Parkinsonism and Related Disorders xxx (2016) 1–8

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Predicting disease progression in progressive supranuclear palsy in multicenter clinical trials

Jee Bang [a, 1], Iryna V. Lobach [b, 1], Anthony E. Lang [c], Murray Grossman [d], David S. Knopman [e], Bruce L. Miller [a], Lon S. Schneider [f, g], Rachelle S. Doody [h], Andrew Lees [i], Michael Gold [j], Bruce H. Morimoto [k], Adam L. Boxer [a, *], on behalf of AL-108-231 Investigators

[a] Memory and Aging Center, Department of Neurology, University of California San Francisco, 675 Nelson Rising Lane, Suite 190, San Francisco, CA, 94158, USA
[b] Department of Epidemiology and Biostatistics, Division of Biostatistics, University of California San Francisco, 550 16th Street, San Francisco, CA, 94158, USA
[c] Department of Neurology, University of Toronto, 399 Bathurst St, McLaughlin 7-418, Toronto, ON, M5T 2S8, Canada
[d] Department of Neurology, University of Pennsylvania, 3400 Spruce St, Philadelphia, PA, 19104, USA
[e] Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN, 55905, USA
[f] Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
[g] Department of Neurology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
[h] Department of Neurology, Baylor College of Medicine, 6550 Fannin St # 1801, Houston, TX, 77030, USA
[i] Institute of Neurology, University College of London, 1 Wakefield Street, London, WC1N 1PJ, UK
[j] UCB BioSciences, Research Triangle, NC, USA
[k] Celerion, 621 Rose St, Lincoln, NE, 68502, USA

ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form
22 March 2016
Accepted 16 April 2016

Keywords:
Progressive supranuclear palsy
Clinical trial methodology

ABSTRACT

Introduction: Clinical and MRI measurements can track disease progression in PSP, but many have not been extensively evaluated in multicenter clinical trials. We identified optimal measures to capture clinical decline and predict disease progression in multicenter PSP trials.

Methods: Longitudinal clinical rating scales, neuropsychological test scores, and volumetric MRI data from an international, phase 2/3 clinical trial of davunetide for PSP (intent to treat population, n = 303) were used to identify measurements with largest effect size, strongest correlation with clinical change, and best ability to predict dropout or clinical decline over one year as measured by PSP Rating Scale (PSPRS).

Results: Baseline cognition as measured by Repeatable Battery for Assessing Neuropsychological Status (RBANS) was associated with attrition, but had only a small effect. PSPRS and Clinical Global Impression (CGI) had the largest effect size for measuring change. Annual change in CGI, RBANS, color trails, and MRI midbrain and ventricular volumes were most strongly correlated with annual PSPRS and had the largest effect sizes for detecting annual change. At baseline, shorter disease duration, more severe depression, and lower performance on RBANS and executive function tests were associated with faster worsening of the PSPRS in completers. With dropouts included, SEADL, RBANS, and executive function tests had significant effect on PSPRS trajectory of change.

Conclusion: Baseline cognitive status and mood influence the rate of disease progression in PSP. Multiple clinical, neuropsychological, and volumetric MRI measurements are sensitive to change over one year in PSP and appropriate for use in multicenter clinical trials.

* Corresponding author.
E-mail addresses: jee.bang@ucsf.edu (J. Bang), iryna.lobach@ucsf.edu (I.V. Lobach), lang@uhnresearch.ca (A.E. Lang), mgrossma@mail.med.upenn.edu (M. Grossman), knopman@mayo.edu (D.S. Knopman), bruce.miller@ucsf.edu (B.L. Miller), lschneid@usc.edu (L.S. Schneider), rdoody@bcm.edu (R.S. Doody), alees@ion.ucl.ac.uk (A. Lees), michael.gold.md@gmail.com (M. Gold), bhmorimoto@gmail.com (B.H. Morimoto), adam.boxer@ucsf.edu (A.L. Boxer).
[1] These authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.parkreldis.2016.04.014
1353-8020/

1. Introduction

Progressive supranuclear palsy (PSP) is a fatal neurodegenerative disease characterized by the aggregation of predominantly 4 microtubule binding domain repeat (4R) tau in neurons and glia [1]. There are several clinical presentations of PSP [2,3] and Richardson's syndrome is the most recognizable and rapidly progressive phenotype, characterized by early and severe gait instability with falls, slowed eye movements progressing to supranuclear ophthalmoplegia, axial rigidity, and variable neuropsychiatric symptoms. There are no effective therapies for PSP; however, a variety of new potential treatments targeting tau are entering clinical trials [4].

The feasibility of conducting pivotal clinical trials in PSP was recently demonstrated in three large, international studies [5–7]. A variety of clinical rating scales (such as PSP Rating Scale); PSPRS [8] and volumetric MRI measurements have been developed and validated for use in PSP based on small, single center studies and then applied to large, international clinical trials with little evidence to support their utility in multicenter settings. We examined data from the 48 center, randomized, placebo controlled phase 2/3 clinical trial of davunetide for PSP (AL-108-231) [6] to identify the best baseline clinical and biomarker outcome measures that: 1) capture clinical decline and 2) predict attrition or disease progression over one year.

