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Effects of long-term treatment with rotigotine transdermal system on dyskinesia in patients with early-stage Parkinson's disease

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ABSTRACT

Purpose: In two 6-month, double-blind, placebo-controlled studies, rotigotine transdermal system was well-tolerated and efficacious monotherapy in early-stage PD. This post hoc analysis of the long-term open-label extensions (NCT00594165; NCT00599196) of these studies assessed incidence and severity of dyskinesia in participants treated with rotigotine, with or without concomitant levodopa, for up to 6 years.

Methods: Open-label rotigotine was titrated to optimal dose (≤16 mg/24 h). Concomitant levodopa was permitted. Dyskinesia data, recorded using the Unified Parkinson's Disease Rating Scale Part IV, were pooled from the two open-label studies.

Results: Of 596 participants who received open-label rotigotine, 299 (50%) remained at trial closure; no patient discontinued due to dyskinesia. In the two studies, median exposure to rotigotine was 1910 days (~5 years, 3 months), and 1564.5 days (~4 years, 3 months). During up to 6 years of open-label rotigotine, 423/596 (71%) received levodopa. Dyskinesias were reported in 115/596 (19%) participants, 90/115 (78%) of who developed dyskinesia after levodopa was added; 25 reported dyskinesia in the absence of levodopa (includes patients who never received open-label levodopa, and those who reported dyskinesia before starting concomitant levodopa). Dyskinesia severity data were available for 107 of the 115 participants. In 56/107 (52%) participants, dyskinesia was considered 'not disabling' for all occurrences; the worst-case severity was 'mildly disabling' for 33/107 (31%), and 'moderately' or 'severely disabling' for 18/107 (17%; 3% of total participants).

Conclusion: During treatment with rotigotine in patients with PD for up to 6 years the incidence of dyskinesia was low, and the dyskinesia was generally 'not disabling' or 'mildly disabling'.

1. Introduction

Although levodopa remains the most efficacious symptomatic treatment for Parkinson's disease (PD), in most patients its long-term use eventually becomes complicated by the development of motor fluctuations and dyskinesia [1,2]. Dyskinesia (in a form of chorea, stereotypy, or dystonic involuntary movements) can result in marked disability and may negatively impact quality of life [3]. Within 4–6 years of initiating levodopa therapy around 40% of patients develop dyskinesia, with almost all patients eventually developing dyskinesia with prolonged treatment [4].

While the pathogenesis of dyskinesia is not fully understood, preclinical and clinical findings suggest that the development of levodopa-induced dyskinesia is related to levodopa's short plasma half-life, which results in pulsatile stimulation of striatal dopamine receptors and altered basal ganglia output [5,6]. Normal striatal dopamine receptor stimulation is thought to consist of both low-frequency continuous tonic stimulation and higher-frequency phasic stimulation. Based on this tonic/phasic hypothesis of

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dopamine release, the concept of continuous dopaminergic drug delivery has emerged as a clinical strategy that may more closely mimic physiologic dopaminergic stimulation [6,7]. Dopamine receptor agonists, which have a longer plasma half-life than levodopa, are often used as first-line therapy in patients with early-stage PD as a strategy to postpone the need for or reduce the dose of levodopa, thereby minimizing the risk of dyskinesia and other levodopa-related motor complications [8,9].

Rotigotine is a dopamine receptor agonist with activity across D1 through D5 receptors as well as select adrenergic and serotonergic sites [10,11]. Rotigotine transdermal system provides continuous dopaminergic stimulation [12], and maintains stable plasma levels over 24 h with a single daily application [13]. Animal studies have suggested that continuous administration of rotigotine may reduce the risk of dyskinetic involuntary movements compared with pulsatile administration of rotigotine or levodopa [14,15]. In two 6-month, randomized, double-blind, placebo-controlled studies, rotigotine transdermal system was shown to be an efficacious and well-tolerated monotherapy in early-stage PD [16–18]. Each study offered enrollment in a prospective, long-term, open-label extension [19,20]. As the longest interventional studies of rotigotine conducted to date, with adjunctive levodopa permitted as required during the open-label extensions, these studies provide an opportunity to assess the long-term incidence of dyskinesia. In this post hoc analysis, results from these open-label extensions were assessed to determine the long-term effect of rotigotine on incidence and severity of dyskinesia in patients who enrolled with early-stage PD, with or without concomitant levodopa.

2. Methods

2.1. Design

Participants completing the 6-month maintenance period of one of two phase III, randomized, double-blind trials of rotigotine transdermal system in patients with early-stage PD (SP512 [17,18]) and SP513 [16]) had the option of enrolling into prospective, single-arm, open-label extension studies of up to 6 years' duration: SP702 (participants from SP512; ClinicalTrials.gov NCT00594165 [19]) and SP716 (participants from SP513; ClinicalTrials.gov NCT00599196 [20]). Participants enrolled in each double-blind study were aged 30 years or older, had been diagnosed with idiopathic PD for up to 5 years, had a Unified Parkinson's Disease Rating Scale (UPDRS) Part III score of ≥10, and a Hoehn and Yahr stage ≤3 (mild-to-moderate PD). Treatment with dopamine receptor agonists or levodopa was not permitted during the double-blind studies or in the 1 month prior to enrollment. Participants were also excluded from entering the double-blind studies if they had taken levodopa for longer than 6 months since PD diagnosis. Levodopa (in combination with benserazide or carbidopa) was allowed, if required, after 1 month of open-label rotigotine maintenance. In addition, the following other anti-Parkinson medications were allowed after 1 month of open-label rotigotine maintenance: MAO-B inhibitors, anticholinergic agents, NMDA-antagonists (e.g., amantadine), entacapone, and modafinil. Complete inclusion and exclusion criteria are published [16–20].

