



Featured Article

Use of white matter reference regions for detection of change in florbetapir positron emission tomography from completed phase 3 solanezumab trials

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Abstract

Introduction: We compared subject-specific white matter (SSWM) and whole cerebellum (CBL) reference regions for power to detect longitudinal change in amyloid positron emission tomography signal.

Methods: Positive florbetapir positron emission tomography scans were analyzed from participants (66 placebo treated and 63 solanezumab treated) with mild dementia caused by Alzheimer's disease from the EXPEDITION and EXPEDITION2 studies. For comparison to CBL, a second normalization was performed on longitudinal data using an SSWM correction factor (SSWM normalization ratio [SSWMnr]). Analysis of covariance assessed baseline to 18-month change between treatment with solanezumab and placebo. Sample and effect size estimations provided magnitude of observed treatment changes.

Results: Longitudinal percent change between placebo and solanezumab using CBL was not significant ($P = .536$) but was significant for SSWMnr ($P = .042$). Compared with CBL, SSWMnr technique increased the power to detect a treatment difference, more than tripling the effect size and reducing the sample size requirements by 85% to 90%.

Discussion: Adjusting longitudinal standardized uptake value ratios with an SSWM reference region in these anti-amyloid treatment trials increased mean change detection and decreased variance resulting in the substantial improvement in statistical power to detect change.

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Keywords:

Alzheimer's disease; Serial PET imaging; Reference region; Solanezumab; Growth mixture model; Trajectory; Disease course; Florbetapir

1. Introduction

Accumulation of β -amyloid ($A\beta$; especially $A\beta_{1-42}$) within the brain is thought to play a critical role in the pathophysiology of Alzheimer's disease (AD), a mechanism referred to as the "amyloid cascade hypothesis" [1–3], albeit

not without controversy [4,5]. Although a number of randomized clinical trials have focused on drug therapies targeting reduced production or increased clearance of $A\beta$ within the brain as a potential treatment for AD [6,7], the outcomes of these studies have not consistently demonstrated a benefit in slowing cognitive or functional decline nor in reducing brain amyloid burden. The first step in maximizing the potential for treatment success with anti-amyloid therapies in clinical trials is enrolling patients

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with positive brain amyloid burden who are likely to benefit from such treatments. Next, use of the most sensitive clinical and biomarker measures to assess treatment outcomes, including optimized tools for assessing longitudinal changes in cortical amyloid plaque burden, is vital.

Amyloid imaging by positron emission tomography (PET) plays a central role as a primary diagnostic tool for measuring fibrillary amyloid plaque burden in living patients and for assessing cross-sectional and longitudinal clinical trial end points. Traditionally, the whole cerebellum (CBL) has been used as a reference region to standardize PET tracer uptake values in longitudinal assessments [8–10] because of its relative lack of neuritic amyloid plaques and well-established positive threshold cutoffs validated in young control subjects and autopsy studies [9,11]. The use of whole brain cortical-to-CBL standardized uptake value ratio (SUVR) cutoffs to determine if a scan is considered positive or negative is often used as inclusion criteria in clinical research. However, for longitudinal studies, there are recent reports suggesting that use of subcortical white matter (WM) as a reference region for SUVR calculations can reduce variability in the data and improve power to detect change in signal over time [12–14]. In addition, it has been suggested that a WM normalization ratio (WMnr) method can be applied to existing CBL SUVR data to preserve use of baseline data while adjusting for WM change in signal over time [12]. This method has been shown to be identical to the use of only WM SUVRs at both baseline and end point when assessing percent change in signal but with SUVR units that are consistent with CBL normalization, thus preserving the ability to use a whole CBL-based positivity threshold for identification of amyloid pathology [12].

Recent clinical trials have used florbetapir PET as a biomarker of cortical amyloid and to assess the impact of treatment effects on underlying pathology. Solanezumab is an immunoglobulin G1 anti-amyloid monoclonal antibody that binds to the mid-domain of the A β peptide and is thought to increase clearance of soluble A β . Preclinical studies using transgenic APPV717F mice demonstrated that administration of the murine anti-A β monoclonal antibody from which solanezumab was derived (m266.2) reduced the deposition of brain amyloid plaque [15] and showed strong correlations between plasma A β accumulation and plaque deposition. EXPEDITION and EXPEDITION2 were identically designed, placebo-controlled phase 3 studies assessing effects of solanezumab on cognitive and functional decline for more than 80 weeks in patients with mild-to-moderate AD. The primary findings for both studies have been published [16,17], reporting no significant benefits in cognition or functioning. However, prespecified secondary analyses of efficacy end points in the pooled mild AD dementia population demonstrated less cognitive (34%) and functional (18%) decline with solanezumab ($n = 659$) versus placebo ($n = 663$) [17–19]. A subset of these patients with mild AD ($N = 251$) had participated in an optional amyloid PET imaging

addendum. Using traditional florbetapir PET analysis with a cortical-to-whole CBL SUVR [20] in those patients with a positive amyloid burden (SUVR > 1.10 [20,21]), a numeric reduction in florbetapir SUVR was observed in the solanezumab group versus the placebo group, although this difference did not reach statistical significance ($P = .17$) [18]. In the present analysis, we conducted a post hoc exploratory comparison of CBL versus subject-specific subcortical WM (SSWM) reference regions using the normalization ratio approach outlined in Landau et al. [12] for determining longitudinal treatment change in florbetapir SUVR in patients with mild AD dementia who were amyloid positive at baseline in the EXPEDITION and EXPEDITION2 phase 3 amyloid imaging substudy.

2. Methods

2.1. Study design

The designs of the solanezumab phase 3 trials, EXPEDITION and EXPEDITION2, have been described previously (ClinicalTrials.gov numbers: NCT00905372 and NCT00904683) [16]. Briefly, both were multinational, randomized, double-blind, placebo-controlled studies of solanezumab 400 mg in outpatients with mild-to-moderate AD dementia. Patients were at least 55 years old and met criteria for probable AD dementia based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria [22]. Patients with Mini-Mental State Examination (MMSE) [23] scores of 16 to 19 (moderate) or 20 to 26 (mild) were allowed to participate. Patients were randomized by investigative site and AD severity (mild/moderate) to ensure an even distribution of severity of disease across treatment groups. Study medication was given intravenously every 4 weeks through Week 76, with final evaluations occurring 4 weeks later at Week 80, such that the total duration was approximately 18 months. Patients were allowed to continue on stable doses of standard of care symptomatic medications, such as acetylcholinesterase inhibitors and memantine, for the duration of the study. The study protocol was approved by the institutional review board at each participating institution, and all participants provided written informed consent. Magnetic resonance imaging (MRI) was performed on all patients at baseline and at Weeks 12, 28, 52, and 80 (or early discontinuation).

In an optional study addendum, amyloid burden was assessed at baseline and at Week 80 (or early termination) by a PET scan using florbetapir F18 [24]. Addenda patients were included in this analysis (placebo, $n = 66$; solanezumab, $n = 63$) if they were diagnosed with mild AD dementia, had ≥ 12 months between baseline and end point scans (18 months or early discontinuation scan), a positive florbetapir PET scan at baseline, defined as a mean cortical-to-CBL SUVR >1.10, and MRI suitable for creation of segmentation maps.

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