



Rotigotine in Hemodialysis-Associated Restless Legs Syndrome: A Randomized Controlled Trial

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Background: Restless legs syndrome (RLS) has been associated with insomnia, decreased quality of life, and increased morbidity and mortality in end-stage renal disease. This randomized controlled trial investigated effects of rotigotine in patients with RLS and end-stage renal disease.

Study Design: Double-blind placebo-controlled study.

Setting & Participants: Adults with moderate to severe RLS (International RLS Study Group Rating Scale [IRLS] ≥ 15) and Periodic Limb Movement Index (PLMI) ≥ 15 who were receiving thrice-weekly hemodialysis enrolled from sites in the United States and Europe.

Intervention: Following randomization and titration ($\leq 21 + 3$ days) to optimal-dose rotigotine (1-3 mg/24 h) or placebo, patients entered a 2-week maintenance period. Polysomnography was performed at baseline and the end of maintenance.

Outcomes & Measurements: Primary efficacy outcome: reduction in PLMI, assessed by ratio of PLMI at end of maintenance to baseline. Secondary/other outcomes (*P* values exploratory) included mean changes from baseline in PLMI, IRLS, and Clinical Global Impression item 1 (CGI-1 [severity of illness]) score.

Results: 30 patients were randomly assigned (rotigotine, 20; placebo, 10); 25 (15; 10) completed the study with evaluable data. Mean (SD) PLMI ratio (end of maintenance to baseline) was 0.7 ± 0.4 for rotigotine and 1.3 ± 0.7 for placebo (analysis of covariance treatment ratio, 0.44; 95% CI, 0.22 to 0.88; *P* = 0.02). Numerical improvements were observed with rotigotine versus placebo in IRLS and CGI-1 (least squares mean treatment differences of -6.08 [95% CI, -12.18 to 0.02 ; *P* = 0.05] and -0.81 [95% CI, -1.94 to 0.33 ; *P* = 0.2]). 10 of 15 rotigotine and 2 of 10 placebo patients were CGI-1 responders ($\geq 50\%$ improvement). Hemodialysis did not affect unconjugated rotigotine concentrations. The most common adverse events (≥ 2 patients) were nausea (rotigotine, 4 [20%]; placebo, 0); vomiting (3 [15%]; 0); diarrhea (1 [5%]; 2 [20%]); headache (2 [10%]; 0); dyspnea (2 [10%]; 0); and hypertension (2 [10%]; 0).

Limitations: Small sample size and short duration.

Conclusions: Rotigotine improved periodic limb movements and RLS symptoms in the short term among ESRD patients requiring hemodialysis in a small-scale study. No dose adjustments are necessary for hemodialysis patients.

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INDEX WORDS: Chronic kidney disease (CKD); dopamine agonist; rotigotine; restless legs syndrome (RLS); periodic limb movements (PLM); periodic limb movement index (PLMI); hemodialysis; end-stage renal disease (ESRD); randomized controlled trial (RCT).

About 12% to 25% of patients with end-stage renal disease (ESRD) are affected by the neurologic disorder restless legs syndrome (RLS).¹⁻³ Patients with RLS have a bothersome urge to move their limbs, particularly their legs, often associated with dysesthesias. Symptoms occur during times of rest, are relieved by movement, and worsen in the evening and

at night. Periodic limb movements (PLM) during sleep (assessed by polysomnography) are present in 85% to 95% of patients with RLS.⁴ Such PLM are often associated with microarousals in those with RLS and thus contribute to sleep disruption. Most assessments of RLS severity rely on subjective ratings of a patient's sensory symptoms. Quantification of PLM provides an

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objective severity measure of the motor component of this disorder. In patients with ESRD, the presence of RLS has been associated with insomnia, decreased quality of life, and increased morbidity and mortality.⁵⁻⁷ Symptoms of RLS may occur during dialysis sessions and are independently associated with premature discontinuation of dialysis.⁸

Treatment for RLS is targeted at easing symptoms and improving sleep quality and quantity. Non-pharmacologic treatment (eg, exercise training)⁹⁻¹¹ or correction of iron deficiency, common in ESRD, may be appropriate therapy for those having mild or infrequent symptoms. However, pharmacologic treatment is often necessary for patients with more severe disease. Monotherapy with either a nonergot dopamine receptor agonist or an $\alpha_2\delta$ calcium channel ligand (only approved in the United States) is currently recommended as the first-line treatment for patients with primary RLS.¹² In addition, levodopa is used in certain European countries, including Germany. However, few studies have investigated the efficacy of these pharmacologic agents in patients with RLS and comorbid ESRD.¹³⁻¹⁵

Rotigotine is a nonergot dopamine receptor agonist administered by a transdermal patch, which provides continuous drug delivery with stable plasma levels over 24 hours.¹⁶ The efficacy of rotigotine transdermal patch in moderate to severe primary RLS has been demonstrated in two 6-month double-blind studies that assessed symptom severity by subjective rating scales^{17,18} and in a 4-week double-blind polysomnography study that used the PLM Index (PLMI; PLM per hour in bed) as the primary outcome measure.¹⁹ The current study was a randomized controlled trial to investigate the efficacy of rotigotine on PLM, sleep, RLS symptoms, and quality of life in patients with RLS and ESRD requiring hemodialysis.

