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Original Article

A method to switch from oral dopamine agonists to rotigotine in patients with restless legs syndrome and mild augmentation

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ABSTRACT

Background: We examined the short- and long-term efficacy and tolerability of a cross-titration algorithm from oral dopamine agonists to the rotigotine transdermal patch in patients dissatisfied with their restless legs syndrome (RLS) treatment, predominantly with mild augmentation.
Methods: Patients with RLS ($n = 20$) were recruited at a single site. The cross-titration consisted of decreasing oral dopaminergic agents (ropinirole by 1 mg or pramipexole by 0.25 mg) and increasing rotigotine by 1 mg every two days. Efficacy and adverse events (AEs) were assessed at one, three, six and 12 months after the switch.
Results: Patients had moderate–severe RLS symptoms at the baseline (mean international restless legs syndrome (IRLS) score 19.4 ± 5.5); 85% had augmentation and 45% reported afternoon RLS symptoms. The baseline mean pramipexole equivalent dose was 0.6 ± 0.3 mg. At Week 5, 85% (17/20) had successfully switched from their oral dopamine agonist to rotigotine (mean dose 2.5 ± 0.6 mg; change in IRLS score: –6.7 ± 8.4, $p = 0.002$); 14 patients were CGI-I responders (much or very much improved). Three patients withdrew due to lack of efficacy. Twelve months after cross-titration, 10 patients continued on rotigotine, of whom four required either higher doses of rotigotine or supplemental RLS medication compared with their optimal Week 5 dose; five patients withdrew due to AEs and two due to lack of efficacy.
Conclusion: A cross-titration to rotigotine was efficacious after five weeks in 70% of patients dissatisfied with RLS treatment, most of whom had mild augmentation. At one year following the medication switch, 50% had discontinued rotigotine due to lack of continued efficacy or side effects.

Restless legs syndrome (RLS) is a common sleep disorder characterized by an irresistible urge to move the legs that often occurs in response to leg dysesthesias. Symptoms are provoked by rest, relieved with movement, and most severe in the evening or at night [1]. Using strict diagnostic criteria, RLS is present in 3–5% of the general population and provokes moderate-to-severe distress in a majority of affected individuals [2].

The immediate-release oral dopamine agonists pramipexole and ropinirole are the most frequently used first-line therapies for RLS. Doses of these medications are generally timed to precede onset of usual symptoms by 1–2 h. However, there is considerable day-to-day variability in RLS symptoms [3]. Patients may experience symptoms prior to usual dosing on some days, and it may be difficult to adjust the timing of the dose(s) so that effective serum concentrations are present at the time of the RLS symptom onset. Indeed, it has been shown that many patients with RLS have daytime symptoms despite treatment [4].

Rotigotine is a nonergolide dopamine agonist formulated as a transdermal patch for once-daily application and approved for the treatment of primary moderate-to-severe RLS [5]. The continuous delivery system provides relatively stable plasma concentration 24 h per day. Consequently, rotigotine may be superior to immediate-release oral dopamine agonists to treat daytime symptoms of RLS [6]. It may also provide relief to patients who must otherwise "chase" RLS symptoms with repeated daily doses of oral dopamine agonists.

The primary complication of long-term use of dopamine agonists for RLS is augmentation, which is an iatrogenic worsening of symptoms [7]. Augmentation is characterized by earlier onset of symptoms, shorter time to symptom onset at rest, spreading of symptoms to other body parts, and/or paradoxical intensification of symptoms with up-titration of dopamine agonists. A recent long-term study demonstrated a relatively low 5% incidence of

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augmentation over 5 years among RLS patients receiving rotigotine within the approved dose range [5]. Rotigotine may also be of value in the treatment of patients who have developed augmentation to immediate-release oral dopamine agonists [8].

For these reasons, clinicians and patients may want to switch a patient currently on an oral dopamine agonist to rotigotine. The tolerability of this transition has been evaluated in patients with Parkinson's disease [9,10], but the optimal method for switching has not been investigated in RLS.

1. Methods

1.1. Subjects

Subjects were eligible if they were ≥18 years of age, had a diagnosis of primary RLS using the International RLS Study Group criteria, were dissatisfied with the current oral treatment or inadequate symptom control, and were currently treated with pramipexole (≤1 mg total daily dose), ropinirole (≤4 mg total daily dose), or carbidopa/levodopa (≤150/600 mg total daily dose), with an unchanged dose of RLS therapeutic medication(s) for the past 30 days. The presence of augmentation was assessed based on National Institutes of Health's minimal criteria and was documented at the baseline [11]. Subjects were excluded if they had another chronic pain syndrome that would interfere with the evaluation of RLS symptoms, if they could not maintain a stable dose of any central nervous system-active medications other than the dopaminergic medication during the study period or if they were unwilling to refrain from as-needed use of RLS medications. All procedures were approved by the Institutional Review Board at Massachusetts General Hospital and all participants provided written informed consent.

