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Minimal Clinically Important Worsening on the Progressive Supranuclear Palsy Rating Scale

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Structured Abstract

Introduction—Despite the widespread use of the PSP rating scale it is not known what change in this scale is meaningful for patients.

Methods—We analyzed data from a large clinical trial in PSP-Richardson’s syndrome (AL-108-231) to calculate minimal clinically important worsening. This was defined as the difference in mean change of PSP rating scale in subjects rated ‘a little worse’ and those rated ‘unchanged’ on the Clinicians’ Global Impression of Change Scale. A multivariate analysis using logistic regression assessed the relationship between clinical worsening, PSP rating scale, depression and activities of daily living.

Results—The minimal clinically important worsening on the PSP rating scale was 5.7 points, corresponding to the mean decline over six months in the trial. Changes in activities of daily living and PSP rating scale were significantly associated with clinical worsening.

Conclusion—Clinically meaningful change is measurable on the PSP rating scale over six months.

Keywords

Progressive supranuclear palsy (PSP); Minimal clinically important change (MCIC); progressive supranuclear palsy rating scale (PSPRS)

Introduction

The Progressive Supranuclear Palsy Rating Scale (PSPRS) [1] is a disease specific measure of severity in patients with progressive supranuclear palsy (PSP). It measures disability across six domains giving a maximum score of 100 with a mean annual increase (deterioration) of around 10 points in patients with PSP. Its validity has been tested in a large patient cohort and the scale has been successfully used in a variety of clinical trials [1–5].

There are no effective therapies for PSP, but increasing numbers of potential therapies are entering clinical trials. To prove therapeutic efficacy in a clinical trial a statistically significant effect on a specific measure of disease severity must be shown. In general this effect should also be clinically meaningful for the target patient population. The PSPRS has been used as the primary end point in several therapeutic trials in PSP [2–5], however the magnitude of change required for a clinically meaningful effect of an intervention is not known. It is possible that the principal effect of a disease modifying therapy may be to reduce the rate of clinical deterioration on a rating scale (such as the PSPRS) with little perceived benefit by the patient. In these circumstances measurement of functional status may be a more appropriate primary end point, however, such rating scales tend not to be specific and may have limited sensitivity to treatment effects. A more sensitive approach would be to determine what degree of change on a disease specific rating scale would be

considered clinically meaningful for a patient or an expert physician who cares for the patient.

A large, international multi-centre phase 2/3 trial of davunetide in PSP enrolled 313 people, who were evaluated over a 12-month period. The primary end point of this trial was the 52-week change in PSPRS as a measure of putative disease modifying activity of davunetide. [2]. Using data from this study we sought to identify the smallest difference in PSPRS perceived as clinical worsening. Identifying this metric will improve our ability to interpret trial results in PSP in a clinically meaningful way and may aid the planning of future interventional trials.

Methods

We analyzed data collected from the multi-centre randomized, double blind, placebo controlled study of davunetide in PSP (Allon Therapeutics) from 2010–2012 [2]. It found no evidence of efficacy and the methods and results of this study have been published elsewhere [2].

Data Analysis

Given the negative results of the trial, we sought to identify the minimal worsening that was perceived as clinically significant. An anchor-based approach using clinical global impression of change (CGI-c) was used to determine minimal clinically important change (MCIC) for the PSPRS. MCIC was defined as mean change of PSPRS in subjects who were rated as “minimally worse” on CGI-c (CGI-c = 5), using investigator-rated scores.

Data were assessed for normality and the change scores on PSPRS were found to be well approximated by a normal distribution. The average change in PSPRS was assessed and the corresponding 95% confidence interval was determined. A repeated measures analysis of variance (ANOVA) was performed using the PROC MIXED procedure in SAS to compare change from baseline scores on the PSPRS with their associated CGI-c score. Separate analyses were performed for each of the six PSPRS subscales. Spearman coefficients were calculated to assess the relationship between changes in PSPRS and CGI-c for visit 5 and 7. These later visits (at 6 months and 12 months) were chosen to avoid both the Hawthorne effect, which has been postulated to contribute to a relatively slow rate of progression of disease early in PSP treatment trials and any tendency to regress towards the mean [1]. As there were no effects of treatment in any of the planned or exploratory analyses from the original study, data from the active and placebo groups were pooled in this study.

Multivariate analysis was performed using logistic regression (adjusting for repeated measures) to assess the relationship between clinical worsening as measured on the CGI-c (Score > 5) and change in baseline PSPRS score, change in Geriatric Depression Scale and change in SEADL. The results from logistic regression analysis were reported as odds ratios and 95% confidence intervals. A two-sided p value less than 0.05 indicated statistical significance. Analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Three hundred and thirteen patients were enrolled in the study, with 150 females (48%) and 163 males (52%). The mean age of patients in the study was 68 ± 6.6 years and at entry mean PSPRS score was 40 (95% CI 39–41). Two hundred and forty-one patients completed the 12 month analysis and mean progression in PSPRS over that period was 11.1 points (95% CI 9.9–12.3). The rate of change (deterioration) in the PSPRS was consistent for all participants regardless of initial disease severity.