METHODS

Patients

The RENALYS trial was a double-blind, randomized, placebo-controlled, 2-arm, parallel-group polysomnography study conducted in the United States and Europe. Adult patients (aged between ≥ 18 and ≤ 85 years) with ESRD requiring hemodialysis (regular dialysis schedule of 3 times weekly for at least 3 months) were eligible to participate if they had a diagnosis of RLS based on the International RLS Study Group (IRLSSG) criteria²⁰ (RLS-diagnostic index score ≥ 11 points²¹), moderate to severe RLS symptoms (IRLSSG Rating Scale [IRLS] score ≥ 15),²² Clinical Global Impression item 1 (CGI-1 [severity of illness] score ≥ 4),²³ and PLMI ≥ 15 PLM/h in bed (assessed by baseline polysomnography). Additional criteria included body mass index of 18 to ≤ 40 kg/m², hemoglobin concentration ≥ 8 g/dL (≥ 4.97 mmol/L), and ferritin concentration ≥ 100 ng/mL at screening (visit 1). Patients were excluded if they had previous treatment with rotigotine, symptomatic orthostatic hypotension, or clinically relevant cardiovascular, venous, or arterial peripheral diseases. Additional exclusion criteria included narcolepsy or other disorders of central hypersomnia, clinically relevant polyneuropathy or varicosis, or additional clinically relevant concomitant diseases. Treatment with dopamine agonists within the 14 days prior to baseline (visit 2) or with levodopa, neuroleptics, or selected other central nervous system-active medications within 7 days prior to baseline was prohibited. Patients who had previously received dopaminergic therapy were required to have had an initial favorable response. Additional patient eligibility criteria are given in *Item S1* (provided as online supplementary material). The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed by a national, regional, or independent ethics committee or institutional review board (*Item S1*), and all patients provided informed consent.

Study Design

Following assessment of eligibility criteria (visit 1) and washout of any prohibited medications, patients were randomly assigned 2:1 to rotigotine or placebo at baseline (visit 2). Randomization was carried out by an interactive web response system (ICON Clinical Research L.P.), with strata defined by region (European Union or United States; *Item S1*). Study treatment was administered

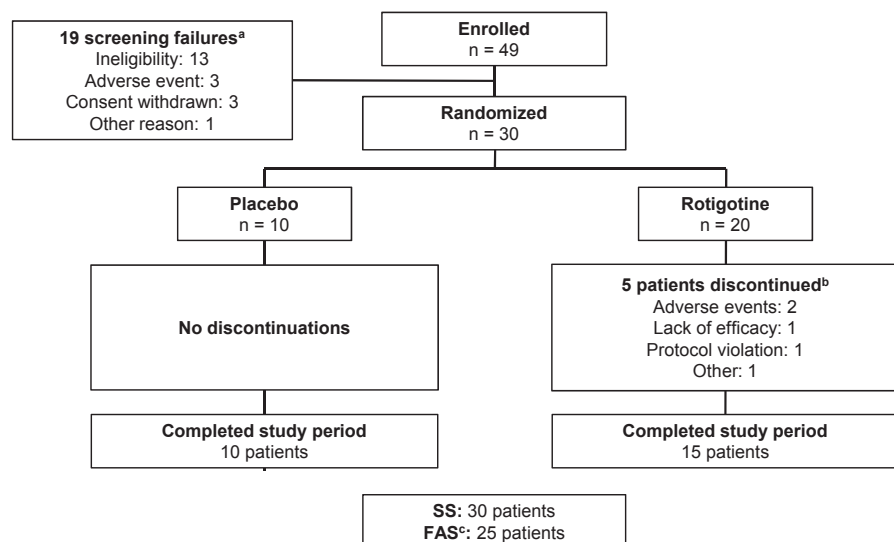


Figure 1. Patient disposition. ^aPatients who were rescreened could have more than 1 reason for screening failure. ^bThree patients discontinued during the titration period. ^cFull analysis set (FAS): all randomly assigned patients who had at least 1 patch applied during the treatment period and who had evaluable polysomnography data at baseline and end of maintenance. Abbreviation: SS, safety set.

Table 1. Baseline Characteristics in Safety Set Population

	Rotigotine (n = 20)	Placebo (n = 10)
Male sex	13 (65)	7 (70)
Age, y	57.2 ± 12.6	50.7 ± 16.3
Age category		
>18-<65 y	15 (75)	8 (80)
≥65 y	5 (25)	2 (20)
BMI, kg/m ²	30.4 ± 4.3	28.9 ± 6.2
Race		
White	13 (65)	4 (40)
Black	6 (30)	2 (20)
Other/mixed	0 (0)	1 (10)
Missing data ^a	1 (5)	3 (30)
Region		
United States	12 (60)	6 (60)
European Union	8 (40)	4 (40)
Dialysis 3 times per week	20 (100)	10 (100)
Dialysis vintage, ^b y	3.7 (0-19)	2.5 (0-22)
Time since first RLS symptoms, y	3.0 (1-13)	5.0 (0-9)
Time since first RLS diagnosis, y	1.0 (0-9)	0.1 (0-5)
Prior RLS therapy	12 (60)	2 (20)
Gabapentin	4 (20)	0 (0)
Levodopa/dopamine agonists ^b	5 (25)	1 (10)
Pregabalin	2 (10)	1 (10)
Psycholeptics ^c	3 (15)	0 (0)
SBP		
During day, mm Hg	140.9 ± 24.4	141.0 ± 9.5
During night, mm Hg	137.6 ± 27.0	144.8 ± 15.2
DBP		
During day, mm Hg	79.1 ± 12.8	83.0 ± 7.4
During night, mm Hg	76.5 ± 15.6	82.4 ± 11.6
Hemoglobin, g/L ^d	121.5 ± 15.7	120.1 ± 13.7
Ferritin, pmol/L ^d	1,613.5 ± 952.2	1,711.8 ± 701.2
Apnea and Hypopnea Index ^e		
≤15	15 (75)	7 (70)
>15	5 (25)	3 (30)
>30	5 (25)	0 (0)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, mean ± standard deviation or median (range).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; RLS, restless legs syndrome; SBP, systolic blood pressure.

