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Original Article

Management of augmentation of restless legs syndrome with rotigotine: a 1-year observational study

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ABSTRACT

Aim: The aim of this study is to assess the effect of switching to rotigotine transdermal patch on severity of restless legs syndrome (RLS) in patients who experienced acute augmentation with previous oral dopaminergics.
Methods: In this 13-month observational study, adults with moderate-to-severe RLS and augmentation were switched to rotigotine per the physician's independent decision. Assessments included Clinical Global Impression severity score (CGI-1); (primary), treatment regimen for switching (secondary), RLS-6, International RLS Study Group Rating Scale (IRLS), and augmentation severity rating scale (ASRS).
Results: A total of 99 patients received rotigotine, of whom 46 completed observational period, and 43 were assessed for effectiveness. A total of 5 patients switched to rotigotine after a >1-day drug holiday, 23 switched overnight, 9 had an overlapping switch, and 6 received ongoing oral dopaminergics with rotigotine for ≥28 days. Of the 99 patients, 57 took concomitant RLS medications (excluding switching medications) on at least 1 day. At the final visit, median change in CGI-1 (Hodges–Lehman estimate [95% CI]) was −2.0 (−2.5, −1.50); 37 of the 43 patients improved by ≥1 CGI-1 category, and 16 of 43 were responders (≥50% improvement). RLS-6 and IRLS scores also improved. Patients had median ASRS of 0 at the final visit indicating "no worsening/occurrence of augmentation." ASRS item 1 showed a shift in mean time of symptom onset (24-h clock) from 12:38 (baseline) to 18:25 (final visit). Most common reasons for withdrawal of rotigotine were adverse events (26 patients) and lack of efficacy (14 patients).
Conclusions: Switching from oral therapies to rotigotine was effective in improving RLS symptoms in 37 of the 43 patients (from the original population of 99 patients) who remained in the study over 13 months.
Clinical trial registration: ClinicalTrials.gov NCT01386944.

1. Introduction

Three non-ergot dopamine receptor agonists (ropinirole immediate-release [IR], pramipexole IR, and rotigotine transdermal patch) are approved for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in the European Union and in the USA, and are recommended as first-line therapies [1]. In addition, the dopamine precursor levodopa is indicated for RLS in certain European countries, including Germany [2]. A recent meta-analysis confirmed the efficacy of these therapies [3]. Augmentation can be a major complication of long-term dopaminergic therapy for RLS, and is characterized by an overall worsening of symptoms beyond the severity experienced before treatment [4]. Clinical features of augmentation, defined by the International Restless Legs Syndrome Study Group (IRLSSG), include increased

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symptom intensity, the emergence of symptoms earlier in the day, a shorter latency to symptom onset during periods of inactivity, the spread of symptoms to areas of the body that were previously unaffected, and a shorter duration of medication effect [4].

While the pathophysiology of augmentation is still not fully understood, dopaminergic hyperstimulation is thought to play a key role [5], and dopaminergic therapy appears to be the main risk factor. With the exception of a few documented cases with the α-2-δ ligand pregabalin [6] and the opioid tramadol [7], augmentation has not been reported with non-dopaminergic agents. It should be noted that this treatment complication has been seen under placebo treatment in several double-blind studies, indicating limited specificity of the currently available assessment methods [8]. Potential risk factors for augmentation include dopaminergic treatment, dose and duration of treatment, and low ferritin levels [5,9–11]. Although comparative data are limited, the incidence of augmentation appears to be higher with levodopa than with longer-acting dopamine receptor agonists [8,12]. As higher dopaminergic dosages may increase the likelihood of developing augmentation [13,14], doses should be kept as low as possible and should not exceed the limit recommended by regulatory authorities [12,15].

According to present recommendations, RLS treatment may be initiated with either a dopaminergic receptor agonist or an α-2-δ ligand (gabapentin enacarbil, approved in the USA and Japan only) [12,16]. Should clinically significant augmentation develop, a change in treatment regimen may be required [17]. With the exception of case studies [18–20], no data are presently available on when and how to switch patients with augmentation to an alternative therapy. Therefore, recommendations for augmentation management are based on clinical experience. According to expert opinion, patients on levodopa are advised to switch to a dopamine receptor agonist or a non-dopaminergic agent such as an opioid or α-2-δ ligand [2,13].

