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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.

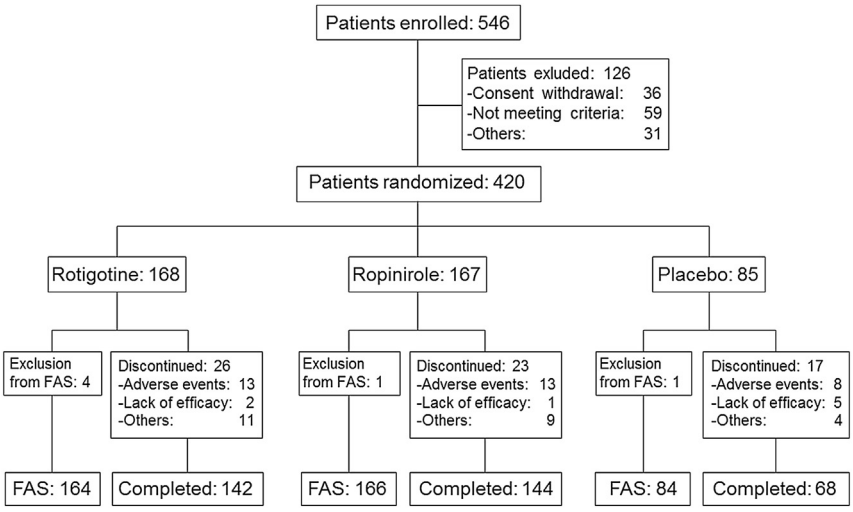

Fig. 1. Disposition of patients. The numbers indicate the number of patients in each category in FAS (full analysis set).

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.

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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.

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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.

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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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