^aData were not collected for patients in France.

^bCategory includes levodopa preparations, pramipexole, and ropinirole.

^cCategory includes clonazepam, meprobamate, and temazepam.

^dRotigotine, n = 18; placebo, n = 9.

^eNumber of apneas or hypopneas per hour of sleep.

by a transdermal patch; active and placebo patches were matched in size and appearance, with rotigotine patches corresponding to doses of 1, 2, and 3 mg/24 h. Doses were uptitrated weekly from 1 mg/24 h of rotigotine (or matching placebo) until the optimal or maximal dose (3 mg/24 h) was reached (maximum titration period, 21 + 3

days). Following titration, patients entered the 2-week maintenance period (visit 5), during which no further dose adjustments were permitted. The end-of-maintenance visit (visit 6) was followed by a taper period (up to 4 days) and a 30 (+3)-day safety follow-up period.

Polysomnography was performed on the 2 consecutive nights prior to baseline (visit 2) and on the 2 consecutive nights prior to the end of the maintenance period (visit 6). Study assessments were scheduled so that the second night of polysomnography started the day after the previous dialysis. Polysomnography was recorded for up to 8 hours (eg, 11:00 PM-7:00 AM), following standard operating procedures.²⁴ Recordings from the second night were used for analysis. Polysomnography recordings were transferred to a central reader and scored by trained personnel according to the American Academy of Sleep Medicine guidelines.²⁵ PLM during sleep and during wakefulness were evaluated in accordance with the World Association of Sleep Medicine Standards²⁶ and the specifications of Walters et al.²⁷ PLM were defined as a series of 4 or more consecutive leg movements of 0.5 to 10 seconds in duration, with an intermovement interval of 5 to 90 seconds.²⁵

Blood samples were collected at the start and end of the maintenance period for measurement of plasma unconjugated and total rotigotine. In addition, 24-hour blood pressure was recorded at baseline and end of maintenance by an ambulatory device (Spacelabs Healthcare Model 90207). These recordings took place 24 hours prior to the scheduled dialysis session. Blood pressure was recorded every 20 minutes during the daytime (6:00 AM-10:00 PM) and once per hour during the night (10:00 PM-6:00 AM). Mean day- and night-time blood pressures were calculated as the mean of all available values recorded during the respective times.

Outcome Measures

The primary outcome was reduction in PLMI, assessed by the PLMI ratio (calculated as PLMI at the end of maintenance/PLMI at baseline). The PLMI ratio was used to account for potential high variability in the PLMI. Secondary outcomes were mean changes from baseline in PLMI, selected polysomnography measures (PLM During Sleep With Arousal Index [PLM during sleep with arousals/hour total sleep time (TST)] and sleep efficiency), and subjective rating scales (IRLS sum score, CGI-1, RLS 6-item questionnaire [RLS-6], RLS quality-of-life questionnaire [RLS-QoL²⁸], and 36-Item Short Form Health Survey [SF-36]). Changes from baseline in PLM during Sleep Index (PLMSI; PLM during sleep/hour TST), PLM During Wakefulness Index (PLM during awake epochs/hour in awake epochs), and sleep parameters (TST, time in sleep stages, wake after sleep onset, and sleep onset latency) were also assessed. Rotigotine plasma concentrations and changes from baseline in mean day- and night-time blood pressures were evaluated. Safety outcomes included adverse events (AEs) and serious AEs.

Statistical Analyses

Sample size calculation was based on the primary efficacy outcome and performed with nQuery Advisor, version 7.0 (Statistical Solutions Ltd.). It was estimated that 24 patients (rotigotine, 16; placebo, 8) were required to provide 90% power to demonstrate the superiority of rotigotine over placebo using a 1-sided test with a 0.025 significance level. Enrollment of 48 patients was planned in order to randomly assign 33 patients (assumed dropout rate, ~30% [eg, owing to screening failures]) and obtain data from 24 completers (assumed dropout rate, ~25%) for the primary analysis.

