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What is a clinically important change in the Unified Dyskinesia Rating Scale in Parkinson's disease?☆

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ABSTRACT

Introduction: Dyskinesia remain a significant problem in Parkinson Disease (PD). The translation process of novel drug targets for dyskinesia has proven difficult with several failures at phase III level. Determining the 'clinically important change' (CIC) for dyskinesia rating scales in phase II clinical trials may assist in optimizing drug development of new anti-dyskinetic treatments. We used a standard phase IIa acute levodopa infusion paradigm to determine for the first time the CIC for dyskinesia using the new UDysRS.

Methods: We performed a randomized, double-blind, placebo-controlled crossover study with eleven PD patients with stable bothersome dyskinesia. We used the following patient-reported clinically important events as CIC anchors: onset, maximum intensity, remission of dyskinesia. Objective dyskinesia scores using the UDysRS part III Impairment were determined at these same events by blinded video-rating. The CIC was determined using the 'within-patient' score change and a sensitivity- and specificity-based approach.

Results: Patients were most aware of 'onset of dyskinesia', followed by 'remission of dyskinesia'. An 11.1-point median change (UDysRS Part III Impairment, $p < 0.0001$) was the CIC for patient-reported remission of dyskinesia from a practically defined-OFF state. A 2.32-point change (UDysRS Part III Impairment) had the best specificity and sensitivity to distinguish between patient-reported remission and perception of dyskinesia.

Conclusions: In this study, we provide the first report of a CIC for the UDysRS Part III Impairment. Early knowledge of a CIC may help inform the decision to advance into phase III trials and contribute for a higher yield of success in finding new anti-dyskinetic treatments.

1. Introduction

Dyskinesia have a significant negative impact on health-related quality-of-life and health-economic outcomes [1,2] in Parkinson's disease (PD). Moderate-to-severe disabling treatment-induced dyskinesia can be experienced by up to 25% of PD patients [3] and current treatment options are scarce. Amantadine and clozapine are the only oral treatment considered 'efficacious' by the Movement Disorder Society [4], however clozapine raises safety concerns [4]. There is still a need to advance research of novel anti-dyskinetic agents [1,5]. Being able to define a clinically important change (CIC) in dyskinesia, i.e., a change in a clinical rating scale that a patient can recognize and value [6], is instrumental to interpret the clinical relevance of a statistical significant change in outcome measures documented in clinical trials and to accurately

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inform sample size requirements for future trials [7]. Dyskinesia are often perceived differently by patients, caregivers and physicians, which emphasizes the need to have a quantification of a CIC for dyskinesia as reported by patients with PD, rather than physicians. In addition, there is a requirement by regulatory agencies to use patient-reported outcomes to document a translation of observed treatment effects into a CIC [7]. In the development of anti-dyskinetic drugs for PD, it is important to recognize that a significant attrition rate exists when translating basic research into an effective treatment, with increased costs and false hopes for patients [8,9]. New paradigms for clinical trial design are warranted to overcome these challenges, namely, for pivotal phase II trials [8] that provide optimal information for the decision to conduct phase III trials [10]. Phase II trials with more informative outcomes will increase the yield of success of confirmatory phase III trials.

In this study, we attempted to implement the concept of CIC using the classical methodology of phase IIa trials for new anti-dyskinetic drugs: the intravenous (i.v.) levodopa infusion paradigm [11]. We aimed to obtain for the first time a value of CIC for the Unified Dyskinesia Rating Scale (UDysRS), a validated scale for dyskinesia in PD [12].

2. Methods

2.1. Study population

2.1.1. Inclusion criteria

United Kingdom PD Society Brain Bank criteria for the clinical diagnosis of idiopathic PD [13], age 30–80 years, stable bothersome (Lang-Fahn Activities of Daily Living Dyskinesia scale ≥ 1), levodopa-induced peak-dose dyskinesia for > 25% of the day (MDS-UPDRS, item 4.1, rating > 2) and stable anti-parkinsonian medications for at least one month prior to study participation.

2.1.2. Exclusion criteria

Hoehn and Yahr score of 5 when "off", UPDRS score of 3–4 for resting/action tremor when "off", cognitive impairment (Montreal Cognitive Assessment < 24) [14], prior surgery for PD, significant medical/surgical disease that could interfere with participation in the study, according to the investigator's clinically judgment.

