or placebo, said Douglas Arnold, MD, McGill University, Montreal, Quebec, Canada, who presented results from a post hoc analysis of 48-week data from the Efficacy and Safety Study of BIIB017 (PEGylated Interferon Beta-1a) in Participants With Relapsing Multiple Sclerosis trial [ADVANCE; NCT00906399].

ADVANCE was a Phase 3 multicenter double-blind study with subjects with RRMS and an Expanded Disability Status Scale (EDSS) £5, who were randomly assigned to treatment with peginterferon beta-1a 125 µg Q2W or Q4W for 96 weeks or to placebo for 48 weeks, then 1 of the 2 peginterferon beta-1a dosing regimens for 48 weeks. Magnetic resonance imaging (MRI) was conducted at baseline and Weeks 24 and 48. Participants were assessed for

1. MRI freedom from measured disease activity (FMDA; defined as no gadolinium-enhancing [Gd+] lesions and no new or newly enlarging T2 lesions at Week 48 compared with baseline),
2. clinical freedom from measured disease activity (defined as no relapses or 12-week confirmed disability progression over 48 weeks), and
3. a composite of both conditions (overall FMDA). A sensitivity analysis was performed using a definition with minimal MRI allowance (no Gd+ lesions at Weeks 24 and 48 and ≤1 new or newly enlarging T2 lesions at Week 48 compared with baseline).

The primary outcome was annualized relapse rate (ARR) at Week 48.

Subjects (n=1516) had a mean age of approximately 36 years, approximately 71% were women, and most (~82%) were white. The mean time since first MS symptom was 6.5 years. A mean of 1.6 relapses had occurred within the previous 12 months. Mean EDSS score was 2.46, and mean T2 lesions and GD+ lesions were 50 and 1.5, respectively.

The primary results of ADVANCE showed that after 48 weeks, both peginterferon beta-1a dose regimens were associated with a significantly reduced relapse rate compared with placebo. These results have already been published [Calabresi PA et al. *Lancet Neurol*