Efficacy analyses were performed for the full analysis set, including all randomly assigned patients who had at least 1 patch applied during the treatment period and who had evaluable polysomnography data at baseline and end of maintenance. Unless otherwise specified, data were analyzed as observed with no imputation of missing values. A post hoc analysis of IRLS, CGI-1,

Table 2. Polysomnographic Assessments in Full Analysis Set Population

	Baseline		Change From Baseline		LS Mean Treatment Difference (95% CI); <i>P</i>
	Rotigotine (n = 15)	Placebo (n = 10)	Rotigotine (n = 15)	Placebo (n = 10)	
PLM parameters					
PLMI: PLM/h in bed ^a	81.8 ± 37.5	85.3 ± 67.3	-23.7 ± 38.7	10.3 ± 21.0	-34.75 (-61.38 to -8.11); 0.01
PLMSI: PLM during sleep/h TST	87.24 ± 48.52	92.45 ± 92.08	-30.24 ± 41.79	4.46 ± 20.24	-35.79 (-63.34 to -8.23); 0.01
PLMSAI: PLM during sleep with arousals/h TST ^a	13.91 ± 8.94	9.65 ± 9.03	-1.61 ± 14.41	4.63 ± 7.16	-5.19 (-15.36 to 4.98); 0.3
PLMWI: PLM during awake epochs/h in awake epochs	79.60 ± 32.91	73.31 ± 35.71	-12.76 ± 47.72	25.21 ± 43.47	-34.60 (-72.41 to 3.22); 0.07
Sleep parameters					
Sleep efficiency: sleep time/time in bed [%] ^a	59.74 ± 17.32	65.41 ± 12.50	7.67 ± 12.32	-2.85 ± 10.35	9.33 (0.37 to 18.28); 0.04
TST, min	284.23 ± 80.18	312.55 ± 60.53	39.30 ± 58.76	-13.05 ± 48.66	46.77 (3.12 to 90.42); 0.04
Stage 1, min	97.30 ± 32.24	95.65 ± 33.14	29.74 ± 40.99	-8.15 ± 34.27	38.60 (8.93 to 68.27); 0.01
Stage 2, min	89.80 ± 38.22	100.15 ± 40.28	3.80 ± 19.82	-1.26 ± 29.76	1.82 (-16.91 to 20.55); 0.8
Stage 3, min	50.50 ± 24.65	67.20 ± 21.98	9.10 ± 29.24	-1.60 ± 27.71	11.43 (-14.97 to 37.83); 0.4
REM, min	46.63 ± 29.44	49.55 ± 18.79	-3.34 ± 27.81	-2.05 ± 24.21	-1.77 (-24.82 to 21.27); 0.9
Sleep onset latency, min	59.20 ± 57.80	44.60 ± 38.65	-18.93 ± 83.87	12.75 ± 34.45	-18.32 (-63.68 to 27.04); 0.4
Wake after sleep onset, min	167.63 ± 75.87	142.60 ± 69.54	-28.80 ± 52.11	-5.95 ± 51.46	-19.96 (-57.08 to 17.16); 0.3

Note: Unless otherwise indicated, values are given as mean ± standard deviation. The full analysis set included all randomly assigned patients who had at least 1 patch applied during the treatment period and who had evaluable polysomnography data at baseline and end of maintenance.

Abbreviations: CI, confidence interval; LS, least squares; PLM, periodic limb movement; PLMI, PLM Index; PLMSAI, PLM During Sleep With Arousal Index; PLMSI, PLM During Sleep Index; PLMWI, PLM During Wakefulness Index; REM, rapid eye movement; TST, total sleep time.

^aSecondary efficacy variable.

RLS-6, and RLS-QoL data was performed for the safety set (all randomly assigned patients who had at least 1 patch applied during the treatment period) with last observation carried forward. Analyses of safety were performed for the safety set.

For the primary outcome, analysis of covariance (ANCOVA) was performed for the log-transformed PLMI ratio, with treatment and region as factors and baseline as a covariate. Least squares means (with 95% confidence intervals [CIs]) were calculated for each treatment, and results were back-transformed for presentation. Treatment effect was estimated on the basis of the ratio of the 2 treatments, as well as on the corresponding 95% CI. For all other efficacy outcomes, summary statistics were provided and ANCOVA analyses were conducted post hoc; *P* values for these outcomes are exploratory.

RESULTS

Patients

This study was conducted in April 2012 to October 2013. Forty-nine patients were enrolled and 30 were randomly assigned from 5 sites in the United States (18 patients) and 7 sites in Europe (12 patients [Finland, France, Germany, and Italy]; Fig 1). Patients randomly assigned to rotigotine had a shorter history of RLS (median, 3 vs 5 years) but a longer time since RLS diagnosis than those randomly assigned to placebo (median, 1 vs 0.1 year; Table 1). All participants had ESRD requiring hemodialysis. Concomitant diseases reported by 10 or more patients were chronic kidney

disease (rotigotine: 14 [70%]; placebo: 8 [80%]), hypertension (16 [80%]; 6 [60%]), gastroesophageal reflux disease (7 [35%]; 5 [50%]), and hyperphosphatemia (7 [35%]; 3 [30%]; Table S1). Prior RLS therapy was reported in 12 of 20 patients in the rotigotine group and 2 of 10 patients in the placebo group. Concomitant medications are shown in Table S2. In total, 25 patients completed the study and were included in efficacy analyses (full analysis set). The 5 patients who discontinued prematurely were all receiving rotigotine; 3 withdrew during titration, and 2 withdrew during the maintenance period (Fig 1). Of 16 rotigotine-treated patients with evaluable dosing data at the start of maintenance, 9 received an optimal daily dose of 3 mg/24 h, 3 received 2 mg/24 h, and 4 received 1 mg/24 h.