The MCIC for minimal worsening in PSPRS score was found to be 5.7 points based on change from baseline scores (95% CI 4.83–6.51, $p < 0.001$). There was no difference when results were split by active agent. The Spearman correlation coefficient for the 12 month data was 0.394 ($p < 0.0001$). The MCIC for each PSPRS subscale is displayed in Table 1.

Multivariate analysis of the data revealed SEADL (OR 0.37, 95% CI 0.30–0.45, $p < 0.001$) and PSPRS (OR 1.05, 95% CI 1.02–1.07, $p < 0.001$) were significantly associated with CGI worsening. Depression as measured on the GDS (geriatric depression scale) did not show any relationship to change in CGI (OR 1.01, 95% CI 0.98–1.05, $p = 0.32$).

Discussion

In this analysis of data from patients enrolled in one of the largest clinical trials in PSP we found that the MCIC for deterioration on the PSPRS is 5.7 points. Bulbar, cognitive and upper limb function domains of the PSPRS contributed most to perceived change in these patients.

This data provides a snapshot of PSP in a homogenous cohort of patients with mid stage PSP, having specifically excluded patients with slowly progressive symptoms or early symptoms ‘at risk’ of developing Richardson syndrome. Thus MCIC of 5.7 points deterioration on PSPRS may not be applicable to patients with early or late stage disease, but is highly relevant for patients most likely to be enrolled in a clinical trials for PSP. In this study the mean change in PSPRS at visit 5 (6 month visit) was 5.8 points (95% confidence interval 4.7–6.9), suggesting that a one year trial should be more than adequate to measure a clinically significant effect of a therapy. Shorter duration studies in PSP may be possible, or perhaps the addition of a six-month interim analysis to determine futility in order to enhance research in this area by reducing trial costs.

The CGI was a clinician rated assessment, performed after a semi-structured interview with the patient and carer. It has been suggested that to truly assess for a clinically meaningful response, a patient rated assessment must be performed due to administration bias when assessment is performed by the treating clinician. This bias was minimized in the present study as the PSPRS and CGI were performed by different clinicians.

It is interesting to note that no correlation was seen between the CGI and the change in GDS. There are varying reports in the medical literature of the prevalence of depression amongst people with PSP [6–8]. The diagnosis is difficult to make in this population, due to

the overlap of features of apathy, pseudobulbar affect and cognitive impairment. There is also often a significant lack of insight and executive dysfunction [9].

A negative correlation on regression analysis was seen between the Schwab and England Activities of Daily living scale (SEADL) and the CGI. This would suggest that patients and their carers are most affected by a global decline in level of function rather than specific changes in cognitive function or physical capabilities.

Individual MCICs were calculated for the subscales of the PSPRS. These subscales vary in the total number of points they contribute to the PSPRS. However, even when corrected for the denominator, the MCIC was relatively high for gait, suggesting that appendicular motor and mentation changes contribute more to morbidity in this stage of disease.

The PSP rating scale does have limitations in assessing progression of disease. It is well recognized that there is often a substantial delay in diagnosis in this condition, with mean delay to diagnosis reported at approximately 3 years in various publications [1, 10]. In the validation study only 13% of patients were assessed early in the disease, with mild clinical symptoms (PSPRS<30) [1]. It is therefore not clear how useful this tool is in the early stages of disease and it may have floor effects during this period.

It has also been reported that various subscales of PSPRS, particularly vertical eye movements and gait, demonstrate ceiling effects [10]. These clinical measures deteriorate early in disease, and have proven to be not useful in measuring decline in PSP [10].

The PSPRS was not designed as a complete and sensitive tool to assess all areas of disability in PSP. It was designed as a pragmatic tool, which can be applied easily and reliably to patients in the clinical setting. It has been used in clinical trials but due to its recognized low sensitivity in measuring areas related to activities of daily living, dysphagia and cognition, it is usually used in a combination with a battery of other tests to ensure all modalities of the disease and associated disability are adequately measured. On a recently published power analysis, the total PSPRS was found to require the fewest number of patients to demonstrate a treatment effect on disease progression over one year when compared to other disease and disability rating scales. [11]

In other conditions, including Parkinson disease, the change required for minimal clinically important worsening has been shown to not correspond to the change for improvement [12, 13]. It has also been demonstrated that the calculated figure for MCIC can be affected by many variables, including whether subjects are given active agent or placebo and the degree of efficacy of the active agent [12, 14]. There is currently no effective long-term treatment for PSP, and therefore while these factors may need to be taken into consideration in future therapeutic trials, they are not currently applicable in the clinical context. The calculation of the MCIC in the PSPRS will allow us to interpret future outcome results in a clinically meaningful way, as opposed to relying only on statistical significance, which cannot differentiate trivial from clinically meaningful results.

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Table 1

Minimal clinically important change in the PSPRS by subscale

PSPRS	MCIC	95% CI	p value
Total	5.67	4.83 – 6.51	<0.0001
Gait	1.89	1.58 – 2.19	<.0001
History	1.31	1.03 – 1.59	<.0001
Limb	0.63	0.43 – 0.84	<.0001
Mentation	0.56	0.31 – 0.81	<.0001
Ocular	1.11	0.86 – 1.37	<.0001
Bulbar	0.51	0.37 – 0.65	<0.0001

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