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Rotigotine vs ropinirole in advanced stage Parkinson's disease: A double-blind study

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ABSTRACT

Objective: To confirm the superiority of transdermal rotigotine up to 16 mg/24 h over placebo, and non-inferiority to ropinirole, in Japanese Parkinson's disease (PD) patients on concomitant levodopa therapy.
Methods: This trial was a randomized, double-blind, double-dummy, three-arm parallel group placebo- and ropinirole-controlled trial. Four-hundred and twenty PD patients whose motor symptoms were not well controlled by levodopa treatment were randomized 2:2:1 to receive rotigotine, ropinirole (up to 15 mg/day) or placebo during a 16-week treatment period followed by a 4-week taper period. The primary variable was change in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (ON state) sum score from baseline to the end of the treatment period.
Results: The difference in the change in the UPDRS Part III (ON state) sum score from baseline to the end of treatment between rotigotine and placebo groups was -6.4 ± 1.2 (95% CI: -8.7 to -4.1; $p < 0.001$), indicating superiority of rotigotine over placebo. The difference between rotigotine and ropinirole groups was -1.4 ± 1.0 (95% CI: -3.2 to 0.5), below the non-inferiority margin, indicating the non-inferiority of rotigotine to ropinirole. Application site reaction was seen in 57.7% of the patients in the rotigotine group and in 18.6% in the ropinirole group ($P < 0.001$). No other safety issue was noted.
Conclusions: Rotigotine was well tolerated at doses up to 16 mg/24 h and showed similar efficacy to ropinirole except that the application site reaction was much higher in the rotigotine group.

1. Introduction

Long-term treatment of Parkinson's disease (PD) with levodopa are frequently complicated by motor fluctuations [1–3]. Ahlskog and Muenter reported 42.1% motor fluctuations and 38.5% dyskinesia in 4–6 years of treatment with levodopa; these figures rose up to 69.6% and 87.8%, respectively, with more than 9 years of treatment [2]. The use of dopamine agonists is associated with lower frequencies of wearing off and dyskinesia compared to levodopa in early stage PD [3,4]. Rotigotine is a non-ergot dopamine agonist, which has been developed as a patch with high selectivity for D2 and D3 receptors [5]. Rotigotine is superior to placebo in patients with early-stage [6–9] and advanced PD patients [10–12]. In addition, rotigotine was non-inferior to ropinirole [8] and pramipexole [10]. A clinical trial conducted in Japan showed superiority of rotigotine over placebo in patients with PD on concomitant levodopa therapy in the dose range of 2–16 mg/24 h [12]. We conducted a randomized, double-blind trial to see the efficacy and safety of transdermal rotigotine in Japanese advanced PD patients. We selected ropinirole as an active comparator drug, as it has been proved to be efficacious both in early stage [13–15] and advanced stage PD patients [16,17]. As the maximum daily dose for rotigotine has been set at 15 mg/24 h in Japan; we used this dose.

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2. Methods

2.1. Design

The study is a randomized, double-blind, double-dummy, three-arm parallel group, placebo- and ropinirole-controlled trial of rotigotine in Japanese PD patients on levodopa. The study was conducted in compliance with ethical principles in accordance with the Declaration of Helsinki, the Pharmaceutical Affairs Law, and the "Ordinance on Good Clinical Practice." The protocol was approved by the institutional review boards of each center, and written informed consent was obtained from all patients participating in the trial. The study has been registered with Clinicaltrials.gov (identifier: NCT01628926) and in the Japan Primary Registries Network (identifier: Japic CTI-090888). The study was financially supported by Otsuka Pharmaceutical Company.

2.2. Patients

Sixty-two sites in Japan participated in the trial, with the patient enrollment commencing in June 2009. We enrolled patients aged 30–79 years and with a diagnosis of PD, Hoehn & Yahr stage of 2–4, and Unified Parkinson's Disease Rating Scale (UPDRS) Part III sum score of ≥10 at screening (ON state), who were experiencing motor fluctuations or whom levodopa could not be increased to an optimal level because of side effects or other reasons. The levodopa doses were not changed from the period 28 days before starting treatment. Diagnosis of PD was made according to the UK Brain Bank criteria [18].

We excluded patients with psychiatric symptoms; orthostatic hypotension; a history of epilepsy or convulsion; a history of serious cardiac disease, arrhythmia, or QT prolongation; abnormal liver function; or a history of allergy to topical agents; and female patients who were pregnant or lactating from the trial. Concomitant use of drugs that may affect the symptoms of PD, cause QT prolongation, or interact with ropinirole was prohibited. Levodopa, selegiline and entacapone could be used concomitantly, provided there was no change in the dose from 28 days before the first dose of the study drug until the end of the treatment period. Anticholinergic drugs, amantadine, droxidopa, and zonisamide could be used concomitantly, provided there was no change in the doses for 14 days before the first dose of the study drug or during the treatment period.

2.3. Randomization and treatment

Eligible patients were randomized 2:2:1 to receive rotigotine, ropinirole, or placebo using a dynamic allocation procedure designed to balance the UPDRS Part III (ON state) sum score, the presence/absence of OFF time, the presence/absence of dystonia in the early morning, and responsiveness to prior dopamine receptor agonists. A double-dummy technique was used to maintain blinding with placebo patches or tablets.

We evaluated the enrolled patients every week until the maintenance dose is determined and every two weeks thereafter. The treatment period consisted of a maximum of 12 weeks of titration and at least 4 weeks of maintenance, and a dose taper period of up to 4 weeks. Rotigotine or placebo patches were applied once daily and ropinirole or placebo tablets were administered three times daily. Rotigotine was delivered at an initial dose of 2 mg/24 h, and the dose was increased to 16 mg/24 h in weekly increments of 2 mg/24 h. Ropinirole was administered at an initial dose of 0.75 mg/day. The dose was increased to 3.0 mg/day in weekly increments of 0.75 mg/day and then was increased to 15 mg/day in weekly increments of 1.5 mg/day. One level of back titration was allowed for rotigotine and ropinirole during the titration period. Dose increments for either drug could be stopped if the optimal dose or the maximally tolerated dose was reached, if adverse events resolved after back titration, or if the maximum dose level was attained. The maintenance dose of rotigotine and ropinirole was determined for each patient considering their efficacy and safety.

2.4. Efficacy measurement

The primary variable was the change in the UPDRS Part III (ON state) sum score from baseline to week 16 of the treatment period (end of treatment, EOT). Secondary variables included changes from baseline to EOT for the time spent in OFF, ON, and ON with troublesome dyskinesia and changes from baseline to EOT for the score in UPDRS Part II (ON), UPDRS Part II (OFF), UPDRS Part II (average ON and OFF state), sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III scores, and PD sleep scale-2 (PDSS-2) [19]. Additional secondary variables were the responder rate sum score (patients with a ≥20% or ≥30% reduction in the UPDRS Part III sum score) (ON state), and the responder rate in terms of the UPDRS Part II (average ON and OFF state) sum score. Patient diaries were utilized, in which each patient described his or her condition as off time, on time, on time with troublesome dyskinesia or sleep in every 30 min every day starting seven days prior to the initial drug administration to EOT. Examination of the patients was done at the ON state.

2.5. Safety

Safety was assessed in all randomized patients who received at least one dose of the test drugs. Safety variables were the frequency of the onset of adverse events, laboratory values, blood pressure/pulse rate, electrocardiogram parameters, skin irritation assessment score, physical and neurologic examination, and frequencies of compulsive disorder and impulse control disorder as assessed by the translated Jay Modified Minnesota Impulsive Disorder Interview [20]. Regurgitation of the cardiac valve and drug dependency were assessed separately by the specialist committees.

2.6. Sample size calculations

Based on the results of the late phase 2 trial of rotigotine in Japanese advanced PD patients on levodopa [12] and the Japanese clinical trial of ropinirole [17], we assumed effect sizes of 5.4 for the rotigotine and 5.0 for the ropinirole group and a standard deviation (SD) of 9.0 for each group. The sample size required to show superiority of rotigotine over placebo was calculated to be 88 and 44 patients for the rotigotine and placebo groups, respectively, with a two-tailed significance level of 5% and 90% power. The margin for non-inferiority of rotigotine to ropinirole was set to 2.5 based on the range of effect size in clinical trials of rotigotine and other non-ergot dopamine agonists [4,21,22]. The number of patients required to achieve 80% power and an upper limit of the 95% confidence interval (CI) for the difference between rotigotine and ropinirole being lower than the non-inferiority margin was 152 per group. Therefore, the target sample size was set as 160 patients each for the rotigotine and ropinirole groups and 80 patients for the placebo group.

2.7. Statistical analyses

The primary analysis of the primary variable was conducted using analysis of covariance (ANCOVA) with treatment group as a fixed factor. The different null hypotheses were tested in a pre-assigned order (closed testing principle). The test procedure started with a two-sided test between rotigotine and placebo with $\alpha = 5\%$. If the *P*-value was significant (i.e., rotigotine was superior to placebo), a non-inferiority test was conducted to compare rotigotine with ropinirole. Non-inferiority was accepted if the 95% CI for the difference between rotigotine and ropinirole was within the pre-defined non-inferiority margin of 2.5. For secondary analyses of the primary variable, ANCOVA was applied with treatment group as a fixed factor and the corresponding baseline value as a covariate. Changes from baseline to EOT in the secondary variables were assessed using ANCOVA. Responder rates were compared between each group using χ^2 tests. Safety variables were summarized using descriptive statistics and between-group comparisons were done using χ^2 tests.

3. Results

We obtained responses from 546 patients. However, 126 patients were not randomized; 36 from consent withdrawal, 59 not meeting the enrollment criteria, 31 from other reasons. Thus 420 patients were randomized (rotigotine 168, ropinirole 167, placebo 85). The full analysis set (FAS) included 414 patients because of three not meeting the enrollment criteria and three not having any valid post-baseline assessment of UPDRS Part III (ON state) sum score, and the safety set 420 patients including all randomized patients who received at least one dose of the test drugs (Fig. 1). The baseline characteristics of the 414 patients are shown in Table 1. There were no differences between groups, except for PDSS-2, which was higher in the placebo group than in the rotigotine and ropinirole groups ($p = 0.023$), and the patients receiving previous treatment with entacapone was higher in the ropinirole group than in the placebo and rotigotine groups ($p = 0.03$).