Efficacy (full analysis set)

Polysomnography Assessments

PLMI was comparable between the 2 treatment groups at baseline, whereas assessments at the end of maintenance showed a reduction in scores for patients receiving rotigotine and an increase for those receiving placebo (Table 2; Fig 2). The mean PLMI ratio (end of maintenance to baseline) was 0.7 ± 0.4

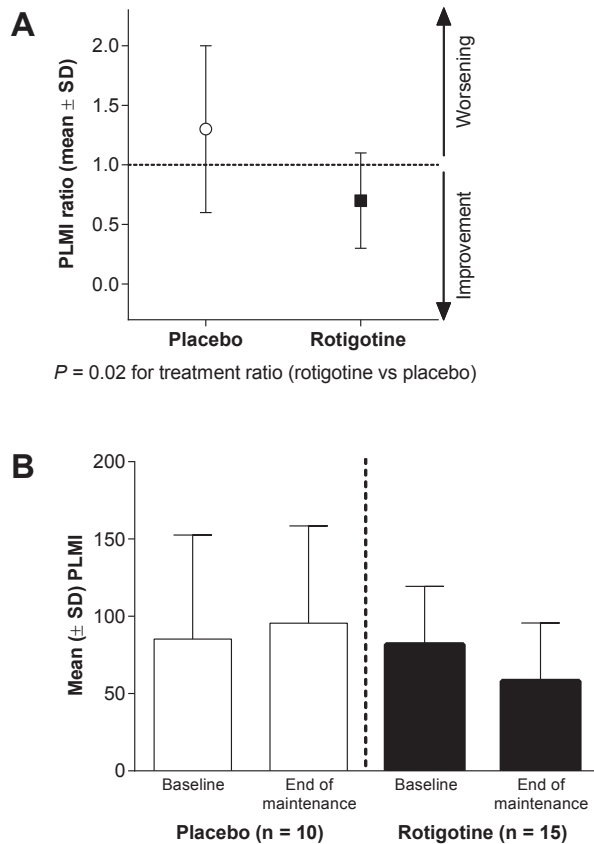


Figure 2. Periodic Limb Movement Index (PLMI). (A) PLMI ratio (end of maintenance to baseline) and (B) PLMI at baseline and end of maintenance. Data for the full analysis set (all randomly assigned patients who had at least 1 patch applied during the treatment period, and who had evaluable polysomnography data at baseline and end of maintenance). Abbreviation: SD, standard deviation.

for rotigotine compared with 1.3 ± 0.7 for placebo (treatment ratio, 0.44; 95% CI, 0.22-0.88; $P = 0.02$). Among patients receiving rotigotine, PLMI improved from 81.8 ± 37.5 at baseline to 58.1 ± 37.6 at end of maintenance (Table 2; Fig 2). The PLMSI was reduced with rotigotine versus placebo (least squares mean treatment difference, -35.79 ; 95% CI, -63.34 to -8.23 ; $P = 0.01$), and sleep efficiency and TST increased (least squares mean treatment differences of 9.33 [95% CI, 0.37-18.28; $P = 0.04$] and 46.77 [95% CI, 3.12-90.42; $P = 0.04$]; Table 2). PLM During Wakefulness Index, sleep onset latency, and wake after sleep onset were reduced with rotigotine; however, ANCOVAs did not indicate treatment differences (Table 2).

Subjective Assessments

Greater numerical reductions in IRLS scores were observed among rotigotine-treated patients who completed the maintenance period (full analysis set) than those receiving placebo (least squares mean treatment difference, -6.08 ; 95% CI, -12.18 to 0.02 ;

$P = 0.05$; Table 3; Fig 3A). Based on IRLS scores at end of maintenance, 11 of 15 patients receiving rotigotine treatment were classified as responders ($\geq 50\%$ improvement), 8 of 15 qualified as remitters (IRLS ≤ 10), and 3 of 15 were symptom free (IRLS = 0). In the placebo group, 2 of 10 patients were classified as IRLS responders, 1 of 10 qualified as a remitter, and no patients were symptom free. Mean CGI-1 scores numerically improved with rotigotine (least squares mean treatment difference, -0.81 ; 95% CI, -1.94 to 0.33 ; $P = 0.2$), with 12 of 15 patients receiving rotigotine and 5 of 10 patients receiving placebo moving to a CGI-1 category of mildly, borderline, or not at all ill (Fig 3B). At end of maintenance, 10 of 15 patients receiving rotigotine and 2 of 10 patients receiving placebo were classified as CGI-1 responders ($\geq 50\%$ improvement in score). RLS-6 scores were reduced in both treatment groups, with greater numerical improvements observed with rotigotine for all items other than item 5 (symptom severity during activities; Table 3). A treatment difference in favor of rotigotine was observed for RLS-6 item 6 (daytime sleepiness/tiredness). Rotigotine-treated patients had a slight numerical improvement in RLS-QoL scores in comparison to those receiving placebo (Table 3). Analysis of subjective RLS assessments for all treated patients (safety set with last observation carried forward) showed mean changes from baseline in IRLS, RLS-6, and RLS-QoL scores that were comparable, though systemically smaller, to those observed in the full analysis set (Table S3).

