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Original Article

Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome

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ABSTRACT

Background: Pramipexole is an effective treatment for restless legs syndrome (RLS), but no controlled studies have lasted >12 weeks.
Methods: RLS patients ($N = 331$) with pretreatment serum ferritin >30 ng/mL were randomly assigned to take double-blind optimized pramipexole (0.125–0.75 mg/d) or placebo for 26 weeks. The primary efficacy endpoint was change in International RLS Study Group Rating Scale (IRLS) score. Other endpoints assessed global change, symptoms, and QoL. Patients maintained symptom diaries. Cases meeting predefined criteria for suspected augmentation were reviewed by a blinded expert panel, which used a predefined algorithm.
Results: Among 321 patients providing post-baseline data, of whom 234 completed 26 weeks, pramipexole was more effective than placebo by multiple endpoints, including an adjusted mean IRLS score change of −13.7 vs. −11.1 ($p = 0.0077$) and an IRLS responder rate (⩾50% score reduction) of 58.6% vs. 42.8% ($p = 0.0044$). Efficacy showed considerable country-to-country variability. Six-Month incidence of confirmed augmentation was 9.2% for pramipexole and 6.0% for placebo. The rate increased with treatment duration for pramipexole but not placebo. Treatment-related adverse events (AEs) were more likely for pramipexole than for placebo, but discontinuation due to AEs was less likely.
Conclusions: During a 6-month period, pramipexole was effective, safe, and generally well tolerated. Because risk of augmentation may have increased over 6 months, it should be studied in longer trials. Beginning or mild augmentation is difficult to distinguish from natural RLS fluctuation, at least in a non-iron-deficient population.

1. Introduction

Dopaminergic treatment is currently the first-line pharmacologic intervention in restless legs syndrome (RLS) [1,2]. For moderate to severe cases, the approved agents include pramipexole, a nonergotamine dopamine agonist with high affinity for the D2-like subfamily of dopamine receptors. In 4 randomized, double-blind phase 3 trials [3–6], a total of approximately 1000 patients received the active drug or placebo for up to 12 weeks. Three of the trials [3–5] had run-in or extension phases lasting up to 46 weeks, all of which corroborated the benefits documented during the double-blind phases. The added phases, however, were partly or wholly open label, and hence could not definitively assess the treatment's long-term effects. The trials also were not designed

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to study augmentation (RLS exacerbation attributed to an ongoing, initially beneficial RLS treatment) or withdrawal (RLS exacerbation if treatment stops).

Here we report the findings of a phase 4, randomized, double-blind, placebo-controlled, dose-titration trial with a multiplicity of long-term (26-week) efficacy endpoints. Safety was judged by profiling adverse events (AEs) and tolerability by rates of premature discontinuation. The safety testing also included assessments for incidence of augmentation, by submission of all suspected cases to a blinded expert panel, and for incidence of withdrawal, by evaluation of RLS severity after each patient's end of treatment.

2. Methods

At 42 sites in 9 European countries, adults (aged 18–85 years) with idiopathic RLS were randomly assigned, at a 1:1 ratio, to receive double-blind pramipexole or placebo. For entry, all patients were required to meet all diagnostic criteria of the International RLS Study Group (IRLSSG) [7], to have a baseline total score >15 on the Study Group's International RLS Rating Scale (IRLS) [8], and to have experienced RLS symptoms at least 2–3 days per week throughout the prior 3 months. Patients were excluded for serum ferritin $\leqslant$30 ng/mL, known hypersensitivity to pramipexole, augmentation during previous RLS treatment, unsuccessful previous treatment with non-ergotamine dopamine agonists (e.g., pramipexole, ropinirole), any non-RLS sleep disorder, any major *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* psychiatric disorder within the prior 2 years, change in any antidepressant regimen within the prior 4 weeks (or any anticipated change), and any use, within the prior 2 weeks, of dopamine agonists, levodopa, or any medication or dietary supplement capable of altering RLS symptoms. Women with childbearing potential were excluded for pregnancy, inadequate contraception, or current breastfeeding of a child. Patients with daytime RLS symptoms were not excluded. The study was approved by the independent ethics committees of the participating countries. Informed, written consent was obtained from all patients prior to randomization.

During the first 4 weeks, treatment was optimized. For pramipexole recipients, treatment commenced with a week at 0.125 mg/d. After weeks 1, 2, 3, and 4, stepwise dosage adjustment was permitted to 0.125, 0.25, 0.50, or 0.75 mg/d (pramipexole dihydrochloride monohydrate), based in each patient on clinically sufficient response (on the Patient Global Impression [PGI] scale [9]) and tolerability. Treatment then continued at the patient's optimized dosage until the end of week 26. All patients were asked to take their treatment once daily, 2–3 h before expected bedtime.

