Parkinsonism and Related Disorders xxx (2012) 1–6

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Treatment of patients with early and advanced Parkinson's disease with rotigotine transdermal system: Age-relationship to safety and tolerability

Wolfgang Oertel [a,*], Peter LeWitt [b,c], Nir Giladi [d], Liesbet Ghys [e], Frank Grieger [f], Babak Boroojerdi [g]

[a] Department of Neurology, Philipps-Universität, Baldingerstrasse, D 35043 Marburg, Germany
[b] Department of Neurology, Henry Ford Hospital, Detroit, MI, USA
[c] Department of Neurology, Wayne State University School of Medicine, Detroit, MI, USA
[d] Department of Neurology, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[e] UCB Pharma, Brussels, Belgium
[f] UCB Pharma, Monheim am Rhein, Germany
[g] UCB Pharma, Raleigh, NC, USA

ARTICLE INFO

Article history:
Received 28 March 2012
Received in revised form
12 June 2012
Accepted 12 June 2012

Keywords:
Dopamine agonist
Elderly
Parkinson's disease
Rotigotine
Safety

ABSTRACT

Although dopamine agonists (DAs) are sometimes perceived as poorly tolerated by the elderly, there is little clinical evidence to support these concerns. Safety and tolerability of rotigotine have been demonstrated in four 6-month randomized placebo-controlled studies: two in early Parkinson's disease (PD) and two in advanced PD. A post hoc analysis of data from these pivotal trials was carried out to compare the adverse event (AE) profiles of younger and older patient populations. Data from early and advanced PD trials were separately pooled and evaluated using two age cut-offs (<65 vs. ≥65 years; <75 vs. ≥75 years). For most AEs, no age-related differences in incidence were observed. In the early PD pool, nausea (38% vs. 30%) and headache (15% vs. 9%) were more frequent in younger (<65 years) compared with older (≥65 years) patients using the 65-year age cut-off. Using the 75-year cut-off, nausea (36% vs. 21%) was more frequent in younger patients (<75 years) and dizziness (15% vs. 28%) was more frequent in older patients (≥75 years). In the advanced PD pool, nausea was more frequent in younger patients using the 65-year age cut-off (24% vs. 19%) and falls were more frequent in older patients using the 75-year age cut-off (8% vs. 13%). In this relatively healthy population which included only few patients aged 75 years or older, rotigotine was generally well tolerated regardless of age. Data from more representative PD populations are required to fully assess potential risks of DA therapy in elderly patients.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that predominantly affects older patients; its incidence rises after the age of 55, with a sharp increase after the age of 60 years [1,2]. Patient age, disease severity and expected duration of treatment are generally taken into account when choosing between PD treatment options [3–5]. Levodopa remains the most effective therapeutic agent for the treatment of PD [6], although its long-term use is associated with the development of motor fluctuations and dyskinesia [7–11]. Dopamine receptor agonists (DAs) are widely used as monotherapy in patients with early PD, and as an adjunctive therapy to levodopa in patients with advanced PD [3].

Advancing age is known to be associated with the clinical progression of PD, particularly the faster progression of motor impairment, decreasing levodopa responsiveness, and more severe dopamine non-responsive gait, postural and cognitive impairment [12]. Older patients metabolize drugs differently to younger patients and may be susceptible to drug side effects, which are often complicated by comorbid conditions [13]. While DAs are frequently used as first-line therapy in younger patients, levodopa is recommended for the elderly [9] who may be less prone to motor complications associated with long-term levodopa therapy [5]. In addition, DAs are associated with a greater risk of developing dopaminergic side effects including hallucinations, impulse control disorders, orthostatic hypotension, somnolence and edema than levodopa [9,14]. There is a perception that DAs should be used with extra care and caution in elderly patients, although there is little clinical evidence to support these concerns [5,13,15–17].

Rotigotine is a DA with activity across D1 through D5 receptors as well as select adrenergic and serotonergic sites. Continuous transdermal delivery of rotigotine maintains stable plasma levels over 24 h with a single daily application [18]. The safety and tolerability of rotigotine transdermal system have been demonstrated in two 6-month studies in patients with early PD [19,20]

* Corresponding author. Tel.: +49 6421 586 6278; fax: +49 6421 586 8955.
E-mail address: oertel@med.uni-marburg.de (W. Oertel).