2.2. Study design

Randomized, double blind, placebo-controlled crossover study, with a washout period of 1–2 weeks. The study included an initial run-in phase, with the purpose of ensuring a levodopa infusion as the first infusion in order for patients to become familiar with the development of dyskinesia and determine the events that help the patient be aware of the presence or absence of dyskinesia using i.v. levodopa; as well as to reduce the placebo effect. The study was approved by the local IRB. All participants provided written informed consent and the study was conducted according to Good Clinical Practice standards.

2.3. Drug administration

Levodopa/vehicle (prepared by the local hospital pharmacy) was infused via a peripheral vein for 2 h. The infusion rate was as used in prior studies [11]; 1.0/mg/kg/hr (if total daily oral levodopa-equivalent dose $\leq$ 1000 mg) or 1.5 mg/kg/hr (if total daily oral levodopa-equivalent dose >1000 mg) [11]. Infusions of levodopa and vehicle were identical in appearance. Oral carbidopa 25 mg was co-administered at baseline and every 2 h to prevent nausea. Domperidone was also administered 10 mg TID, 3 days before each levodopa/vehicle infusion. Subjects were instructed to have a low-protein (<5 g of protein) breakfast on visit days.

2.4. Study procedures, assessments

The study consisted of 4 visits over 7 ± 2 weeks, including a screening visit (visit 1), a run-in levodopa infusion visit (visit 2) and two randomized visits (Visit 3 and Visit 4) of levodopa or placebo infusion. The process of randomization (computer generated randomization list) and allocation was conducted independently by the local hospital pharmacy and remained concealed until the end of the study. The three infusion visits were similar in design with a washout period of 1–2 weeks between visits. At each infusion visit (visits 2, 3, 4) a video protocol was administered, incorporating all features required to rate dyskinesia using the validated UDysRS part III Impairment scale [12] (due to the infusion tubing, the item *dressing* was excluded). The assessment protocol was administered when patients were 12 h off PD medications (practically-defined "off" state) and repeated every 30 ± 5 min during the 2-h infusion of levodopa/placebo, followed by up to a maximum of 2 h post-infusion. *Post-hoc* rating of the scales was performed by 3 movement disorders neurologists blinded to the visit. Mean ratings were determined to give a single score. An anchor-based approach was used to determine a CIC. Three anchors chosen to determine a CIC were: 1. Onset, 2. Maximum intensity and 3. Remission of dyskinesia. Patients were asked about these three different clinically important events every 15 min. A questionnaire using a 5-point Likert scale was used as an external anchor. The questions were tailored according to data collected at screening visits regarding experience of dyskinesia for each study participant, including location and triggering factors. These triggers were reproduced during the treatment infusion. A response of *Agree* or *Strongly agree* was considered confirmatory of the patient experiencing one of the pre-determined clinically important events. Blood pressure and pulse were recorded in the practically defined off state and at every hour. Adverse events were determined by direct questioning of patients during infusion visits and after the first week post-infusion visit by telephone contact.

2.5. Data analysis

Collected data during levodopa and placebo infusion visits were used regardless of the treatment sequence. For each assessment, scores were averaged among the 3 raters. Results were expressed as median and inter-quartile range and mean ± standard deviation (95%). The CIC was calculated by two methods: 1) *"Within-patients" score change* comparing the median change scores in UDysRS part III Impairment at each patient reported clinically important event and the practically defined OFF state (default value = 0) during levodopa infusion, using a non-parametric test (Wilcoxon signed-rank test). 2) *Sensitivity- and specificity-based approach* using a Receiver Operator Characteristic (ROC) curve method and a sensitivity and specificity analysis to determine the optimal cut-off for a score change that can distinguish between reporting or not a clinical important event during treatment with levodopa. In a secondary analysis, we assessed the cut-off for optimal sensitivity regardless of the value of specificity, considering that a higher sensitivity would be a useful measure for drug screening in a phase II study. $P \leq 0.05$ was considered significant. The statistical analyses were performed using the Stata v12.0 (StataCorp, College Station, TX: StataCorp LP).

3. Results

3.1. Clinical and demographic characteristics

11 stable bothersome dyskinesia PD subjects were recruited, nine