3.1. Treatment

After the start of the study, 26 patients in the rotigotine group, 23 in the ropinirole group and 17 in the placebo group discontinued the study. The most common reason for discontinuation was adverse events (AE) (13, 13, and 8 patients in the rotigotine, ropinirole, and placebo groups, respectively). None of these patients were seriously ill after the discontinuation of the test drugs.

Of the 420 patients in the safety analysis set, 381 (153, 153, and 75 patients in the rotigotine, ropinirole, and placebo groups, respectively) entered the dose maintenance period. Of these patients, 24.8% (38 patients), 28.8% (44 patients), and 41.3% (31 patients) in the rotigotine, ropinirole, and placebo groups, respectively, received dose increases up to the maximum maintenance dose. The mean maintenance doses were 12.9 mg/24 h and 9.2 mg/day in the rotigotine and ropinirole groups, respectively.

3.2. Efficacy variables

The change in the UPDRS Part III (ON state) sum score from baseline to EOT in the FAS was −10.9 ± 8.1, −9.5 ± 8.7, and −4.5 ± 9.7 (mean ± SD) in the rotigotine, ropinirole, and placebo groups, respectively. The difference between the rotigotine and the placebo group was −6.4 (95% CI: −8.7 to −4.1; $p < 0.001$), and that between the ropinirole and the placebo group was −5.1 (95% CI: −7.4 to −2.8; $p < 0.001$), showing superiority of rotigotine and ropinirole over placebo. The difference between the rotigotine and the ropinirole group was −1.4 (95% CI: −3.2 to 0.5, $p = 0.156$) showing the non-inferiority of rotigotine to ropinirole.

Regarding motor fluctuations (110/164 = 67.1% in the rotigotine,113/166 = 68.1% in the ropinirole, and 57/84 = 67.9% in the placebo group, no statistical difference), off period decrease was 1.4 h in the rotigotine, 1.9 h in the ropinirole, and 0.4 h in the placebo group. The differences between the rotigotine and the placebo and the ropinirole and the placebo group were significant ($p = 0.009$ and $p < 0.001$, respectively). The difference between the rotigotine and the ropinirole group was not significant ($P = 0.148$).

The comparisons between groups for other efficacy variables are shown in Table 2. The difference in the UPDRS Part II (average ON and OFF state) sum score between the rotigotine and the placebo group was −2.4 (95% CI: −3.3 to −1.5; $p < 0.001$) and that between the ropinirole and the placebo group was −1.8 (95% CI: −2.7 to −0.8; $p < 0.001$), while the difference between the rotigotine and the ropinirole group was −0.6 (95% CI: −1.4 to 0.1; $p = 0.106$). The difference in the UPDRS Part II (OFF state) sum score between the rotigotine and the placebo group was −2.4 (95% CI: −3.9 to −0.9; $p = 0.002$) and that between the ropinirole and the placebo group was −1.4 (95% CI: −2.9 to 0.0; $p = 0.058$), while the difference between the rotigotine and the ropinirole group was −1.0 (95% CI: −2.2 to 0.2; $p = 0.114$).

Significantly more patients in the rotigotine group were classified as responders for UPDRS Part III (ON state), UPDRS Part II (average ON and OFF state), and the sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III compared with the placebo group (Table 2). The ropinirole group also showed similar results compared with the placebo group. More patients in the rotigotine group were classified for 20% responder rate on UPDRS Part III (ON state), 30% responder rate on UPDRS Part II (average ON and OFF state), and 20% responder rate on the sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III compared to the ropinirole group.

3.3. Safety outcomes

Adverse events occurred in 88.7% (149/168 patients), 77.8% (130/167 patients), and 69.4% (59/85 patients) in the rotigotine, ropinirole, and placebo groups, respectively. Adverse events with an incidence of ≥3% are shown in Table 3. Most adverse events were mild to moderate in severity, and the proportion of patients with severe adverse events was similar in all three groups (8% in both rotigotine and placebo groups, and 7% in the ropinirole group). Only application site reaction was higher in the rotigotine than in the ropinirole and the placebo group (57.7%, 18.6% and 15.3%, respectively). All application site reactions were mild or moderate in intensity. Skin irritation was evaluated using a six-grade skin irritation assessment (−, ±, +, ++, +++, ++++). Only 2.4% of patients in the rotigotine group and none in the ropinirole and placebo groups had a score of +++ (concurrent erythema, edema and papule; serous papule; and vesicle) during the dose titration period. The proportion of patients in the rotigotine group with a score of +++ during the dose maintenance period was 0.7%. No patients had skin irritation with a score of ++++ (large blisters). Three subjects in the rotigotine group discontinued the trial from skin irritation.

Dyskinesias occurred in 16.1% (27/168), 13.8% (23/167), and 1.2% (1/85) of patients in the rotigotine, ropinirole and placebo groups, respectively. The difference between the rotigotine and the ropinirole group was not significant. Adverse events leading to treatment discontinuation occurred in 7.7% (13/168), 7.8% (13/167), and 9.4% (8/85) of patients in the rotigotine, ropinirole, and placebo groups, respectively. Sudden onset of sleep was observed in one patient each in the rotigotine and ropinirole groups. Neither case required treatment discontinuation or dose reduction.

Serious adverse events, which required hospitalization, occurred in seven patients in the rotigotine, five in the ropinirole, and six in the placebo group. Among them, serious adverse events related to the test drugs include gastric ulcer, torticollis, and spinal compression fracture and posture abnormality in three patients in the rotigotine group, worsening of PD in one in the ropinirole group, and angina pectoris and worsening of PD in the placebo group.

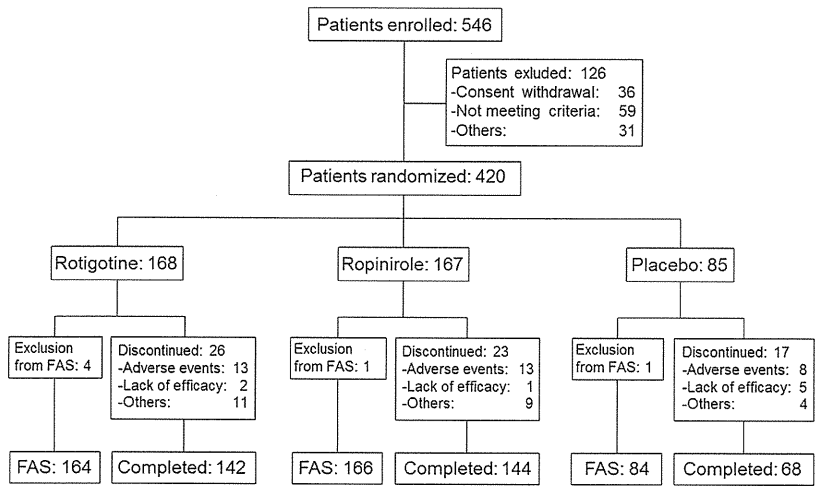

Fig. 1. Disposition of patients. The numbers indicate the number of patients in each category in FAS (full analysis set).

Table 1
Baseline patient characteristics (full analysis set, $n = 414$).

	Rotigotine ($n = 164$)	Ropinirole ($n = 166$)	Placebo ($n = 84$)	p-Value
Gender				
Male	61 (37.2%)	68 (41.0%)	42 (50.0%)	0.152[a]
Female	103 (62.8%)	98 (59.0%)	42 (50.0%)	
Age (years)	64.8 (8.8)	67.0 (7.9)	65.3 (7.9)	0.066[b]
Duration of PD (years)	7.0 (4.9)	6.8 (4.2)	7.0 (4.2)	0.880[b]
Wearing off	107 (65.2%)	110 (66.3%)	57 (67.9%)	0.918[a]
Dyskinesias	42 (25.6%)	43 (25.9%)	15 (17.9%)	0.319[a]
Levodopa dose (mg)	367.7 (151.9)	350.6 (125.3)	370.5 (146.6)	0.764[b]
Previous concomitant anti-Parkinson's medication				
Entacapone	40 (24.4%)	57 (34.3%)	33 (39.3%)	0.033[a]
Anticholinergic drugs	33 (20.1%)	32 (19.3%)	16 (19.0%)	0.973[a]
Amantadine	39 (23.8%)	40 (24.1%)	27 (32.1%)	0.306[a]
Selegiline	60 (36.6%)	69 (41.6%)	35 (41.7%)	0.594[a]
Droxidopa	12 (7.3%)	11 (6.6%)	8 (9.5%)	0.709[a]
Zonisamide	16 (9.8%)	13 (7.8%)	12 (14.3%)	0.271[a]
Hoehn & Yahr average	2.7 (0.6)	2.8 (0.6)	2.8 (0.6)	0.204[b]
UPDRS Part III (ON state)	25.8 (10.6)	25.8 (11.0)	25.6 (10.4)	0.970[b]
UPDRS Part II (average ON and OFF state)	11.0 (6.2)	10.6 (5.6)	11.1 (7.0)	0.978[b]
UPDRS Part II (ON state)	8.5 (5.9)	7.8 (5.7)	7.9 (6.7)	0.357[b]
UPDRS Part II (OFF state)	14.9 (8.4; $n = 110$)	15.3 (6.9; $n = 114$)	15.8 (9.4; $n = 58$)	0.562[b]
Sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III	36.9 (15.2)	36.4 (15.2)	36.7 (16.0)	0.909[b]
PDSS-2	12.3 (8.9)	14.3 (9.2)	15.0 (9.2)	0.023[b]
OFF time (hr)	4.5 (3.4; $n = 111$)	5.0 (3.6; $n = 113$)	4.9 (3.0; $n = 57$)	0.359[b]
ON time (hr)	13.1 (3.6)	12.5 (3.8)	12.6 (3.7)	0.375[b]
ON time with troublesome dyskinesias (hr)	2.4 (2.6; $n = 23$)	1.6 (1.5; $n = 16$)	0.7 (1.2; $n = 5$)	0.079[b]

Data are means (SD) or number (%).
UPDRS: unified Parkinson's disease rating scale; PDSS: Parkinson's disease sleep scale.
In this clinical trial, we defined FAS as follows; Those who were given the trial drugs at least once and at least one evaluation for the efficacy was made. However, those patients who violated GCP, those who do not fulfill the enrollment criteria, and those who meet the exclusion criteria are not included in the FAS. According to this criteria, three patients met the exclusion criteria, and in three patients there was no efficacy evaluation after enrollment to the study.
[a] χ^2 test.
[b] Kruskal–Wallis test.