2. Methods

2.1. Source of data

The data for this study were taken from the previously reported AL-108-231 (clinicaltrials.gov, NCT01110720) international, randomized, double-blind, placebo-controlled, phase 2/3 trial of davunetide for PSP [6]. The study enrolled 313 patients with PSP (Richardson's syndrome) at 48 centers in Australia, Canada, France, Germany, the United Kingdom and the United States. The intent to treat population (n = 303) of individuals who were randomized to davunetide or placebo and had at least one post-baseline assessment of both primary and secondary outcomes was used for analyses of baseline variables that predicted dropout.

2.2. Inclusion criteria

To be included in the AL-108-231 study, participants had to meet modified criteria for probable or possible PSP based on the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study [5]. Individuals had to be between 41 and 85 years of age at disease onset with at least a 12-month history of early and prominent postural instability or falls, supranuclear ophthalmoplegia or decreased downward saccade velocity, and prominent axial rigidity. Participants were required to be able to either ambulate independently or take at least five steps with minimal assistance. Individuals could participate only if they had PSP symptoms for less than 5 years, or if for more than 5 years with a PSPRS of 40 or greater at screening. Detailed inclusion and exclusion criteria are described in the primary study manuscript [6].

2.3. Clinical data

The primary endpoints were the change in PSPRS and Schwab and England activities of daily living scale (SEADL) [9] over one year. The PSPRS consists of six categories including daily activities, behavior, bulbar, oculomotor, limb motor, and gait/midline. Scores range from 0 to 100, with higher scores indicating more severe disease. SEADL is a measure of overall disability based on interviews with the patient and the informant, and is scored on an 11-point ordinal scale (10% intervals starting with 0 indicating vegetative functions, up to 100% indicating complete independence).

Secondary outcome measures included the Clinical Global Impression of Change (CGIC) [10] and brain ventricular volume as measured on MRI scans as described below [6]. In addition, exploratory outcomes were obtained including: the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; test domains include memory, visuospatial, language, and attention) [11], three additional assessments of executive function (color trails, phonemic fluency, and letter-number sequencing), the Geriatric Depression Scale (GDS) [12], the Clinical Global Impression of Disease Severity (CGIds) [13], and additional volumetric MRI scan measurements of the whole brain, midbrain, and superior cerebellar peduncle (SCP). A total of 217 patients completed the neuropsychological testing.

2.4. MRI data (n = 214)

To be included in the clinical trial all participants had to complete a baseline volumetric T1-weighted MRI scan on a 1.5 T or 3 T scanner. Whole brain and ventricular volumes were generated using the boundary shift integral technique, and midbrain and SCP volumes were generated using label propagation in statistical parametric mapping 5 (SPM5) at the Mayo Clinic Aging and Dementia Imaging Research Laboratory as previously described [6]. Brain volumes were adjusted for total intracranial volume (TIV) to control for head size differences where appropriate. Pons volume was not obtained. All scanners were calibrated using a standard phantom and MRI analyses were conducted blinded to treatment assignment. Five subjects were excluded from the original dataset (n = 219), because they were deemed to be influential outliers (well below the 25th or far above the 75th percentile of annual change), likely due to artifacts introduced during the initial MRI analysis.

2.5. Statistical analysis

We combined data from the placebo and davunetide groups since extensive analyses of the davunetide trial dataset revealed no differences between groups at baseline. The absolute value of Cohen's d between the treatment arms for baseline demographics, primary and secondary outcomes ranged [0.01, 0.14]; for MRI measures [0.01, 0.07], and in change in measures over time for primary and secondary outcomes ranged [0.01, 0.24]; and for change in MRI measures [0.01, 0.15]. Baseline values and 52-week change from baseline values in clinical ratings, neuropsychological measures, and MRI volumes were presented using estimates of central tendency (mean, proportion) and variance. Effect of baseline characteristics on drop out was examined using logistic regression models. Concordance between the observed 52-week change in PSPRS and the corresponding change in other measures was measured using Pearson R^2 and Spearman correlation coefficients where appropriate. All estimates include 95% confidence intervals. The relationship of the baseline evaluations to the 52-week change in PSPRS was explored with univariate and multivariate linear regression models. These models were performed with and without adjustments for potential confounders: baseline PSPRS, age, gender, disease duration, treatment group assignment (davunetide or placebo), tau haplotype, CoQ10 use, and MMSE.

We further examined the effect of baseline evaluations on trajectory of PSPRS across all patients using linear mixed effects models. These models accommodate repeated measures of PSPRS and allow the baseline evaluations to have impact on the overall trajectory both in slope (speed of PSPRS change) and intercept. The

Please cite this article in press as: J. Bang, et al., Predicting disease progression in progressive supranuclear palsy in multicenter clinical trials, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.04.014