1353-8020/$ – see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.parkreldis.2012.06.009

and two 6-month studies in patients with advanced PD [21,22]. A post hoc analysis of data from these four pivotal trials was carried out to compare the safety and tolerability profile of rotigotine in younger and older PD patient populations receiving treatment under controlled study conditions.

2. Methods

This retrospective analysis was based on data from four randomized, double-blind, placebo-controlled trials of rotigotine transdermal system in patients with early (SP512 [19,23], SP513 [20]) and advanced PD (CLEOPATRA-PD [SP515] [21], PREFER [SP650] [22]). Detailed methods for each of these studies have been reported previously [19–23]. All four trials were conducted in accordance with the declaration of Helsinki and Good Clinical Practice and were approved by the relevant institutional review boards or ethics committees; written informed consent was obtained from all patients prior to participation.

Eligibility criteria for the early PD trials included idiopathic PD of less than 5 years in duration, at least two of the cardinal signs of PD (bradykinesia, resting tremor, rigidity or postural instability), a Hoehn and Yahr clinical stage of III or less, a Unified Parkinson's Disease Rating Scale (UPDRS) motor examination (part III) score of at least 10 and a Mini-Mental State Examination (MMSE) score of 25 or more. Patients were excluded if they had atypical Parkinson's syndrome; a history of pallidotomy, thalamotomy, deep brain stimulation or fetal tissue transplant; clinically relevant hepatic, renal or cardiac dysfunction and/or a history of myocardial infarction within the previous 12 months; a history of symptomatic orthostatic hypotension; a current diagnosis of epilepsy; a history of seizures, stroke or transient ischemic attack within the previous year; and/or any other clinically significant medical condition, psychiatric condition or laboratory anomaly which, in the opinion of the investigator, would interfere with their ability to participate in the trial. Concomitant treatment with a DA or levodopa/carbidopa was not permitted within 28 days of baseline. Following titration, patients received their optimal dose of rotigotine (2–6 mg/24 h [SP512], 2–8 mg/24 h [SP513]) or placebo as once-daily transdermal patches for 24 weeks in SP512 and 33 weeks in SP513 (Supp. Table 1).

Patients who were enrolled in the advanced PD trials were required to have had idiopathic PD for at least 3 years with an average of 2.5 h 'off time' per day, and were receiving a stable dose of levodopa for at least 28 days prior to baseline. Other eligibility criteria included a Hoehn and Yahr stage of II–IV in both the 'on' and 'off state' and an MMSE score of 25 or more. Exclusion criteria were consistent with those reported for the early-PD trials, patients were additionally excluded if they had dementia, active psychosis or hallucinations. Patients were not allowed to exceed their baseline levodopa dose during the maintenance period. In CLEOPATRA-PD, patients received their optimal dose of 4–16 mg/24 h rotigotine or placebo as once-daily transdermal patches for 16 weeks, whereas in PREFER patients received a fixed dose of 8 or 12 mg/24 h rotigotine or placebo transdermally for 24 weeks (Supp. Table 1).

Adverse events (AEs) (including impulse control disorders) reported spontaneously by the patient or observed by the investigator were documented over the course of each trial. All AEs were recorded, irrelevant of suspected causality. Data from the early and advanced PD trials were separately pooled, and evaluated categorically using two age cut-offs – 65 and 75 years – resulting in the comparison of patients aged <65 with those ≥65 years, and of patients aged <75 with those ≥75 years. Comparisons were made of the incidence of AEs, severity of AEs, and discontinuations due to AEs. A serious adverse event was defined as any untoward medical occurrence that was fatal, life threatening, resulted in persistent or significant disability/incapacity, required or prolonged in-patient hospitalization, was a congenital anomaly/birth defect, or was considered to be an important medical event. For the 65-year age cut-off, AEs which occurred in ≥5% of rotigotine-treated patients and had a difference in incidence of ≥5% between younger and older patients were considered to be of relevance. Due to a low number of patients aged 75 years or older, a 5% difference in AE incidence between those aged <75 years and those aged ≥75 years was not considered sufficient to identify age-related differences in AEs (as 5% of rotigotine-treated patients aged ≥75 years was 1.5 patients in the early PD pool and 3.5 patients in the advanced PD pool). Therefore, AEs reported by ≥5% of rotigotine-treated patients for which there was a ≥10% difference in incidence between the <75-year old and the ≥75-year old patients were identified. In addition, the incidences of AEs considered to be of particular importance to the elderly – somnolence, hallucinations, orthostatic hypotension, peripheral edema and falls – were evaluated. All data reported are descriptive.