QTc prolongation (>500 ms) in ECG was noted in two patients in the ropinirole group, but none in the rotigotine and placebo groups. The committee's assessment of results was of no clinically significant worsening of cardiac valve regurgitation in any patients. Non-significant difference was found regarding drug dependency. Impulse control disorder rates were non-significantly higher for ropinirole (6.6%) than rotigotine (3.5%), or placebo (3.5%).

Table 2
Efficacy variables at end of treatment (full analysis set, last observation carried forward).

	Change from baseline (least squares (LS) mean or %)			Comparison for rotigotine vs placebo		Comparison for rotigotine vs ropinirole	
	Rotigotine ($n = 164$)	Ropinirole ($n = 166$)	Placebo ($n = 84$)	Difference	p-Value (95% CI)	Difference	p-Value (95% CI)
Changes form baseline							
UPDRS Part III (ON state)	−10.9	−9.5	−4.5	−6.4	<0.001 (−8.6, −4.2)	−1.4	0.137 (−3.2, 0.4)
UPDRS Part II (average ON and OFF state)	−3.6	−3.0	−1.2	−2.4	<0.001 (−3.3, −1.5)	−0.6	0.106 (−1.4, 0.1)
UPDRS Part II (ON state)	−2.8	−2.3	−0.6	−2.2	<0.001 (−3.1, −1.3)	−0.5	0.201 (−1.2, 0.3)
UPDRS Part II (OFF state)	−4.9; $n = 109$	−3.9; $n = 111$	−2.4; $n = 57$	−2.4	0.002 (−3.9, −0.9)	−1.0	0.114 (−2.2, 0.2)
Sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III	−14.6	−12.5	−5.7	−8.8	<0.001 (−11.7, −6.0)	−2.0	0.091 (−4.4, 0.3)
PDSS-2	−3.7	−3.0	−1.1	−2.6	<0.001 (−4.1, −1.1)	−0.7	0.277 (−1.9, 0.6)
OFF time (hr)	−1.4; $n = 110$	−1.9; $n = 113$	−0.4; $n = 57$	−1.1	0.009 (−1.9, −0.3)	0.5	0.148 (−0.2, 1.2)
ON time (hr)	1.4	1.6	0.2	1.2	<0.001 (0.6, 1.8)	−0.2	0.426 (−0.7, 0.3)
ON time with troublesome dyskinesias (hr)	0.3; $n = 22$	0.2; $n = 16$	−1.2; $n = 5$	1.5	0.166 (−0.7, 3.7)	0.1	0.860 (−1.3, 1.5)
Responder analysis							
UPDRS Part III (ON state)							
20% responder	80.5	69.1	56.6	23.9	<0.001 (11.6, 36.1)	11.4	0.017 (2.1, 20.7)
30% responder	69.5	60.6	39.8	29.8	<0.001 (17.1, 42.4)	8.9	0.090 (−1.4, 19.2)
UPDRS Part II (average ON and OFF state)							
20% responder	65.2	56.7	47.0	18.2	0.006 (5.2, 31.2)	8.5	0.116 (−2.1, 19.1)
30% responder	55.9	43.3	28.9	27.0	<0.001 (14.6, 39.4)	12.6	0.023 (1.8, 23.4)
Sum of UPDRS Part II (average ON and OFF state) + UPDRS Part III							
20% responder	78.3	66.5	51.8	26.5	<0.001 (14.0, 38.9)	11.8	0.017 (2.2, 21.4)
30% responder	68.3	57.9	37.3	31.0	<0.001 (18.3, 43.6)	10.4	0.052 (−0.0, 20.8)

Change from baseline to EOT was assessed using analysis of covariance with baseline value as covariate.
Adjusted LS means were calculated. Inter-group comparisons for responder rate were performed using the χ^2 test.
UPDRS: Unified Parkinson's Disease Rating Scale; PDSS: Parkinson's disease sleep scale.

4. Discussion

We showed superiority of rotigotine and ropinirole to placebo and non-inferiority of rotigotine to ropinirole up to 15 mg/day for the primary efficacy variable (UPDRS Part III sum score) in this study. In addition, we showed reduction in off time in patients with motor fluctuations treated with rotigotine and ropinirole compared with placebo. There was no difference between rotigotine and ropinirole treatment.

As the maximum dose of ropinirole (15 mg/day) is lower in this study compared to those reported in the western literature (24 mg/day) [3,13–17], whether or not this difference might have resulted in non-inferiority of rotigotine to ropinirole should be discussed. First of all, 15 mg/day of ropinirole is the maximum approved dose in Japan. Although the maximum administered dose of ropinirole in this study was lower than those in the western literature, the magnitude of improvement as measured by UPDRS Part III sum score are similar between western and Japanese patients [13–17]. This may in part be due to the difference in the body weight. As none of the previous studies have addressed the question as to the dose–response relationship on ropinirole, we compared the average dose of ropinirole and efficacy in the previous studies. In the present study, average daily maintenance dose of ropinirole was 9.2 mg/day and the average motor UPDRS score decreased from 25.8 to 16.3 (9.5 points difference) after 16 weeks and off time decreased by 1.9 h (34% reduction) in the ropinirole group. In the study by Korczyn et al. the final dose of ropinirole was 12.0 mg at three years' treatment [14]. The motor UPDRS reduced from 23 to 14 at 24 weeks after the randomization. In the study by Rascol et al. the average daily dose of ropinirole was 16.5 mg and the UPDRS motor score decreased from 23 points to 14 points at 24 weeks [3]. In the study by Lieberman et al. [16], there was no description in the final average dose of ropinirole. Therefore, the magnitude of the motor UPDRS decrease is about the same in these studies. We wanted to compare the improvement in wearing off with different doses of ropinirole; however, this was difficult because the total number of patients who showed improvement in wearing off was not described [16].

Rotigotine is a patch formulation, which provides stable and continuous stimulation of dopamine receptors. Continuous dopaminergic drug delivery was thought to be an effective strategy for PD patients. Rotigotine was well tolerated, and there were no significant safety issues with doses up to 16 mg/24 h compared to ropinirole up to 15 mg/day except the high incidence of application site reactions in the rotigotine group, which may limit the use of rotigotine. In conclusion, once-daily administration of the rotigotine patch is a favorable option for the treatment of PD patients on levodopa.

Author contributions

YM: Coordinating investigator. Conception of study design; organization of the study; review and critique of the statistical analysis; writing of the first draft; review and critique of all drafts.

NH: Coordinating investigator. Conception of study design; organization of the study; execution of the study; review and critique of the statistical analysis; review and critique of all drafts.

TK: Coordinating investigator. Conception of study design; organization of the study; execution of the study; review and critique of the statistical analysis; review and critique of all drafts.

KH: Coordinating investigator. Conception of study design; organization of the study; execution of the study; review and critique of the statistical analysis; review and critique of all drafts.

MM: Coordinating investigator. Conception of study design; organization of the study; execution of the study; review and critique of the statistical analysis; review and critique of all drafts.

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M Takahashi: Conception of study design; organization of the study; execution of the study; review and critique of the statistical analysis.

TT: Design of the statistical analysis; execution of the statistical analysis; review and critique of the statistical analysis.

MN: Medical expert. Conception of study design; organization of the study; review and critique of the statistical analysis; writing of the first draft; review and critique of all drafts.

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YM is an advisory board member for Otsuka Pharmaceutical Co., Ltd. and has received personal compensation for attending advisory board meetings.

Table 3
Treatment-emergent adverse events occurring with an incidence of ≥3% in at least one group (safety analysis set). *n* (%).

	Number of patients (%)			*P* value	
	Rotigotine (n = 168)	Ropinirole (n = 167)	Placebo (n = 85)	Rotigotine vs placebo	Rotigotine vs ropinirole
Any adverse event	149 (88.7)	130 (77.8)	59 (69.4)	<0.001	0.008
Application site reactions[a]	97 (57.7)	31 (18.6)	13 (15.3)	<0.001	<0.001
Nasopharyngitis	28 (16.7)	24 (14.4)	13 (15.3)	0.78	0.562
Dyskinesia	27 (16.1)	23 (13.8)	1 (1.2)	<0.001	0.555
Nausea	25 (14.9)	23 (13.8)	7 (8.2)	0.133	0.772
Vomiting	11 (6.5)	11 (6.6)	2 (2.4)	0.153	0.988
Somnolence	11 (6.5)	9 (5.4)	2 (2.4)	0.153	0.655
Contusion	7 (4.2)	2 (1.2)	6 (7.1)	0.325	0.093
Orthostatic hypotension	5 (3.0)	7 (4.2)	4 (4.7)	0.483	0.549
Blood creatine kinase increased	5 (3.0)	6 (3.6)	1 (1.2)	0.374	0.752
Hallucination[b]	3 (1.8)	6 (3.6)	0	0.215	0.306
Back pain	3 (1.8)	5 (3)	2 (2.4)	0.759	0.469
Cystitis	3 (1.8)	3 (1.8)	4 (4.7)	0.181	0.994
Upper respiratory tract inflammation	3 (1.8)	1 (0.6)	3 (3.5)	0.389	0.317
Peripheral edema	0	2 (1.2)	3 (3.5)	0.014	0.155

Comparisons were made using the χ^2 test.
The safety set (420 patients) includes all randomized patients who received at least one dose of the test drugs and the safety evaluation is done.
[a] Corresponds to the MedDRA term "Application and instillation site reactions".
[b] Corresponds to the MedDRA terms "Hallucination", "Hallucination, visual", "Hallucination, auditory".

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YM was a Professor of Neuroregenerative Medicine at Kitasato University School of Medicine, a position donated by Nippon Boehringer Ingelheim Co., Ltd and Medtronic Japan Co., Ltd. YM was also an advisory board member for Nippon Boehringer Ingelheim Co., Ltd.. YM is an advisory board member for FP Pharmaceutical Corporation, Otsuka Pharmaceutical Co., Ltd., Abbott Japan Co., Ltd., and Kyowa Hakko Kirin Co., Ltd., and he has received personal compensation for attending advisory board meetings.