2.2. Procedures

In the double-blind studies, participants were randomized to receive once-daily transdermal patches of placebo or rotigotine (2–6 mg/24 h) in SP512, and placebo, rotigotine (2–8 mg/24 h), or oral ropinirole (up to 24 mg/day) in SP513. At the end of double-blind maintenance, treatment was de-escalated to 2 mg/24 h rotigotine. All participants entering the open-label studies, including those who were treated with placebo or ropinirole in the double-blind studies, received open-label rotigotine titrated to their optimal dose (up to 6 mg/24 h in SP702, up to 8 mg/24 h in SP716). The optimal dose was defined following discussion between the participant and the investigator, taking into account the potential for improvement of disease symptoms and the participant's adverse event (AE) profile. After the first year of open-label maintenance, up-titration to a maximum dose of 16 mg/24 h was permitted. During open-label maintenance, dose adjustments of rotigotine were permitted at any time at the discretion of the investigator. The investigator was encouraged to increase rotigotine to maximum allowed dose before adding/increasing levodopa or other anti-Parkinson medications. Participants were maintained at their optimal dose until rotigotine became commercially available or the sponsor closed the trial, whichever came first. Maintenance visits were scheduled at the end of the first month of open-label maintenance and at 3-month intervals thereafter [19,20].

2.3. Rotigotine exposure and levodopa use

The extent of rotigotine and levodopa exposure during the open-label studies was reported and included assessments of dose, time to treatment initiation (levodopa only), and duration of treatment.

2.4. Assessment of dyskinesia

Dyskinesia was assessed using UPDRS Part IV, Complications of therapy (in the past week) item 32 (dyskinesia duration) and item 33 (dyskinesia disability) criteria. Item 32: "What proportion of the waking day are dyskinesia present? (historical information)", where a score of 0 = none, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%. Dyskinesia was defined as present if the response to UPDRS IV item 32 was >0. Item 33: "How disabling are the dyskinesia? (historical information, which may be modified by office examination)", where a score of 0 = Not disabling, 1 = Mildly disabling, 2 = Moderately disabling, 3 = Severely disabling, and 4 = Completely disabling. The incidence and severity of dyskinesia were therefore based on participant report, with the opportunity to modify the responses following investigator examination. UPDRS Part IV assessments were performed at every open-label clinic visit.

The incidence of dyskinesia in relation to levodopa use was assessed, and was defined as the first episode of dyskinesia occurring 1) in the absence of levodopa or 2) after starting levodopa. Dyskinesia in the absence of levodopa included participants who experienced dyskinesia but never received levodopa during the study, and participants whose first onset of dyskinesia occurred before their first dose of levodopa. Therefore, participants who reported their first dyskinesia in the 'absence of levodopa' may have subsequently received concomitant levodopa. Dyskinesia was also assessed by duration of PD at double-blind baseline (and duration of PD at the first episode of dyskinesia), and stratified by gender and age at double-blind baseline. The age cohorts (<50, 50–<65, 65–<75, and ≥75 years) are in line with age cut-offs used to identify age-related differences in AEs in studies of rotigotine [21].

2.5. Statistical analyses

Analyses of pooled data from the two open-label studies are reported; analyses include participants randomized to ropinirole during the SP513 double-blind study (n = 160). All participants who received at least one dose of open-label study medication were included in the safety set. UPDRS IV analyses were performed on the safety set, as observed. End of maintenance was defined as the last available value from the maintenance period. Data were analyzed descriptively and no statistical significance testing was performed.

3. Results

3.1. Participants

Of the 632 participants who completed double-blind treatment, 598 (95%) chose to enter the open-label extensions; 596 participants received open-label rotigotine and were included in the safety set. 299/596 (50%) participants were still in the study when rotigotine became commercially available or at the time of closure by the sponsor (4–6 years after the onset of open-label rotigotine treatment); 145 (24%) withdrew prematurely due to AEs, 34 (6%) due to lack of efficacy, and 120 (20%) because of other reasons (Fig. 1) Full patient disposition are reported in the primary manuscripts [19,20]. No participant discontinued due to dyskinesia. Pooled baseline demographic data are listed in Table 1.

3.2. Rotigotine exposure and levodopa use

The mean ± SD rotigotine dose at the end of treatment was 7.2 ± 3.4 mg/24 h (median 6 mg/24 h) in SP702 and 8.2 ± 3.8 mg/24 h (median 8 mg/24 h) in SP716. The median exposure duration to rotigotine during SP702 was 1910 days (~5 years, 3 months; range 1–2188 days), and during SP716 was 1564.5 days (~4 years, 3 months; 5–2154 days).

A total of 23 (4%) participants who entered the open-label studies had received levodopa (for less than 6 months) prior to the double-blind studies. During up to 6 years of open-label