Pharmacokinetics (Safety Set)

Plasma concentrations of dose-normalized unconjugated rotigotine were similar at the start of maintenance (geometric mean, 0.0505 [ng/mL]/mg; $n = 16$) and end of maintenance/withdrawal visit (0.0563 [ng/mL]/mg; $n = 15$). Geometric mean values for dose-normalized total rotigotine were also comparable at both times (start of maintenance, 0.3561 [ng/mL]/mg [$n = 16$]; end of maintenance/withdrawal, 0.4000 [ng/mL]/mg [$n = 15$]).

Blood Pressure (Safety Set and Full Analysis Set)

At baseline, mean systolic (SBP) and diastolic blood pressure (DBP) values were comparable in both treatment groups (Table 1). Among patients receiving rotigotine (safety set), slight mean reductions in daytime (SBP, -0.6 ± 14.3 mm Hg; DBP, -0.3 ± 9.7 mm Hg) and night-time (SBP, -1.2 ± 12.1 mm Hg; DBP, -1.2 ± 8.9 mm Hg) blood pressures were observed at end of maintenance compared to baseline. In comparison, increases from baseline in daytime (SBP, 4.8 ± 6.8 mm Hg; DBP, 2.4 ± 3.7 mm Hg) and night-time (SBP, 4.3 ± 14.8 mm Hg; DBP,

Table 3. Subjective Assessments in the Full Analysis Set Population

	Baseline		Change From Baseline		LS Mean Treatment Difference (95% CI); <i>P</i>
	Rotigotine (n = 15)	Placebo (n = 10)	Rotigotine (n = 15)	Placebo (n = 10)	
IRLS	25.7 ± 5.0	24.4 ± 5.1	-15.9 ± 9.1	-8.6 ± 7.2	-6.08 (-12.18 to 0.02); 0.05
RLS-6					
Item 1: Satisfaction with sleep	6.1 ± 1.7	5.7 ± 1.9	-2.8 ± 3.2	-1.1 ± 3.5	-1.37 (-3.91 to 1.17); 0.3
Item 2: Severity when falling asleep	6.6 ± 2.1	5.8 ± 2.7	-4.4 ± 2.9	-2.8 ± 2.9	-1.08 (-3.23 to 1.08); 0.3
Item 3: Severity during the night	6.2 ± 2.0	5.9 ± 1.9	-4.7 ± 3.1	-3.2 ± 2.6	-1.25 (-2.96 to 0.46); 0.1
Item 4: Severity when at rest	3.7 ± 2.1	4.9 ± 2.0	-2.6 ± 2.2	-1.6 ± 3.2	-1.85 (-3.86 to 0.17); 0.07
Item 5: Severity during activities	2.5 ± 2.5	2.8 ± 2.7	-1.6 ± 2.7	-1.6 ± 2.1	-0.22 (-1.54 to 1.11); 0.7
Item 6: Daytime sleepiness/tiredness	5.3 ± 2.1	5.7 ± 1.6	-3.4 ± 2.3	-1.6 ± 2.0	-2.13 (-3.67 to -0.60); 0.009
RLS-QoL	24.9 ± 7.4	31.3 ± 10.8	-10.7 ± 10.9	-10.2 ± 10.8	-2.67 (-12.42 to 7.08); 0.6
SF-36 ^a					
Mental Component Summary score	54.1 ± 11.3	41.0 ± 10.9	2.2 ± 10.1	6.4 ± 6.6	2.87 (-4.67 to 10.42); 0.4
Physical Component Summary score	35.7 ± 11.3	38.2 ± 6.5	3.8 ± 6.3	-0.3 ± 8.7	2.87 (-2.85 to 8.59); 0.3

Note: Unless otherwise indicated, values are given as mean ± standard deviation. The full analysis set included all randomly assigned patients who had at least 1 patch applied during the treatment period, and who had evaluable polysomnography data at baseline and end of maintenance.

Abbreviations: CI, confidence interval; IRLS, International Restless Legs Syndrome Rating Scale; LS, least squares; RLS-6, restless legs syndrome 6-item questionnaire; RLS-QoL, restless legs syndrome quality-of-life questionnaire; SF-16, 36-Item Short Form Health Survey.

^aAn increase in score indicates an improvement; for all other outcomes, a reduction in score indicates an improvement.

2.9 ± 9.0 mm Hg) blood pressures were observed with placebo. Post hoc analysis of night-time blood pressure dipping was performed for the full analysis set. The numbers of patients with a dip (>10% reduction from day to night) in DBP (baseline, 3 of 15; end of maintenance, 5 of 15) and SBP (baseline, 1 of 15; end of maintenance, 4 of 15) increased with rotigotine. In the placebo group, 2 of 10 patients were DBP dippers at baseline and 1 of 10 was at end of maintenance. No patients receiving placebo were classified as SBP dippers.