3. Results

3.1. Early PD trials

The early PD pool comprised 609 patients, of whom 395 received rotigotine. The age range of patients was similar in both the rotigotine (33–86 years) and placebo groups (30–84 years). The majority (56%) of patients in the early PD trials were younger than 65 years with only 9% of all patients aged 75 years or older. There was little difference between age cohorts in mean UPDRS scores and duration of PD at baseline (Table 1).

Using the 65-year age cut-off, nausea, headache and constipation were found to be the only AEs reported by ≥5% of rotigotine-treated patients that occurred with a ≥5% difference in incidence between the younger (<65 years) and older (≥65 years) patients (rotigotine treatment group; Table 2). However, the incidences of nausea and headache were greater among the younger patients, and that of constipation was greater among the older patients. In the placebo group, nausea was also reported by more of the younger than older patients and somnolence by more of the older than younger patients but there was little difference between age cohorts in the incidence of headache or constipation (Table 2). When the 75-year age cut-off was applied, nausea and dizziness were the only AEs reported by ≥5% of rotigotine-treated patients that occurred with a ≥10% difference in incidence between the younger (<75 years) and older (≥75 years) patients (rotigotine treatment group; Table 2). As for the 65-year age cut-off, the incidence of nausea was higher in the younger than the older patients; in contrast, dizziness was reported more frequently in the ≥75-year age group. These trends were also seen among patients who received placebo (Table 2).

No serious AEs (SAEs) or AEs of severe intensity occurred with a ≥5% difference in incidence between younger and older patients using the 65-year age cut-off, or a ≥10% difference using the 75-year age cut-off, whether patients were randomized to rotigotine or placebo. The incidences of perception disturbances and confusion and disorientation were generally low (≤5%) with both rotigotine (Fig. 1A) and placebo, regardless of age. The observed incidences of peripheral edema (rotigotine, 7–8%; placebo, 6–8%)

Table 1
Baseline demographics of early and advanced PD patients.

	Early PD				Advanced PD			
	<65 years (n = 343)	≥65 years (n = 266)	<75 years (n = 555)	≥75 years (n = 54)	<65 years (n = 286)	≥65 years (n = 367)	<75 years (n = 543)	≥75 years (n = 110)
Patients, n (%)								
Rotigotine	229 (67)	166 (62)	366 (66)	29 (54)	197 (69)	237 (65)	364 (67)	70 (64)
Placebo	114 (33)	100 (38)	189 (34)	25 (46)	89 (31)	130 (35)	179 (33)	40 (36)
Male, n (%)	217 (63)	151 (57)	340 (61)	28 (52)	197 (69)	229 (62)	357 (66)	69 (63)
Age, years, mean ± SD	54.7 ± 7.3	70.9 ± 4.4	60.2 ± 9.3	77.9 ± 2.5	56.3 ± 6.6	72.1 ± 4.9	62.5 ± 8.3	78.3 ± 2.7
Age range, years	30–64	65–86	30–74	75–86	33–64	65–87	33–74	75–87
Patients with prior/concomitant PD meds, n (%)	195 (57)	127 (48)	295 (53)	27 (50)	286 (100)	367 (100)	543 (100)	110 (100)
UPDRS II + III, mean ± SD	30.6 ± 13.0	32.5 ± 11.7	31.4 ± 12.6	31.5 ± 10.8	35.4 ± 16.1	42.0 ± 17.5	38.3 ± 17.0	43.0 ± 17.8
Duration of PD, years, mean ± SD	1.4 ± 1.4	1.3 ± 1.3	1.4 ± 1.4	1.2 ± 1.3	7.8 ± 4.0	8.5 ± 4.7	8.2 ± 4.5	7.9 ± 4.5

Please cite this article in press as: Oertel W, et al., Treatment of patients with early and advanced Parkinson's disease with rotigotine transdermal system: Age-relationship to safety and tolerability, Parkinsonism and Related Disorders (2012), http://dx.doi.org/10.1016/j.parkreldis.2012.06.009