1.2. Study design

This was an open-label cross-titration study assessing the tolerability and efficacy of a standardized switch from oral dopamine agonists to the rotigotine patch. At a baseline visit, clinical severity measures were assessed and a patch application was demonstrated. A detailed cross-titration schedule specifically tailored for each subject was provided based on the following algorithm: For the first two days, rotigotine at a dose of 1 mg/24 h was applied, usually in the morning, and the usual daily dosage of oral dopamine agonist was decreased by 1 mg for ropinirole, 0.25 mg for pramipexole, or 50/200 for carbidopa/levodopa. On the morning of Day three, the subject and investigator had a phone discussion, and if RLS symptoms were not well controlled in the two previous days, an increase in rotigotine to 2 mg/24 h for Days three and four was advised. Regardless of the change in the rotigotine dose, on Days three to four the oral dopaminergic agent was again decreased by the same amount. On Days five to six, the taper continued as above with a reduction in the dose of ropinirole/pramipexole/levodopa by 1 mg/0.25 mg/50 mg. As above, if the symptoms were not well controlled on Days three to four as determined by phone contact on the morning of Day five, an increase in rotigotine to 3 mg/24h was advised (unless dose-limiting side effects were present). On Day seven, ropinirole/pramipexole/levodopa in the subjects who continued to be on them were again tapered by 1 mg/0.25/50 mg, at which point all the subjects were taken off their oral medication. Further phone contacts occurred weekly in the second and third week after initiating the rotigotine cross-taper. Subjects remained on a stable dose of rotigotine for the final third week unless 1) they reported uncontrolled RLS symptoms and had not reached the maximum rotigotine dose at a previous titration opportunity, in which case they were advised to increase the dose by 1 mg or 2) the side effects required a dose reduction. No rotigotine dose changes were allowed for the final maintenance week. The final visit took place approximately 28 days after the subject's last dose of oral dopamine agonist (35 days after initiating the cross-titration), at which time RLS symptoms and adverse events (AEs) were again assessed. Patients on other medications for RLS (e.g. pregabalin/gabapentin) were required to maintain stable (without increasing or decreasing) doses throughout the switch period. Phone contacts with all the subjects who continued on rotigotine occurred at three, six and 12 months after initiating the cross-titration. International restless legs syndrome (IRLS) severity score, AEs, and concomitant medications for RLS were collected at these planned contacts.

1.3. Assessments

AEs were collected at each face-to-face and phone contact. The primary efficacy measure was the IRLS score assessed at Week five. Investigators also completed the Clinical Global Impression of Change (CGIC) scale at the final visit [12]. Subject-reported scales completed at the Week five visit included the RLS-6 [13], the Epworth Sleepiness Scale [14], the Patient Global Impression of Change (PGIC) [15], and the Preference of Medication (POM) [16] scale. The POM scale describes preferences between two medications and is scored from 1 = "much better, I prefer this medication" to 5 = "much worse, I much prefer my previous medication."

1.4. Statistical analysis

The primary endpoint, the tolerability of switching from an oral dopamine agonist to rotigotine, was calculated as the proportion of subjects who were able to discontinue their oral dopamine agonist and maintain treatment with rotigotine at the Week five visit. The secondary endpoints are 1) overall efficacy of the RLS symptom control on rotigotine, measured by the IRLS at Week five and Month 12 visits versus the baseline IRLS score, 2) the RLS-6 scales, calculated as a mean score for each scale during the final treatment week versus the baseline, 3) patient satisfaction with treatment, assessed by the POM scale and the Patient and Clinician Global Impression of Improvement scales (PGI-I and CGI-I, respectively). The last observation carried forward was used for patients who withdrew from the study due to discontinuation of rotigotine. ANCOVA was used to compare IRLS scores at the baseline versus visits at five weeks and 12 months, with the baseline medication dose (pramipexole equivalents: 0.25 mg pramipexole = 1 mg ropinirole = 50 mg levodopa) as a covariate [10]. Other repeated-measures endpoints (RLS-6) were compared using the paired sample t-test. Spearmann correlations between baseline variables and change in IRLS were computed as values were non-normally distributed. The POM scale and PGIC/CGIC are presented descriptively. The treatment response was determined based on a CGI-I of very much or much improved. AEs are presented in a descriptive format. The significance for all tests was set a priori at $p < 0.05$. Data are presented as mean ± standard error.

2. Results

Characteristics of the 20 enrolled subjects are shown in Table 1. The mean age was 66.0 ± 12.1 years with males making up 35% of patients. The duration of RLS symptoms ranged from two to 63 years with a mean of 22.5 ± 18 years, and the mean RLS treatment duration ranged from two to 30 years with a mean of 11.4 ± 7.2 years. Dopaminergic treatment was present for a mean of 7.6 ± 5.2 years. At the baseline, the patients had moderate RLS symptoms (the mean IRLS score 19.4 ± 5.5), the mean pramipexole equivalent dose was 0.6 ± 0.3 mg, and 30% were taking gabapentin in addition to their oral dopamine agonist. The majority of patients (17 of 20) reported augmented RLS symptoms, with nine of 20 reporting