Safety and Tolerability (Safety Set)

AEs were reported by 12 (60%) patients receiving rotigotine and 5 (50%) patients receiving placebo (Table 4). Two patients had hypertension of moderate intensity while receiving rotigotine. Both patients were receiving medications for this condition prior to study start. One patient reported an application site reaction (MedDRA [Medical Dictionary for Regulatory Activities] high-level term “application and instillation site reactions”) of mild pruritus while receiving 2 mg/24 h of rotigotine; no application site reactions were reported for placebo. Serious AEs were reported for 3 patients receiving rotigotine (foot fracture [n = 1]; anxiety, chest pain, and dyspnea [n = 1]; and abdominal pain [n = 1]) and 1 patient receiving placebo (gastrointestinal infection). Two rotigotine-treated patients discontinued prematurely owing to AEs. One withdrew following a confusional state; this AE occurred on day 9 of rotigotine treatment (dose at onset: 1 mg/24 h) and

was considered to be nonserious, moderate in intensity, and related to study medication. Following withdrawal of rotigotine treatment, the AE resolved within 2 days. The other patient withdrew after having a number of serious AEs (anxiety, chest pain, and dyspnea). These AEs occurred on day 27 of rotigotine treatment while the patient was receiving a dose of 3 mg/24 h and were considered to be severe in intensity and related to the study medication. Following withdrawal of rotigotine, the chest pain resolved in 3 days, anxiety resolved in 24 days, and dyspnea resolved in 38 days.

DISCUSSION

Rotigotine transdermal patch significantly reduced PLM, as assessed by the PLMI ratio. To our knowledge, this is the first double-blind placebo-controlled study to investigate rotigotine therapy for moderate to severe RLS in patients with ESRD treated by hemodialysis. Reduction in PLM with rotigotine was supported by a reduction in PLMSI and accompanied by improvements in certain sleep parameters.

Sleep problems are common in patients with ESRD, particularly those with RLS, and contribute to reduced quality of life.⁶ The severity of PLM during sleep has been linked to increased risk for cardiovascular and cerebrovascular disease²⁹ and increased mortality in this patient population.^{30,31} A higher frequency of PLM has been reported in patients with uremic RLS than in patients with the idiopathic form of the

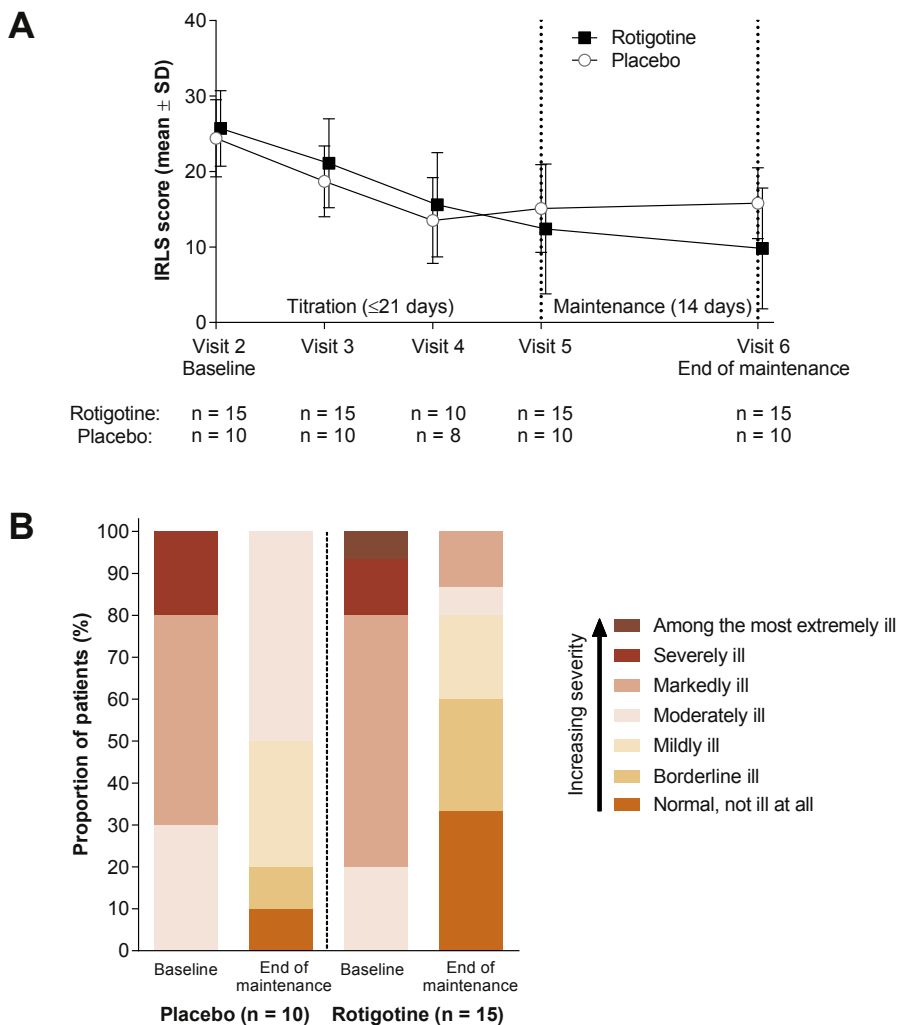


Figure 3. Subjective outcomes. (A) International Restless Legs Syndrome Study Group Rating Scale (IRLS) score and (B) Clinical Global Impression item 1 severity scale category at baseline and end of maintenance. Data for the full analysis set (all randomly assigned patients who had at least 1 patch applied during the treatment period and who had evaluable polysomnography data at baseline and end of maintenance). Abbreviation: SD, standard deviation.