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ORIGINAL COMMUNICATION

Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial

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Abstract Rotigotine, a non-ergot dopamine receptor agonist, offers potential for continuous dopaminergic stimulation that could avoid the fluctuations observed with traditional treatments. We conducted a randomized, double-blind, placebo-controlled trial in Japanese patients with advanced Parkinson's disease (PD) to investigate the efficacy and safety of rotigotine. Inclusion criteria included the presence of motor complications, such as wearing off, on–off, delayed-on/no-on, any circumstances that could interfere with levodopa dose escalation because of side effects, or declining levodopa efficacy. The enrolled patients received once-daily applications of rotigotine transdermal patches or matched placebo patches. A total of 174 patients were randomly assigned to rotigotine (87 patients) or placebo (87 patients). The full analysis set included 172 patients (86 for the rotigotine group and 86 for the placebo group). The maximum maintenance dose of rotigotine was set at 16 mg/24 h. The changes in unified PD rating scale Part III scores from baseline to the end of the trial were -10.1 ± 9.0 (mean $\pm$ standard deviation) in the rotigotine group and -4.4 ± 7.4 in the placebo group ($p < 0.001$). There was a significantly greater reduction in the off-time ($p = 0.014$) in the rotigotine group. Rotigotine was well tolerated, with serious adverse events being reported in only three patients in each group. Rotigotine at doses of up to 16 mg/24 h is efficacious and safe in Japanese patients with advanced PD.

Keywords Rotigotine · Randomized controlled trial · Advanced Parkinson's disease · Wearing off · Dyskinesia

Introduction

Levodopa, a dopamine precursor that is converted to dopamine in the brain, has been the mainstay treatment for Parkinson's disease (PD) for over 40 years, and is still the

On behalf of the Rotigotine Trial Group. Members of the Rotigotine Trial Group are listed in Appendix.

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most effective treatment for the disease [1]. However, long-term treatment of PD patients with levodopa causes motor complications such as wearing off and dyskinesia [2–8]. Indeed, wearing off and dyskinesia were observed in 45 and 34 % of patients who were treated with levodopa for 5 years [5]. It has been suggested that the intermittent stimulation of dopamine receptors by levodopa, which is administered orally and has a short half-life, may play a role in the generation of the motor fluctuations seen in PD patients treated with the drug; therefore, continuous dopaminergic stimulation (CDS) is emerging as a key therapeutic strategy for the treatment of PD [9–12].

Rotigotine (Neupro®), a non-ergot dopamine receptor agonist with activity across the D1 to D5 receptors [13, 14], is a new formulation that ensures continuous dopaminergic stimulation for the treatment of PD [15]. It is a silicone-based once-daily transdermal patch that maintains a stable plasma rotigotine level over a period of 24 h [16–18]. Approximately 44 % of the rotigotine delivered via transdermal patch is systemically available, and systemically absorbed rotigotine is metabolized rapidly [16].

It has been reported that rotigotine (delivered at up to 16 mg/24 h) and pramipexole (up to 4.5 mg/day orally) both reduced off-time compared with placebo [19]. In another randomized, double-blind, placebo-controlled trial, the patients given rotigotine (delivered at up to 12 mg/24 h) experienced significant decreases in off-time [20].

The present randomized, double-blind, placebo-controlled, two-arm parallel group trial was performed to determine the safety and efficacy of rotigotine transdermal patches delivering up to 16 mg of rotigotine per day in patients with advanced-stage PD. Since wearing off is not observed in all patients with advanced PD, we sought to examine the effects of rotigotine at doses of up to 16 mg/24 h in combination with levodopa on changes in the unified PD rating scale (UPDRS) Part III scores as the primary variable.

Patients and methods

The present trial was a randomized, double-blind, placebo-controlled, two-arm parallel group trial. The trial was registered at Clinicaltrials.gov (identifier: NCT01628848), and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Patients

The trial was approved by the institutional review boards of the 38 centers where the trial was conducted. Informed consent was obtained from all patients before enrollment. Two-hundred and fourteen patients with advanced PD, aged 30–79 years, and with Hoehn and Yahr stage II–IV and a UPDRS Part III sum score of ≥10 ("on" period), were enrolled. Patients had to have received a stable levodopa dose for ≥28 days before starting the trial, and had to show problematic motor complications such as wearing off, on–off phenomenon, or delayed-on/no-on circumstances that could interfere with levodopa dose escalation because of side effects, or declining levodopa efficacy. Subjects were considered to have been on the optimal L-dopa treatment when they were enrolled in the study, even though the dose of L-dopa was low in many of them.

Patients were excluded if they had met any of the following criteria: previous surgery for PD; psychiatric symptoms (for example, confusion, hallucination, delusion, excitation, delirium, and abnormal behavior); orthostatic hypotension; a history of epilepsy or convulsion; clinically relevant hepatic, renal or cardiac disorders; a prolonged QTc interval (QTc interval >450 ms twice during screening or a mean QTc interval of two electrocardiograms of >450 ms in males or >470 ms in females at baseline); a history of skin sensitivity to adhesives or other transdermal medications; or if they were pregnant, nursing, or a woman of child-bearing potential. Patients who had previously received other dopamine agonists or neuroleptics were also excluded. Anti-PD agents such as levodopa, selegiline, amantadine, and anti-cholinergic agents were permitted if the patients were on a stable dose for >28 days before baseline and providing the dose was maintained throughout the trial period.

Trial design

The trial consisted of a 4-week screening period, a maximum 8-week dose-titration period, a 4-week maintenance period, a 2-week tapering period, and a 1-week safety follow-up period. Eligible patients were randomly assigned to receive rotigotine or placebo in a 1:1 ratio using a dynamic allocation procedure designed to balance the distribution of UPDRS Part III sum scores and the off-time between the groups. Subjects received either once-daily rotigotine or placebo transdermal patch. Patients were instructed to rotate the application site (abdomen, thigh, hip, flank, shoulder, upper arm) on a daily basis to minimize application site reactions. The starting rotigotine was 2 mg/24 h. The dose was increased with a weekly increment of 2 mg/24 h to a maximum of 16 mg/24 h during the dose-titration period. If the drug was not tolerated, dose adjustment was allowed. However, further dose adjustment was not permitted after the end of the dose-titration period. The subjects, investigators and all trial personnel remained blinded to the treatments throughout the trial period.

Outcome variables

The primary efficacy variable was the absolute change in UPDRS Part III sum score from baseline to the end of treatment (EOT). Secondary variables included the absolute changes in off-time, UPDRS Part II (average ON and OFF state) sum score, UPDRS Part II (ON state) sum score, UPDRS Part II (OFF state) sum score, and the Hoehn and Yahr scale.

The 20 and 30 % responder rates (defined as the percentage of subjects who achieved ≥20 and ≥30 % reductions in UPDRS Part III scores from baseline to EOT, respectively) were calculated based on patient diaries. In a subgroup analysis, the changes from baseline to EOT in the UPDRS Part III and Part II (average ON and OFF state) scores and the off-time were assessed for their possible associations with age, baseline UPDRS sum score, and Hoehn and Yahr stage.

Safety and tolerability were assessed based on adverse events and changes in vital signs, body weight, electrocardiogram findings, and laboratory parameters.

Statistical methods

The sample size in the present trial was selected based on the hypothesis that rotigotine treatment would improve UPDRS Part III scores better than placebo. Assuming a difference in the change in the UPDRS Part III score from baseline between the two groups of 5 and a standard deviation of 11, 85 patients in each treatment group was considered sufficient to detect a significant difference between the two groups with a power of >80 %. For the primary efficacy analysis, Student's t test with a two-sided type 1 error rate of 5 % was used to compare the changes in UPDRS Part III scores from baseline to EOT between the placebo and rotigotine groups. The responder rates were compared between the two groups using two-sided χ^2 tests. For secondary variables, the groups were compared using the Kruskal–Wallis test for continuous variables or χ^2 tests for categorical variables [21]. Efficacy variables were evaluated using the full analysis set (FAS), which was defined as all randomized patients who received at least one dose of trial medication. If there were any missing values, the last observation was carried forward. All randomized patients were included in the safety analysis set (SAS).

Results

Trial subjects

The trial was conducted between August 2006 and September 2007. Figure 1 shows the patient disposition and flow through the trial. A total of 214 patients were enrolled and 174 were randomly assigned to rotigotine or placebo groups. The FAS comprised 172 patients after exclusion of two patients; one who fulfilled an exclusion criterion and another who had deviated from the trial protocol (Fig. 1).

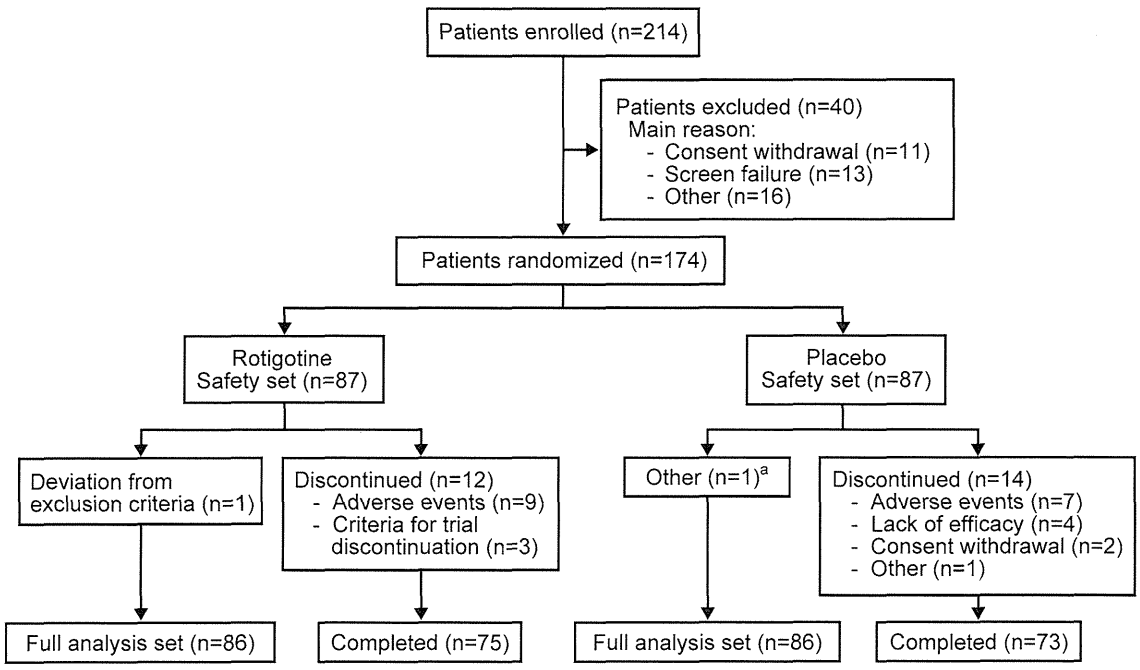

Fig. 1 Patient disposition and flow of patients through the trial. [a]The subject was excluded from the full analysis set and discontinued the trial because of a significant protocol deviation (accidental prolactin measurement in week 2)