Clinical studies have indicated low incidence of augmentation with rotigotine, the only long-acting dopamine agonist approved for RLS [14,21]. Continuous delivery of rotigotine via a transdermal patch maintains stable plasma levels over 24 h [22] In a 5-year open-label study, clinically significant augmentation (Max Planck Institute criteria) was seen in 39 (13%) patients on rotigotine, of whom 15 (5%) were administered a dose within the licensed range of 1–3 mg/24 h [14]. The present pilot study was conducted to offer exploratory data for rotigotine in patients who experienced augmentation with their previous oral dopaminergic therapy. This observational study was conducted to assess the effects of switching to the rotigotine patch on RLS symptom severity in patients with augmentation and report data on the management of augmentation in routine clinical practice.

2. Methods

2.1. Design

AURORA (ClinicalTrials.gov: NCT01386944) was a 13-month observational study conducted in German neurology centers. Feasibility assessments were carried out to ensure that all participating physicians had particular expertise in the diagnosis and treatment of patients with RLS and augmentation. Physicians followed routine practice in reaching treatment decisions and treating their patients. Due to preexisting augmentation, the physician made the decision to switch to treatment with rotigotine. This decision was made before including the patients in the study; therefore, study participation did not influence the patient's medical treatment. Patients received oral dopaminergic therapy as either monotherapy or in combination with other medications up to the time of the switch. According to the routine medical practice, characteristics of augmentation (National Institutes of Health [NIH] minimal criteria) were documented at baseline [23]. Treatment according to the European Summary of Product Characteristics for rotigotine transdermal patch was recommended [24]. Patients were evaluated per routine medical practice and no additional diagnostic or monitoring procedures were applied. A total of seven study visits were recommended, with an observational period of 13 months per patient. Visit 1 (baseline) took place at the time of the decision to switch to rotigotine, Visit 2 around 1–7 days post baseline (corresponding to withdrawal from oral dopaminergic treatment, with or without concomitant rotigotine), and Visit 3 up to 28 days post baseline (corresponding to the end of the rotigotine titration phase), followed by four quarterly visits in accordance with routine medical practice (eg, Visit 4: ~4 months, Visit 5: ~7 months, Visit 6: ~10 months, and Visit 7: ~13 months post baseline). As the study was observational, no washout of previous dopaminergic medications was conducted, and all changes in treatment regimen were at the physician's discretion.

2.2. Patients

Inclusion criteria were as follows: (1) adult patients with a diagnosis of moderate or severe RLS; (2) augmentation due to previous oral dopaminergic therapy; (3) the physician's treatment decision was made before the patient was included in the study and was independent of study participation; and (4) the patient had been informed and had given written informed consent for the additional use of his/her medical data. Patients were excluded if they had a diagnosis of secondary RLS or a confirmed iron deficiency (serum ferritin levels were documented if available). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and the observational plan was reviewed by national and local Independent ethics committees.

2.3. Outcome measures

The primary outcome measure was the change from baseline in Clinical Global Impression severity score (CGI-1; seven-point scale) [25] over the course of the study. The change in treatment regimen used for switching to rotigotine (assessed up to 28 days after entering the study) was defined as the secondary outcome. Other variables included CGI-1 responders (≥50% decrease in CG1-1 score relative to baseline), the time taken to switch to rotigotine, change in RLS-6 Scale [26] scores over the course of the study, and change in International RLS Study Group Rating Scale (IRLS) [27] scores at Visit 5 (~7 months) and 7 (~13 months). Augmentation Severity Rating Scale (ASRS)[l] [28] total score over the course of the study was assessed in comparison to RLS symptom severity at the baseline visit, although this use of the scale has not been validated. In addition to the predefined study outcomes, a post hoc assessment of ASRS item 1 ("During the past week, at what time did your RLS symptoms usually start?") was performed. Safety assessments included incidence of adverse events (AEs) and serious AEs. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA). Serious AEs were defined as any AEs (irrespective of a suspected causal relationship to rotigotine) that led to death or were life threatening, required inpatient hospitalization or prolonged existing hospitalization, led to persistent or significant disability or incapacity, led to a congenital anomaly or birth defect, or were considered to be clinically significant or important. Finally, we performed a post hoc analysis of the doses of oral dopaminergic medications taken at the time of initiation of rotigotine. Levodopa-equivalent doses were calculated per Tomlinson et al [29].