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Original Investigation

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 (≤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 (≥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. Nonpharmacologic 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) criteria[20] (RLS-diagnostic index score ≥ 11 points[21]), 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/m^2, 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

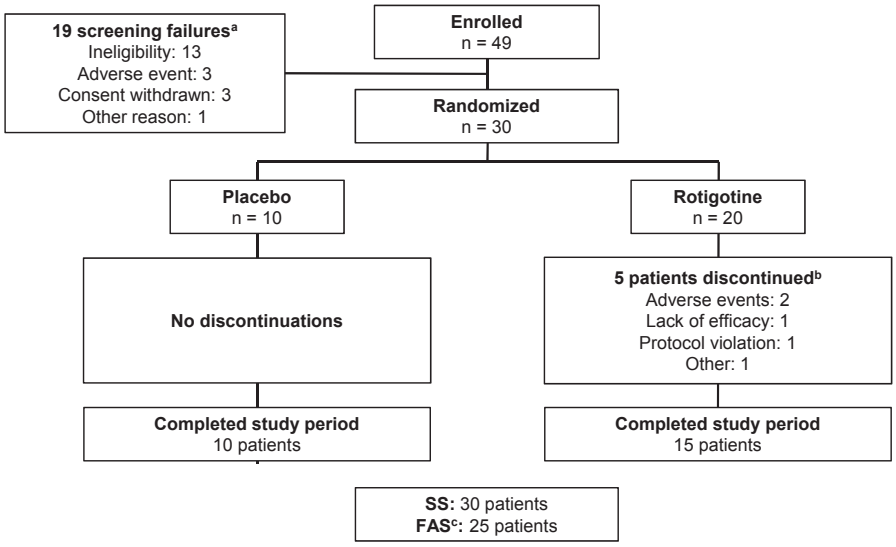

Figure 1. Patient disposition. [a]Patients who were rescreened could have more than 1 reason for screening failure. [b]Three patients discontinued during the titration period. [c]Full analysis set (FAS): all randomly assigned patients who had at least 1 patch applied during the treatment period and who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