Table 1 Baseline characteristics according to treatment group (full analysis set)

	Rotigotine ($n = 86$)	Placebo ($n = 86$)	p value[a]
Sex			
Male	34 (39.5 %)	44 (51.2 %)	0.126[c]
Female	52 (60.5 %)	42 (48.8 %)	
Age (years)	67.0 (6.8)	66.8 (8.3)	0.658[d]
Duration of PD (years)	7.5 (6.0)	5.4 (3.0)	0.037[d]
Hoehn and Yahr stage			
2	11 (12.8 %)	22 (25.6 %)	0.200[c]
2.5	22 (25.6 %)	20 (23.3 %)	
3	45 (52.3 %)	38 (44.2 %)	
4	8 (9.3 %)	6 (7.0 %)	
UPDRS Part II (average ON and OFF state) sum score	11.8 (6.1)	10.3 (4.6)	0.132[d]
UPDRS Part II (ON state) sum score	8.8 (5.6)	8.1 (4.8)	0.322[d]
UPDRS Part II (OFF state) sum score	16.9 (9.3) ($n = 55$)	14.0 (5.7) ($n = 59$)	0.193[d]
UPDRS Part III sum score	28.1 (12.2)	26.2 (10.4)	0.365[d]
Daily off-time (h)	6.6 (3.5)[b] ($n = 54$)	6.0 (3.4)[b] ($n = 57$)	0.383[d]
>0	56 (65.1 %)	59 (68.6 %)	0.627[c]
0	30 (34.9 %)	27 (31.4 %)	
Levodopa (mg/day)	348.8 (170.3)	329.1 (132.5)	0.756[d]
Concomitant medications			
Anticholinergics	19 (22.1 %)	11 (12.8 %)	0.108[c]
Amantadine	36 (41.9 %)	31 (36.0 %)	0.434[c]
Selegiline	42 (48.8 %)	41 (47.7 %)	0.879[c]

Data are means (SD) or number (%)

PD Parkinson's disease, *UPDRS* Unified Parkinson's Disease Rating Scale

[a] Rotigotine versus placebo

[b] Average for 7 days prior to baseline

[c] Chi-square test

[d] Wilcoxon two-sample test

There were no significant differences in baseline demographics or clinical variables between the treatment groups (Table 1). At the end of the dose-titration period, 50.6 % of the rotigotine group entering the maintenance period had reached the maximum dose of 16 mg/24 h.

Efficacy

The change in UPDRS Part III score from baseline to EOT was significantly greater in the rotigotine group than in the placebo group ($p < 0.001$). Patients treated with rotigotine showed a mean reduction in UPDRS Part III score of 10.1 points, while those in the placebo group showed a mean reduction of 4.4 points (Table 2). The mean difference (rotigotine − placebo) between the two groups for the change in UPDRS Part III score was −5.7 [95 % confidence interval (CI) −8.2 to −3.2]. Significantly more patients in the rotigotine group were classified as responders, with improvements in UPDRS Part III scores of ≥20 % (73.3 vs. 43.0 %) or ≥30 % (64.0 vs. 29.1 %) compared with the placebo group, corresponding to mean differences (rotigotine − placebo) of 30.2 % (95 % CI 16.2–44.3 %, $p < 0.001$) and 34.9 % (95 % CI 20.9–48.9 %, $p < 0.001$), respectively.

In terms of other secondary variables, the between-group differences for the changes in UPDRS Part II (average ON and OFF state) score, UPDRS Part II (OFF state) score, and off-time were −2.2 (95 % CI −3.1 to −1.2, $p < 0.001$), −2.6 (95 % CI −4.2 to −1.1, $p < 0.001$) and −1.4 (95 % CI −2.5 to −0.3, $p = 0.014$), respectively.

In subgroup analyses, the differences in the change in UPDRS Part III scores from baseline to EOT between the rotigotine and placebo groups were −1.7 and −7.3 in subjects with baseline scores of <20 and ≥20. The between-group differences in the changes in UPDRS Part II (average ON and OFF state) scores were −0.5 and −3.3 in subjects with baseline scores of <10 and ≥10. The between-group differences in the changes in off-time were

Table 2 Changes in outcomes from baseline to the end of the maintenance period (full analysis set with last observation carried forward)

	Rotigotine[a]	Placebo[b]	Treatment comparison (rotigotine − placebo)		
	Mean (SD)	Mean (SD)	Mean (SE)	95 % CI	*p* value
UPDRS Part III (change from baseline values)	−10.1 (9.0)	−4.4 (7.4)	−5.7 (1.3)	−8.2, −3.2	<0.001[c]
UPDRS Part III					
20 % responder rate[e]	73.3 %	43.0 %	30.2 %	16.2 %, 44.3 %	<0.001[d]
30 % responder rate[e]	64.0 %	29.1 %	34.9 %	20.9 %, 48.9 %	<0.001[d]
UPDRS Part II (average ON and OFF state) (change from baseline)	−3.8 (3.6)	−1.6 (2.6)	−2.2 (0.5)	−3.1, −1.2	<0.001[c]
UPDRS Part II (ON state) (change from baseline)	−3.0 (3.7)	−1.2 (2.6)	−1.9 (0.5)	−2.8, −0.9	<0.001[c]
UPDRS Part II (OFF state) (change from baseline)[f]	−4.6 (4.5)	−1.9 (3.6)	−2.6 (0.8)	−4.2, −1.1	0.001[c]
Off-time (change from baseline)[f]	−2.1 (3.1)	−0.7 (2.8)	−1.4 (0.6)	−2.5, −0.3	0.014[c]

CI confidence interval

[a] $n = 86$ for UPDRS Parts III and II (ON state); $n = 82$ for UPDRS Part II (average ON and OFF state); $n = 51$ for UPDRS Part II (OFF state); $n = 54$ for off-time

[b] $n = 86$ for UPDRS Parts III and II (average ON and OFF state) and II (ON state); $n = 57$ for UPDRS Part II (OFF state); $n = 56$ for off-time

[c] *t* test

[d] Chi-square test

[e] 20 and 30 % responder rates were defined as the percentages of subjects who achieved ≥20 and ≥30 % reductions in UPDRS Part III scores from baseline to EOT

[f] UPDRS Part II (OFF state) and off-time are shown for patients in whom "off" time was observed

−2.3, −0.5, −2.2 and −1.4 in subjects with baseline time of ≤1, 1–2, 2–3, and >3 h, respectively. In subjects stratified by baseline Hoehn and Yahr scores of 2, 2.5, 3, and 4, the between-group differences were as follows: −3.8, −4.8, −6.2 and −7.2, respectively, for the change in UPDRS Part III sum scores; −1.3, −0.9, −2.5, and −4.9, respectively, for the change in UPDRS Part II (average ON and OFF state); and 0.0, −1.8, −1.4, and −0.9, respectively, for change in off-time.

Safety

Overall, 94.3 % (82/87) of the subjects in the rotigotine group and 88.5 % (77/87) of the subjects in the placebo group reported at least one adverse event (AE) during the treatment period. A summary of the treatment-emergent AEs with an incidence of ≥5 % in either group is shown in Table 3.

The most common treatment-emergent AEs that occurred more frequently in the rotigotine group than in the placebo group were application site reactions (50.6 vs. 18.4 %), nausea (19.5 vs. 5.7 %), somnolence (13.8 vs. 1.1 %), constipation (10.3 vs. 1.1 %), vomiting (10.3 vs. 1.1 %), postural dizziness (8.0 vs. 1.1 %), and anorexia (6.9 vs. 0.0 %). All application site reactions were mild or moderate in intensity.

AEs that led to discontinuation were reported by 12.6 % of the rotigotine-treated patients and 8.0 % of the placebo-

Table 3 Treatment-emergent adverse events with an incidence of ≥5 % in any group

Adverse event by preferred term	Rotigotine ($n = 87$)			Placebo ($n = 87$)		
	n[a]	%[a]	AEs[b]	n[a]	%[a]	AEs[b]
Any system organ class	82	94.3	333	77	88.5	194
Nausea	17	19.5	17	5	5.7	8
Constipation	9	10.3	9	1	1.1	1
Vomiting	9	10.3	10	1	1.1	1
Application site reaction	44	50.6	46	16	18.4	21
Application site erythema	8	9.2	14	4	4.6	5
Application site pruritus	5	5.7	5	4	4.6	4
Nasopharyngitis	18	20.7	20	13	14.9	19
Fall	6	6.9	6	7	8.0	7
Bruise	5	5.7	5	3	3.4	4
Increased blood creatine phosphokinase	7	8.0	7	3	3.4	3
Anorexia	6	6.9	6	0	0	0
Dyskinesia	12	13.8	13	7	8.0	7
Dizziness	7	8.0	8	2	2.3	2
Postural dizziness	7	8.0	7	1	1.1	2
Headache	5	5.7	5	2	2.3	2
Somnolence	12	13.8	12	1	1.1	1
Hallucination, visual	8	9.2	10	2	2.3	2

[a] Number of subjects reporting at least one adverse event

[b] Number of individual adverse events occurring among the subjects in that group

treated patients. Six serious AEs (anemia, malaise, increased blood creatine phosphokinase, neuroleptic malignant syndrome, delusion, and auditory hallucination) occurred in three patients in the rotigotine group. A causal relationship to the trial medication was ruled out for all of the events, except for anemia. Four serious AEs (inguinal hernia, gastroenteritis, bacterial arthritis, and loss of consciousness) occurred in three patients in the placebo group and a causal relationship to the trial medication was not ruled out for any event, except for loss of consciousness. These AEs occurred across multiple body systems with no obvious trends. No deaths occurred in this trial.

No subject in the rotigotine group had a QTc interval $\geq$500 ms or a change from baseline QTc interval of $\geq$60 ms. Rotigotine had no clinically significant effect on QTc interval.

Discussion

In the 172 subjects in the FAS (86 subjects treated with rotigotine and 86 subjects treated with placebo), rotigotine significantly reduced UPDRS Part III scores compared with placebo, demonstrating superiority of rotigotine over placebo ($p < 0.001$). Rotigotine also reduced UPDRS Part II (average ON and OFF state) sum scores and the off-time between baseline and EOT. The reduction in UPDRS Part II off-state was particularly noteworthy, and suggests that rotigotine may be effective throughout the day by improving symptoms in the off-state, as well as the on-state. Although dyskinesia was more common in the rotigotine group, the risk/benefit profile of rotigotine, particularly the improvement in off-state, may outweigh the problems. Taken together, the results of the present trial show that rotigotine improves motor functions, activities of daily living, and off-time in advanced PD patients treated with levodopa, and that continuous dopaminergic stimulation with rotigotine is an important treatment option for advanced PD.

