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Parkinson's disease

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Statement of the issue

Pharmaceutical research on the next generation of therapeutics for Parkinson's (PD), Alzheimer's (AD), and other neurodegenerative disorders has focused on ways to interrupt or retard the progression of disease. Studies of PD disease progression raise significant clinical study design issues given the slow and variable progression of illness requiring long studies over several years and difficulty in assessing native disease due to the need for symptomatic medication and inability to completely washout effects of symptomatic treatments. In addition, clinical trials of disease progression/modification typically recruit patients in the very early stages of disease when diagnostic certainty is poorest, even amongst movement disorder specialists, resulting in misdiagnosis rates of 10-14% of study subjects.

All these factors help underscore the important role of objective biomarkers of disease progression in PD progression studies, including imaging biomarkers of dopaminergic function using PET or SPECT. Unfortunately, the use of these imaging biomarkers for novel drug development in PD has generated controversy based on early studies demonstrating poor correlation between clinical and imaging measures of disease progression and the concern that treatment could influence the imaging outcome measure[1,2]. These initial studies also identified a number of patients who met operational diagnostic criteria for PD but had normal scans referred in the literatures as SWEDD (scans without evidence of dopaminergic deficit).

Current state of the art

More recent studies, including the recently completed PRECEPT study of 800 de novo PD patients in a double-blind placebo-controlled trial of a putative neuroprotective drug refines the current understanding of the use of scintigraphic methods for PD drug development. In this trial, subjects underwent dopamine transporter imaging at baseline and 22 months following randomization to one of three dose of CEP1347 or placebo. 91 of 800 de novo subjects (11.4%) had normal baseline dopamine transporter scans. In follow-up over 2-3 years, the great majority of these subjects demonstrated clinical features not consistent with the diagnosis of PD despite meeting initial enrollment criteria. The INSPECT (USA) and AMADEUS (EU) studies directly assessed the short-term effects of common anti-PD treatments, dopamine agonists or levo-dopa on imaging measures in PD subjects. Between these two studies over 150 drug naïve PD patients were scanned at baseline, after standardized 12 week treatment of l-dopa, dopamine agonist, or no therapy, and after 8 week medication washout. In this controlled setting there was no demonstrable effect of dopamine replacement therapy on striatal binding ratios for either 123-I FP-CIT or 123-I b-CIT.

Conclusion

Recent large studies employing imaging biomarkers of dopaminergic function in PD drug trials now suggest a potential screening role for imaging to improve the accuracy of diagnosis in de novo PD. The effects of commonly used PD medications have not been demonstrated to have effect of quantitative imaging measures of DAT density in carefully controlled treatment trials.

References

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