disorder.^{32,33} In the current study, patients had a high frequency of PLM at baseline, with a mean PLMI > 80/h. A PLMI > 50/h is generally considered to be severe. Although a significant improvement in PLMI ratio was observed with rotigotine, the PLMI for both treatment groups remained above the >50/h cutoff at the end of the 2-week maintenance period

(58.1 with rotigotine). Given the persisting high rates of PLM at end of treatment, the clinical significance of the observed reduction in PLMI with rotigotine is unclear. In contrast, a longer study in patients with idiopathic RLS (4-week maintenance period) showed a reduction in PLMI from 50.9 to 8.1 with rotigotine.¹⁹

In addition to improving motor outcomes, rotigotine treatment had beneficial effects on sleep, with improvements versus placebo in sleep efficiency and TST. Sensory symptoms of RLS also improved with rotigotine, as indicated by numerical improvements in subjective rating scale scores. The observed ~16-point reduction in IRLS score with rotigotine corresponded to a shift from severe (IRLS, 21-30) to mild symptoms (IRLS, 1-10).²² In comparison, patients receiving placebo had an ~9-point reduction in IRLS score, with a shift from severe to moderate (IRLS, 11-20) symptoms. These results were consistent with those for the CGI-1, with the majority of rotigotine-treated patients (and 50% of patients receiving placebo) improving to a category of mildly, borderline, or not at all ill. Numerical improvements

Table 4. Adverse Events Reported by 2 or More Patients in the Safety Set

MedDRA Preferred Term	Rotigotine (n = 20)	Placebo (n = 10)
Any	12 (60)	5 (50)
Nausea	4 (20)	0 (0)
Vomiting	3 (15)	0 (0)
Diarrhea	1 (5)	2 (20)
Headache	2 (10)	0 (0)
Dyspnea	2 (10)	0 (0)
Hypertension	2 (10)	0 (0)

Note: Values are given as number (percentage).

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

were observed with rotigotine versus placebo in severity of RLS during various periods of the night and day, in addition to sleep satisfaction and daytime tiredness, as assessed by the RLS-6. Quality-of-life scores (RLS-QoL and SF-36) varied between treatment groups at baseline, with a difference of ~13 points in the SF-36 Mental Component Summary score. Slight numerical improvements were observed with rotigotine versus placebo. It should be noted that this study was powered for assessment of the primary outcome (PLMI ratio) only. All *P* values for secondary outcomes are exploratory and do not indicate statistical significance.

Serum plasma concentrations of unconjugated and total rotigotine were stable over the maintenance phase, which indicates lack of accumulation, and were similar to those seen in patients with RLS with and without impaired renal function.^{16,34} This supports earlier demonstrations that rotigotine dose adjustments are not required for patients with reduced kidney function, including those receiving hemodialysis.³⁴ Elimination of rotigotine from plasma is comparable in healthy individuals and patients with different stages of chronic kidney diseases, and rotigotine is not removed by the dialysis procedure.³⁴ In contrast, dose modifications are needed for pramipexole treatment.³⁵

Analyses of ambulatory blood pressure–monitoring data indicated slight numerical reductions in nighttime and daytime blood pressures and slight increases in the number of night-time dippers with rotigotine. Further studies with larger numbers of patients and longer treatment durations are warranted to fully investigate the effects of rotigotine on blood pressure and night-time blood pressure–dipping status. The AE profile of rotigotine was consistent with that reported in other studies of patients with idiopathic RLS.^{17–19} In our small group of rotigotine-treated patients, 2 AEs of hypertension were reported; however, both cases were in patients with preexisting antihypertensive treatment. Given that dermatologic conditions are common among patients with ESRD,³⁶ it is notable that only 1 patient had a skin reaction following patch application. However, longer studies are needed to fully evaluate the tolerability of rotigotine in hemodialysis patients.

Limitations of the study were primarily its small number of patients and short treatment duration. Confirmatory studies are needed to fully assess the efficacy of rotigotine in patients with ESRD treated by hemodialysis. There were some potential imbalances between treatment groups at baseline; for example, the rotigotine group included a higher proportion of pretreated patients. Patients in whom previous dopaminergic treatment had failed were excluded from the study for ethical reasons. This may

have enriched the sample for likely responders. Finally, because patients had to fulfill stringent eligibility criteria, those enrolled may not be fully representative of the wider hemodialysis population with RLS.

In the current short-term small-scale study, rotigotine was efficacious in improving PLM in patients with ESRD treated by hemodialysis who had moderate to severe RLS. Confirmatory trials are warranted to determine whether rotigotine transdermal patch may be of benefit in this patient population.

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SUPPLEMENTARY MATERIAL

Table S1: Concomitant diseases reported by ≥ 5 patients, safety set.

Table S2: Concomitant medications taken by ≥ 10 patients, safety set.

Table S3: Subjective assessments in safety set population, last observation carried forward.

Item S1: Supplementary methods.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2015.12.027>) is available at www.ajkd.org

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