In an earlier phase III trial performed in the United States (CLEOPATRA-PD trial), the mean difference between rotigotine (with doses of up to 16 mg/24 h) and placebo for the change in UPDRS Part III scores from baseline to EOT was −4.4 [19]. In a phase III trial conducted in Europe (PREFER trial), the between-group differences were −3.4 and −5.3, when rotigotine was administered at doses of up to 8 mg/24 h and 12 mg/24 h, respectively [20]. In the present trial, the between-group difference was −5.7, with rotigotine administered at doses of up to 16 mg/24 h. The mean reductions in off-time were −1.58 h in the CLEOPATRA-PD trial, −1.8 (8 mg/24 h) and −1.2 (12 mg/24 h) h in the PREFER trial, and −1.4 h in the present trial. From this comparison, the improvement in UPDRS Part III was greater in the present trial compared with the trials in the United States and Europe, while the reduction in off-time was similar in all three trials.

It is worth noting that the administered doses of concomitant medications differed in each trial [19, 20]. The mean administered doses of levodopa in the phase III trials conducted in Europe and the United States ranged from 600 to 700 mg [19, 20], while that in the present trial was 380 mg. Monoamine oxidase-B inhibitors were used in 10–20 % of patients in the trials performed in Europe and the United States, compared with 50 % of patients in the present trial. When the present trial was conducted, marketing authorization for the catechol *O*-methyltransferase inhibitor entacapone had not been granted in Japan; therefore, this drug was not used by any of the patients in the present trial.

The International Conference on Harmonization E14 guidelines require a thorough QT/QTc study for all new drugs, including at supratherapeutic doses—doses well above the maximum clinically expected dose [22]. Therefore, Malik et al. performed a thorough assessment of QT/QTc in patients with advanced PD treated with rotigotine. They found that application of supratherapeutic doses of up to 24 mg/24 h did not affect the QTc interval, indicating that rotigotine did not adversely affect cardiac repolarization in patients with a QTc >500 ms. Furthermore, they found that rotigotine did not cause any change in QTc of >60 ms from baseline [17]. Thus, rotigotine is well tolerated and safe at doses up to 16 mg/24 h.

Conclusion

In Japanese patients with advanced PD, rotigotine improved activities of daily living and motor symptoms, and greatly reduced both off-time and UPDRS Part II score (OFF state) compared with placebo. The rotigotine transdermal patch was efficacious and safe with once-daily application within a dose range of 4–16 mg/24 h in this trial. No significant safety issues were observed with doses of up to 16 mg/24 h.

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Conflicts of interest YM is a Professor of Neuroregenerative Medicine, a position donated by Nippon Boehringer Ingelheim Co., Ltd. and Medtronic Japan Co., Ltd., at Kitasato University School of Medicine. YM is also an advisory board member for Nippon Boehringer Ingelheim Co., Ltd., FP Pharmaceutical Corporation, Otsuka Pharmaceutical Co., Ltd., Abbott Japan Co., Ltd., and Kyowa Hakko Kirin Co., Ltd., and he received personal compensation for attending advisory board meetings. MN received speaker's honoraria from Dainippon Sumitomo Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., and Otsuka Pharmaceutical Co., Ltd. TK received honoraria, support for travel to meetings, and fees for participation in review activities

from FP Pharmaceutical Corporation, Novartis Pharma K.K., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Otsuka Pharmaceutical Co., Ltd. KH received personal compensation for attending advisory board meetings from Otsuka Pharmaceutical Co., Ltd. MM received honoraria for consulting and/or lecturing from GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Novartis Pharma K.K., and Otsuka Pharmaceutical Co., Ltd. MT received honoraria for consulting from Otsuka Pharmaceutical Co., GlaxoSmithKline K.K., and UCB Japan Co. Ltd. NH is an advisory board member for Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Kyowa Hakko Kirin Co., Ltd., and MSD K.K., and has received honoraria from Nippon Boehringer Ingelheim Co., Ltd., GlaxoSmithKline K.K., Novartis Pharma K.K., FP Pharmaceutical Corporation, Takeda Pharmaceutical Company Limited., Janssen Pharmaceutical K.K., Daiichi Sankyo Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Dainippon Sumitomo Pharma Co., Ltd. JI and TT are employees of Otsuka Pharmaceutical Co., Ltd.

Appendix: Members of the SPM 962 Rotigotine Trial Group

The authors wish to thank the following additional members of the SPM 962 Rotigotine Trial Group, who participated in this trial as investigators: Takashi Kimura, Hidenao Sasaki, Mikio Shoji, Takashi Abe, Atsushi Takeda, Itaru Toyoshima, Kazuo Yoshizawa, Toshiaki Kamitani, Kimihito Arai, Shigeki Tanaka, Sadako Kuno, Fusako Yokochi, Hiroshi Kurisaki, Noriko Kawashima, Shinji Ohara, Kouichi Mizoguchi, Toshihiko Ohashi, Tetsushi Atsumi, Akira Inukai, Tatsuya Hattori, Hideyuki Sawada, Harutoshi Fujimura, Nobuyoshi Yoshikawa, Sonoko Nozaki, Mitsutoshi Yamamoto, Hiroaki Miyaoka, Masahiro Nagai, Noriko Nishikawa, Tatsuo Yamada, Naokazu Sasagasako, Takayuki Kondo, Shigehiro Imamura, Yoshito Sonoda, Satoshi Takahashi, and Hitoshi Yamada.

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Hyposmia and cardiovascular dysautonomia correlatively appear in early-stage Parkinson's disease

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ABSTRACT

Objective: Olfactory dysfunction is considered to precede motor symptoms and early markers of Parkinson's disease (PD), while the relative time at which cardiovascular dysautonomia appears in PD is not well understood. To assess the appearance of cardiovascular dysautonomia in PD, we evaluated its relation to olfactory dysfunction in early-stage PD patients.
Methods: Twenty-three non-demented PD patients within 2 years from the onset of motor symptoms were enrolled. We evaluated olfactory dysfunction by the Odor Stick Identification Test for Japanese (OSIT-J) and analyzed its relationship to the results of other cardiovascular autonomic tests and cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy.
Results: There was a correlation between olfactory scores and increased blood pressure in both the norepinephrine ($r = 0.75$, $p < 0.0001$, $n = 21$) and dobutamine ($r = 0.57$, $p = 0.0087$, $n = 20$) infusion tests and cardiac MIBG uptake ($r = 0.42$, $p = 0.049$, $n = 23$). The fall in orthostatic blood pressure during the head-up tilt test was not correlated with the olfactory scores, but the Valsalva maneuver revealed that OSIT-J scores correlated with the pressure recovery time from phase III to the return of blood pressure to baseline ($r = 0.54$, $p = 0.037$, $n = 15$) and with the magnitude of blood pressure overshoot during phase IV ($r = 0.67$, $p = 0.0016$, $n = 20$).
Conclusion: Our results demonstrate that extensive components of the cardiovascular sympathetic system as well as the olfactory system are correlatively impaired in the early stage of PD, suggesting that degeneration of broad aspects of the cardiovascular sympathetic system occurs concurrently with olfactory system degeneration during the premotor phase of PD.

1. Introduction

Previous reports showed a correlation between olfactory dysfunction and cardiovascular dysautonomia, particularly of the cardiac sympathetic system, in Parkinson's disease (PD) patients [1,2], but the subjects of these studies included advanced-stage PD patients. Impaired olfaction, or hyposmia, is one of the representative non-motor symptoms in PD patients, and exists from the prodromal stage when motor symptoms have not yet appeared [3]. It was also reported that decreased cardiac ^{123}I-metaiodobenzylguanidine (MIBG) uptake is observed in early-stage PD patients [4]. Degeneration of the cardiac sympathetic system in the early stage of PD is also confirmed from a pathological viewpoint [5]; however, it remains unclear how early the cardiovascular dysautonomia appears and how closely it relates to olfactory impairment in PD patients. To clarify these obscure points, we assessed cardiovascular dysautonomia and its relation to olfactory dysfunction in early-stage PD patients.

2. Methods

2.1. Subjects

A total of 107 PD patients who met the diagnostic criteria of the UK Parkinson's Disease Society Brain Bank [6] underwent cardiovascular autonomic tests at Nagoya University Hospital between March 2009 and March 2013. Individuals who had diabetes mellitus, any known heart disease, dementia (MMSE score of less than 24),

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and any diseases other than PD showing parkinsonism or dysautonomia were excluded. No patient had abnormal findings on magnetic resonance imaging (MRI), such as brainstem or cerebellar atrophy, striatal atrophy, or abnormal intensity, suggesting multiple system atrophy [7]. After excluding patients who had nose disease and those whose disease duration were more than 2 years from the onset of motor symptoms, 23 patients with early-stage PD were recruited into the study. Disease duration was calculated based on the time when the PD patients were aware of motor symptoms (not the time of diagnosis). This study was approved by the ethical committee at Nagoya University Graduate School of Medicine, and all subjects provided informed written consent before participation.

2.2. Odor Stick Identification Test for Japanese (OSIT-J)

The OSIT-J included 12 odorants familiar to Japanese subjects: India ink, wood, perfume, menthol, Japanese orange, curry, cooking gas, rose, Japanese cypress (hinoki), sweaty-smelling clothes, condensed milk, and roasted garlic [8]. Test odorants were microencapsulated in a melamine resin and contained within an odorless solid cream that was dispensed in a lipstick container. The examiner painted each odor stick in a 2-cm circle on a thin paraffin paper, folded the paraffin paper in half, rubbed the paper to grind the microcapsules, and then passed it to the subject. Subjects received the paper, opened it in front of their nose, and sniffed it. Next, they chose 1 of 6 possible answers: 4 odor names, 1 of which was correct, and 2 others ('unknown' and 'not detected'). The total number of correct answers for the 12 odorants was defined as the OSIT-J score. Maximum OSIT-J score is 12 points (normal = 8–12 points) [9]. The validity of utilizing OSIT-J to assess olfactory dysfunction has been reported several times in our country, and it is also widely used for evaluation in PD patients [1,8].