After weeks 1, 4, 6, 12, 18, and 26, all patients underwent on-site evaluation of treatment efficacy, treatment compliance, AEs, and augmentation. At each of these visits, patients assessed themselves by IRLS (the trial's primary outcome measure) and PGI, and were assessed on the Clinical Global Impressions-Global Improvement (CGI-I) scale [9]. For each IRLS assessment, each patient was asked to read each of the instruments 10 items and provide the required self-rating on a patient worksheet while the examiner remained available to clarify any misunderstandings a patient may have had and to record the patient's responses on an investigator worksheet. Self-assessment tools also included the Johns Hopkins Restless Legs Syndrome Quality of Life Questionnaire (RLS-QoL) [10] and the RLS-6 set of scales [11]. All investigators received training on study procedures including all scales and worksheets and the patient diary (described below).

The trial's sample size was based on detection of treatment efficacy. For 26-week change in mean IRLS total score, documentation of a 4.5-point difference between pramipexole and placebo at a 2-sided 5% significance level with 90% power would require that each group have 151 patients. Recruitment of 160 per group was therefore planned. Testing of mean IRLS change was, by analysis of covariance (ANCOVA), adjusted for baseline, country, and treatment group. For IRLS, CGI-I, and PGI, responder rates were defined, respectively, as the proportion of patients with at least a 50% reduction from their baseline total IRLS score, the proportion classified as at least "much improved," and the proportion classifying themselves as at least "much better." Among these endpoints, IRLS and CGI-I responder rates were the trial's key secondary outcomes. All responder-rate findings were subjected to Cochran–Mantel–Haenszel test, and all other efficacy findings to van Elteren test (stratified by country). In all analyses, $p < 0.05$ was considered statistically significant.

Adverse events were identified by asking each patient at each trial visit, "How have you felt since your last visit?" Mild AEs were defined as being easily tolerated, moderate AEs as interfering with usual activities, and severe AEs as preventing usual activities. Serious AEs were defined as being life-threatening or resulting in death or significant incapacity, requiring hospitalization, or requiring medical or surgical intervention to prevent such outcomes. All AEs occurring within 48 h after a patient's last intake of trial medication were classified as having happened under treatment. After weeks 4, 12, and 26, supine and standing pulse rate and diastolic and systolic blood pressure were measured.

Because augmentation would be identifiable only in reference to initial response to treatment, all patients were asked to maintain an RLS symptom diary for the week preceding randomization and the week preceding each scheduled evaluation. For each hour of each of those weeks, the diary documented the severity of a patient's RLS symptoms (none; mild/nonbothersome; bothersome), their time of onset, and the patient's status (sleeping, awake and active, awake but at rest). At all scheduled evaluations, investigators administered an augmentation questionnaire enabling them to screen for suspected augmentation by four standards: IRLSSG criteria [7], developed at a National Institutes of Health workshop and published in 2003; current international criteria (Max-Planck-Institute criteria) [12], developed at a European RLS Study Group consensus conference and published in 2007; a score $\geqslant$5 on the 3-item Augmentation Severity Rating Scale (ASRS) [13]; and an investigator's own judgment, including reliance on diary data. A positive finding on any of these was cause for case referral to an independent, 4-member expert panel. In accordance with current criteria [12], only patients treated for $\geqslant$4 weeks could be considered. To ensure that case referrals were based on thorough, uniform knowledge of augmentation, all investigators had undergone training by the expert panel's chairperson.

For each referred case, the expert panel, blinded to the subject's treatment group, reviewed all available data using a predefined algorithm (Table 1), so as to achieve a consensus in confirming or excluding augmentation or in judging the data to be insufficient for a decision. In the absence of consensus, the panel's chairperson made the final decision. The counts referred to below as "classified augmentation" include not only confirmed augmentation but also all referred cases judged to have insufficient data. The counts referred to as "confirmed augmentation" include only cases in which the data were judged to be sufficient.

Withdrawal was defined as a posttreatment increase (i.e., worsening) of $\geqslant$4 points on a patient's IRLS score, as measured 7 ± 1 days after cessation of treatment. The comparison was with the higher of the patient's scores at screening and randomization.

3. Results

3.1. Study subjects

Of 331 randomized patients, 329 received treatment (starting, for the first subjects, in May 2007, and ending, for the last subjects,