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*

2014]. Additionally, interim 2-year results support the maintenance of benefit and the significantly greater efficacy of the Q2W dose regime (vs the Q4W regime) [Deykin A et al. *Neurology* 2014].

The objective of the post hoc analysis presented by Dr. Arnold was to assess FMDA in patients treated with peginterferon beta-1a during Year 1 of ADVANCE. Results of the analysis showed that significantly more subjects receiving Q2W dosing achieved overall FMDA from baseline to Week 48 (33.9%) compared with those receiving placebo (15.1%; p<0.0001) or Q4W dosing (21.5%; p<0.0001). Between Week 24 and Week 48, 60.2% of subjects receiving Q2W dosing achieved FMDS compared with 28.9% receiving placebo (p<0.0001) or Q4W dosing (36.6%; p<0.0001) Subjects on the Q4W dosing were more like to achieve overall FMDA than were those receiving placebo.

Among subjects achieving MRI FMDA only, significantly (p<0.0001) higher proportions were from the group receiving Q2W dosing compared with those receiving placebo or Q4W dosing at both time points. Subjects in the Q4W dosing group were significantly (p<0.05) more likely to achieve MRI FMDA compared with those receiving placebo.

At both time points (baseline to Week 48 or Week 24 to Week 48), subjects in the Q2W dosing group were significantly (p<0.001) more likely to achieve clinical FMDA than were those receiving placebo or Q4W dosing. However, the proportion of patients achieving clinical FMDA was not significantly different between the 2 peginterferon beta-1a dosing regimens.

The robustness of these findings was confirmed with sensitivity analyses allowing for minimal MRI activity. Peginterferon beta-1a Q2W values were significantly (p<0.0001) greater than placebo and Q4W values. Q4W values were significantly (p<0.02) greater than placebo values.

These data, along with previous findings, support the use of peginterferon beta-1a as an effective treatment for patients with RRMS, with the benefit of less frequent subcutaneous administration.

Asymptomatic Carotid Stenosis Is Associated With Cognitive Dysfunction

Written by Maria Vinall

Moira C. Dux, PhD, University of Maryland School of Medicine and Baltimore VA Medical Center, Baltimore, Maryland, USA, presented results from a cross-sectional study that demonstrated significantly worse cognition in patients with asymptomatic carotid stenosis compared with patients with vascular risk factors but no stenosis. The difference was driven primarily by poor motor and processing speed and learning and memory in patients with asymptomatic carotid disease, with deficits ranging from mild to moderate.

Several published studies have identified evidence of cognitive impairment in patients with asymptomatic carotid disease. However, methodologic issues, such as the use of healthy controls, the use of differing cognitive testing, and inadequate standardization of scores, have raised questions regarding the validity of these findings.

The Asymptomatic Carotid Stenosis: Cognitive Function and Plaque Correlates study (ClinicalTrials.gov identifier NCT01353196) was designed to provide a comprehensive assessment of neuropsychological function in patients with asymptomatic carotid stenosis compared with patients with similar vascular risk factors but no evidence of carotid stenosis. A total of 67 consecutive patients with ≥50% carotid stenosis and no prior transient ischemic attack or stroke as well as 60 control patients with risk factors for vascular disease but no evidence of carotid stenosis underwent comprehensive cognitive testing (Table 1). The presence and degree of stenosis were confirmed by duplex ultrasonography, while asymptomatic status was determined by neurologic and National Institutes of Health Stroke Scale testing.

Table 1. Neuropsychological Battery

Focus of Test	Test
Learning and memory	Hopkins Verbal Learning Test–Revised
	Brief Visuospatial Memory Test–Revised
Motor/processing speed	Trail Making Test Part A
	Grooved Pegboard Test
Executive function	Trail Making Test Part B
	Rey Complex Figure Test–Copy
Attention/working memory	Wechsler Adult Intelligence Scale–III: Digit Span Forward
	Wechsler Adult Intelligence Scale–III: Digit Span Backward
Language	Verbal Fluency (phonemic and semantic)
	Boston Naming Test (2nd edition)

Test scores were adjusted for age, sex, education, and race using standardized normative data. An overall index of cognitive function and 5 domain-specific composite scores were calculated. Independent-sample t tests were used to compare groups, and Cohen's d was calculated to determine effect sizes.

The proportion of vascular risk factors was similar in both groups (Table 2).