2.3. Cardiovascular autonomic function tests

All participants abstained from food in the morning, and any drugs that might influence the cardiovascular system, including anti-parkinsonian drugs, were discontinued at least 12 h before testing. Four participants had taken antihypertensive medication (beta-blocker = 1, angiotensin receptor blocker = 2, and angiotensin converting enzyme inhibitor = 1), that were discontinued only 24 h before testing for safety reasons. Tests were conducted successively in the morning. For analysis of the coefficient of variation of R–R intervals (CVR-R), 100 successive electrocardiogram R–R intervals were sampled during the recording period (FDX-4521, Fukuda, Tokyo, Japan). The CVR-R was automatically calculated as a percentage of the standard deviation of the R–R intervals divided by their mean. After a bed rest of 5 min, an electrocardiogram recording in the supine position with normal breathing was collected. Next, we undertook the same recording with slow, deep breathing at a frequency of 6 times per minute to observe a maximal CVR-R response. Then, we performed the Valsalva maneuver by having the subjects exhale into a mouthpiece at an expiratory pressure of 40 mmHg for 15 s. We checked the fluctuation of blood pressure and heart rate, judged whether the patients exhibited phase I–IV responses, and calculated the pressure recovery time from phase III to the return of blood pressure to baseline and the magnitude of blood pressure overshoot during phase IV. Next, we administered the head-up tilt table test. After resting for at least 5 min in a supine position, patients were tilted up to 60° in a stepwise manner (20°, 40°, and 60° for 5 min each) [10–12], and changes in systolic blood pressure at 60° compared with the initial value in the supine position were determined. We diagnosed orthostatic hypotension when patients showed a reduction in systolic blood pressure of at least 20 mmHg in the 60° position [13]. Then, to assess denervation supersensitivity to norepinephrine [12], a dilute norepinephrine solution (1 μg/mL) was administered intravenously for 3 min at a rate of 3 μg/min, and exaggerated systolic blood pressure pressor responses, representing peripheral denervation, were collected. After the patients rested again for at least 10 min, dobutamine (4 μg/kg/min; 0.5 mL/min) was administered for 5 min by continuous intravenous infusion via a brachial venous cannula using a constant infusion pump. The average values for blood pressure during the last 3 min of infusion were compared with the initial value. Pressor responses to dobutamine can detect cardiac beta1-sympathetic denervation supersensitivity at low doses [11]. We previously reported that PD patients demonstrated an excessive pressor response compared with normal controls in the dobutamine infusion test, and that this response was correlated with reduced cardiac MIBG uptake [11]. During testing, continuous noninvasive cardiovascular monitoring was performed using the Task Force Monitor (CNSystems Medizintechnik AG, Austria). A six-channel electrocardiogram was recorded continuously using four spot electrodes. Beat-to-beat blood pressure measurements were obtained by finger plethysmography of the index finger on the right hand, and continuously corrected to blood pressure in the brachial artery of the left arm, obtained by the oscillometric technique.

2.4. Cardiac-MIBG scintigraphy

Cardiac-MIBG scintigraphy was performed on another day within 2 weeks of the above autonomic function test. MIBG (111 mBq) was injected intravenously. Early images were obtained 15 min after the injection, and delayed images were obtained after 3 h. Myocardial MIBG uptake was measured using the heart-to-mediastinal uptake ratio (H/M). None of our patients had taken drugs known to affect MIBG uptake (e.g., tricyclic antidepressants, Ca^{++} blockers, or selegiline).

2.5. Statistical analyses

JMP software, version 7 (SAS Institute, Cary, North Carolina) was used for statistical analyses. Significant differences were defined at $p < 0.05$. Correlations of the OSIT-J scores with the results of cardiovascular autonomic function tests, cardiac MIBG uptake, and clinical ratings were assessed with the Spearman's rank correlation test. Values were expressed as mean ± SD (standard deviation).

3. Results

3.1. OSIT-J scores and clinical features

The OSIT-J scores and clinical features of the patients are summarized in Table 1. The average OSIT-J score was 4.7 ± 2.4 (range, 0–8). The average modified Hoehn–Yahr scale, UPDRS motor score, and MMSE score were compatible with previous reports evaluating early-stage PD patients [14,15]; thus, the subjects in our study seemed to be an average group of early-stage PD patients within two years from motor symptom onset.

3.2. Association with cardiovascular dysautonomia

The OSIT-J scores were significantly correlated with increases in blood pressure in the norepinephrine ($r = 0.75$, $p < 0.0001$, $n = 21$) and dobutamine ($r = 0.57$, $p = 0.0087$, $n = 20$) infusion tests and with cardiac MIBG uptake expressed by the H/M ratio ($r = 0.42$, $p = 0.049$, $n = 23$) (Fig. 1).

Orthostatic hypotension was observed in only one patient, who had an OSIT-J score of 1. But, OSIT-J scores were not correlated with the fall in systolic blood pressure during head-up tilt test ($p = 0.60$). There was also no correlation between OSIT-J scores and CVR-R recorded with normal breathing ($p = 0.36$, $n = 20$). The CVR-R response recorded with slow, deep breaths was performed in 15 participants. Although not significant, there was a tendency for the OSIT-J scores to be correlated with the maximal CVR-R response recorded with slow, deep breaths ($r = 0.43$, $p = 0.11$, $n = 15$) (Fig. 2).

Three patients did not undergo the Valsalva maneuver because they were unable to exhale up to 40 mmHg pressure. The remaining 20 patients all showed blood pressure decreases as a phase II response and 13 of them showed a phase IV response of blood pressure increase. The OSIT-J scores were significantly correlated with the pressure recovery time from phase III to the return of blood pressure to baseline ($r = 0.54$, $p = 0.037$, $n = 15$) and the magnitude of blood pressure overshoot during phase IV ($r = 0.67$, $p = 0.0016$, $n = 20$) (Fig. 3). On the other hand, no correlations were found between OSIT-J scores and modified Hoehn–Yahr scores ($r = 0.042$, $p = 0.85$, $n = 23$), UPDRS motor scores ($r = 0.18$, $p = 0.41$, $n = 23$), or the MMSE scores ($r = 0.023$, $p = 0.93$, $n = 19$).

Table 1
Clinical characteristics of the patients.

Characteristic	Value
Number of patients	$N = 23$
Age, mean ± SD (range) (years)	62.1 ± 8.3 (44–73)
Male/female	12/11
Disease duration, mean ± SD (range) (months)	12.7 ± 5.2 (6–24)
Modified Hoehn–Yahr scale, mean ± SD (range)	1.5 ± 0.6 (1–2.5)
UPDRS motor score, mean ± SD (range)	11.6 ± 6.5 (4–30)
MMSE, mean ± SD (range)	28.3 ± 1.7 (26–30)
OSIT-J score, mean ± SD (range)	4.7 ± 2.4 (0–8)

UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; OSIT-J = Odor Stick Identification Test for the Japanese.

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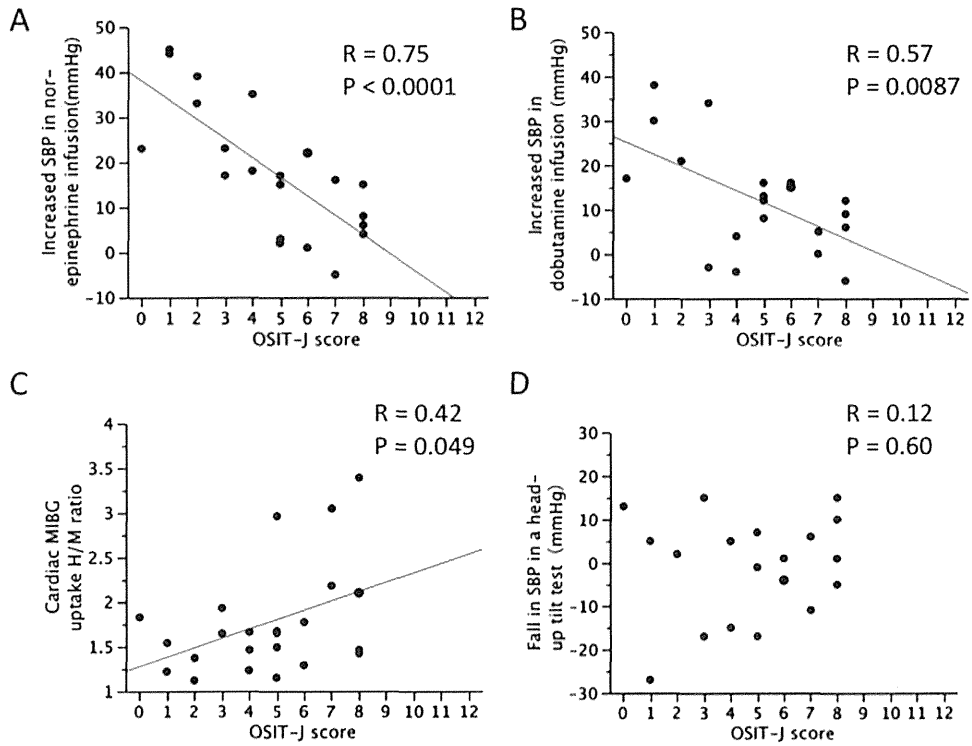

Fig. 1. Relationship between OSIT-J scores and the results of cardiovascular autonomic tests and cardiac MIBG uptake. A. Relationship between OSIT-J scores and increased SBP in the norepinephrine infusion test. B. Relationship between OSIT-J scores and increased SBP in the dobutamine infusion test. C. Relationship between OSIT-J scores and the cardiac MIBG uptake H/M ratio. D. Relationship between OSIT-J scores and the fall in SBP in the head-up tilt test. Maximum OSIT-J score is 12 points (normal = 8–12 points). OSIT-J = Odor Stick Identification Test for the Japanese; SBP = systolic blood pressure; MIBG = ^{123}I-metaiodobenzylguanidine; H/M ratio = heart-to-mediastinal ratio.

4. Discussion

This is the first report of a detailed evaluation of the association between cardiovascular dysautonomia and olfactory dysfunction in early-stage PD patients, although some studies have demonstrated such correlations in a population including advanced-stage PD patients [1,2]. It was also reported that cardiac MIBG uptake in PD patients within 5 years of the start of motor symptoms was significantly correlated with olfactory function, suggesting both of these two clinical indicators are impaired similarly in the relatively early stage of PD [16]. Our findings of correlations of OSIT-J scores with increased blood pressure in both the norepinephrine and dobutamine infusion tests as well as with cardiac MIBG uptake further extended the view that the olfactory system and broad aspects of cardiovascular sympathetic functions beyond cardiac MIBG uptake are impaired correlatively at an earlier stage of PD than previously reported.

Hyposmia is reported to be already present during early-stage PD, but is not significantly correlated with disease duration or clinical rating of motor status [17]. Therefore, olfactory dysfunction is a useful marker for early diagnosis [18]. Moreover, hyposmia was reported to occur before the appearance of motor symptoms, during the premotor phase [3]. According to Braak et al., Lewy body pathology is initially confined to the medulla oblongata and

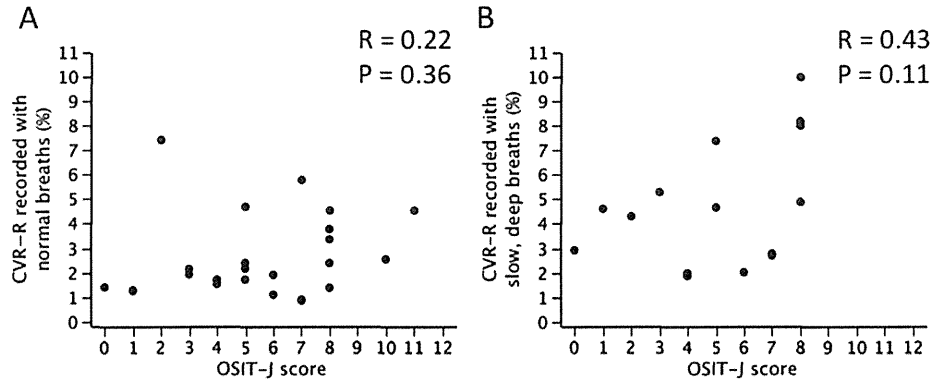

Fig. 2. Relationships between OSIT-J scores and CVR-R. A. Relationship between OSIT-J scores and CVR-R recorded during normal breathing. B. Relationship between OSIT-J scores and CVR-R recorded during slow, deep breathing. OSIT-J = Odor Stick Identification Test for the Japanese; CVR-R = coefficient of variation of R–R intervals.

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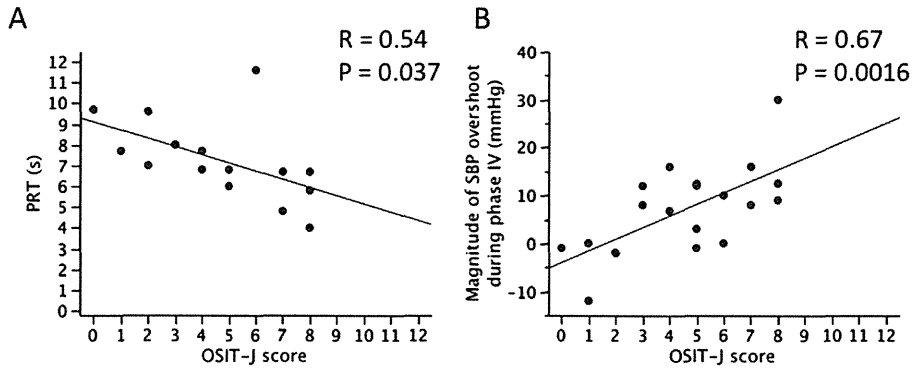

Fig. 3. Relationships between OSIT-J scores and aspects of the recordings during the Valsalva maneuver. A. Relationship between OSIT-J scores and the PRT in the Valsalva maneuver. B. Relationship between OSIT-J scores and the magnitude of SBP overshoot during phase IV in the Valsalva maneuver. OSIT-J = Odor Stick Identification Test for the Japanese; PRT = pressure recovery time from phase III to the return of blood pressure to baseline; SBP = systolic blood pressure.

olfactory nucleus; lesions ascend the lower brainstem, and then spread to the brain cortex with disease progression [19]. They also hypothesized that degenerative lesions progress from the olfactory system and intestinal system [20]. But the time course and appearance of cardiovascular dysautonomia and its pathological background remained unclear. From a pathological viewpoint, the occurrence of Lewy bodies [21], the decrease/loss in tyrosine hydroxylase-immunoreactive nerve fibers [22], and the aggregation of alpha-synuclein [23] have all been demonstrated in the broader cardiac peripheral autonomic nervous system of patients with incidental Lewy body disease (ILBD), which is considered a premotor PD status [24]. In addition, alpha-synuclein pathology of the peripheral autonomic nervous system, such as the sympathetic ganglia of the spinal cord, has also been reported in ILBD [25]. Moreover, the existence of circumscribed alpha-synucleinopathy within the sympathetic ganglion or pericardial nerve was reported in consecutive autopsies of elderly patients with ILBD [26]. Therefore, extensive components of the cardiovascular sympathetic system are considered to degenerate from the premotor stage in PD patients. Taken together, our data reflects previous pathological observations that both extensive cardiovascular sympathetic systems and olfactory system involvement assessed by alpha-synuclein/Lewy body pathology occur in the premotor phase of PD, and may suggest that the degeneration of both systems occurs contemporarily.

We did not, however, find a correlation between OSIT-J scores and decreased systolic blood pressure in the head-up tilt table test, which a previous report demonstrated [1]. The fall in orthostatic blood pressure response reflects not only one simple element, such as peripheral denervation sensitivity elicited by norepinephrine infusion, but rather multifactorial elements, including circulating plasma volume and sympathetic and parasympathetic function in both the central and peripheral nervous systems [27]. Thus, orthostatic hypotension in PD patients may be regulated by multiple factors beyond the autonomic components. These mechanical contributions to orthostatic hypotension may be one reason for the absence of correlation between olfactory dysfunction and orthostatic hypotension. We found however that PD patients with olfactory dysfunction exhibited an abnormal response to the Valsalva maneuver. The pressure recovery time from phase III to the return of blood pressure to baseline was found to vary directly with severity of adrenergic impairment [28]. Moreover, the absence of a phase IV increase in blood pressure following the Valsalva maneuver was demonstrated in patients with orthostatic hypotension [29], and was considered to detect impairment of cardiovascular sympathetic function. Our findings of a correlation between the olfactory scores and the pressure recovery time from phase III to the return of blood pressure to baseline and the magnitude of blood pressure overshoot during phase IV also indicates that latent cardiovascular sympathetic dysfunction as well as olfactory dysfunction exist during the early stage of PD.

Although not significant, OSIT-J scores tended to correlate with the maximal CVR-R response recorded during slow, deep breathing as previously reported [1]. According to a previous study, CVR-R is significantly correlated with cardiac MIBG uptake in PD patients, and cardiac parasympathetic dysfunction was concluded to occur concurrently with cardiac sympathetic denervation in early-stage PD [30]. The small sample size may be one of the reasons for the lack of the significance in our study. The correlation between cardiac parasympathetic function and olfactory impairment in early PD needs to be further studied.

Some limitations of our study should be noted. First, a period of 5 half-lives is ideal for the withdrawal of medications, but in our study antihypertensive medications (taken once a day) were discontinued only 24 h before testing for safety reasons. Second, some values were calculated retrospectively and data for maximal CVR-R response recorded with slow, deep breaths and the pressure recovery time from phase III to the return of blood pressure to baseline in the Valsalva maneuver were not available for these calculations.

In conclusion, we demonstrated that the olfactory system and extensive components of the cardiovascular sympathetic system are similarly impaired in the early stage of PD. Braak et al. hypothesized that degenerative lesions progress from the olfactory and intestinal systems [19,20], while the appearance of cardiovascular dysautonomia remained unclear. Our results suggest that degeneration of extensive components of the cardiovascular sympathetic system may occur concurrently with degeneration of the olfactory system during the premotor phase of PD.

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Role of cardiac sympathetic nerves in preventing orthostatic hypotension in Parkinson's disease

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ABSTRACT

Purpose: Cardiac sympathetic denervation is associated with orthostatic hypotension (OH) in Parkinson's disease (PD); however, the physiological role of cardiac sympathetic nerves has yet to be elucidated. To clarify the role of the heart in orthostatic stress, we evaluated whether cardiac sympathetic nerves can alter cardiac activity and systolic blood pressure (BP) in association with elevations or depressions of total peripheral resistance during the head-up tilt test.

Methods: Ninety-five PD patients and 17 normal controls were enrolled. Using impedance cardiography, we measured total peripheral resistance, stroke volume, heart rate, and systolic BP during the head-up tilt test. Cardiac denervation was defined as a heart-to-mediastinum ratio <1.7 for cardiac ^{123}I-meta-iodobenzylguanidine uptake on delayed images.

Results: At 60° tilt, total peripheral resistance decreased from the initial value in 49 PD patients. Among these, 36 patients exhibited cardiac denervation with severe reductions in systolic BP but little change in stroke volume; among these patients 22 had OH. The remaining 13 patients without cardiac denervation exhibited significant increases in stroke volume and well-preserved systolic BP with no OH. On the other hand, 46 patients had elevations in total peripheral resistance and reduced stroke volume, but little change in systolic BP, regardless of the presence or absence of cardiac denervation. Only one of these patients experienced OH.

Conclusion: Under orthostatic stress, cardiac sympathetic denervation with failure to increase total peripheral resistance leads to large reductions in systolic BP. However, patients without cardiac denervation exhibited a positive inotropic response against vasodilatation, which may prevent OH.

1. Introduction

Orthostatic hypotension (OH) is a non-motor feature of Parkinson's disease (PD). It is also one of the most disabling features, and understanding its mechanism and providing appropriate management is very important [1]. However, the precise mechanism of OH is not well understood. Cardiac and extra-cardiac noradrenergic denervation and baroreflex failure are likely to induce OH in PD patients [2]; however, the clinical significance of cardiac denervation is not well understood. Cardiac denervation is associated with fatigue [3], lowered cardiac contractility during exercise [4], and chronotropic insufficiency during exercise in the premotor phase [5]. PD patients with OH have a more severe loss of sympathetic innervation than PD patients without OH [2]. Infusions of tyramine result in differences in cardiac contractility, and impaired cardiac contractility in PD patients has been associated with OH [6]. These observations indicate that cardiac sympathetic nerves may play a role in blood pressure (BP) regulation in orthostatic stress. However, no study has directly evaluated the role of cardiac sympathetic nerves during orthostatic stress in PD patients. Further, failure of the peripheral vasoconstrictor response during orthostatic stress may account for OH [7], but such an impaired vascular response in PD patients has not been shown.

In the present study, we determined whether PD patients exhibited an impaired peripheral vasoconstrictor response, investigated the cardiac response in association with elevations or depressions in total peripheral resistance, and clarified the role of cardiac sympathetic nerves during orthostatic stress using the head-up tilt test.

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