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Original Article

A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome

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Abstract

Objective: To assess the long-term safety and efficacy of ropinirole in the treatment of patients with restless legs syndrome (RLS) over 52 weeks.
Methods: A 52-week, multicentre, open-label continuation study involving 310 patients, conducted in 11 countries. Eligible patients from four parent studies were invited to participate. At parent study entry, all patients had a score of $\geqslant$15 on the International Restless Legs Scale (IRLS). In this continuation study, all participants received ropinirole, 0.25–4.0 mg once daily, for 52 weeks. The primary study objective was to evaluate the safety of ropinirole. Efficacy was assessed by change in IRLS score, as well as by global improvements (clinical global impression [CGI] scale) and improvements in measures of sleep, work productivity, and quality of life.
Results: Overall, 251 (81.0%) patients completed the study. The mean ropinirole dose at study end was 1.90 mg/day. A total of 282 patients (91.3%) reported $\geqslant$1 adverse event. For the majority of patients, the reported adverse events were mild or moderate in intensity. The most common adverse event was nausea. Adverse events led to discontinuation in 8.7% of patients. At week 52, IRLS scores improved by an average of 12.0 points from baseline, and 82.8% of patients were 'much improved' or 'very much improved' on the CGI-improvement scale. Ropinirole treatment was also associated with improvements in measures of sleep and quality of life.
Conclusions: Ropinirole was well tolerated and therapeutic efficacy was maintained over 52 weeks in patients with RLS.

Keywords: Restless legs syndrome; Ropinirole; Open-label clinical trial; Efficacy; Long-term safety; Sleep; Quality of life

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterised by sensations that typically affect the legs (and less frequently the arms), which are often

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described as creeping, crawling or pulling. These sensations are accompanied by an irresistible urge to move the legs. They occur primarily at rest, in the evening or at night, and are relieved, at least in part, by movement or activity.

In many cases, RLS is associated with disrupted sleep and complaints of insomnia, which can have a significant impact on a subject's daytime function and quality of life [1]. In addition to sensory symptoms, which occur during wakefulness, motor symptoms – periodic leg movements during either sleep (PLMS) or nocturnal wakefulness (PLMW) – occur and are observed during polysomnography in patients with RLS [2]. PLMS also contribute to sleep disruption and resulting daytime fatigue [3].

As well as being an idiopathic disorder, RLS can be secondary to other conditions including pregnancy [4,5], iron deficiency [6,7], end-stage renal disease [8], and uraemia [9].

The prevalence of RLS in several studies is 5–10% of the adult population (for any severity or frequency of symptoms) [10–13]. However, despite the observed prevalence and the publication of updated diagnostic criteria for RLS by the International Restless Legs Syndrome Study Group (IRLSSG) [14], there remains a high level of under-diagnosis. In a primary care study of over 23,000 patients, only one quarter of the RLS cohort were given a diagnosis of RLS when consulting primary care physicians about their symptoms [1].

Given the significant impact of RLS on patient quality of life [15], a number of medications have been used to treat RLS. These include benzodiazepines, opiates, and anticonvulsants [1]. However, these agents have important potential concerns; there is a risk of dependency (with opiates and benzodiazepines, for example) [16], particularly relevant when considering long-term treatment; and, although particularly widespread, there is limited support for their use in RLS [17,18] in the form of case reviews and small studies. More recently, dopaminergic agents have been recommended as the treatment of choice for RLS by the American Academy of Sleep Medicine's practice guidelines [17,19].

The efficacy of L-dopa, a traditional dopaminergic agent, in RLS has been demonstrated in several trials [20,21]. However, L-dopa has been associated with a high frequency of augmentation of RLS symptoms (an increased severity of symptoms, earlier daily onset of symptoms or spread of symptoms to other parts of the body) in a high proportion of patients [22]. Augmentation can limit the long-term use of L-dopa in patients with RLS.

Dopamine agonists offer an alternative, and a recent evidence-based review of dopaminergic treatment of RLS, conducted by a task force of the American Academy of Sleep Medicine, highlighted that there has been a shift in focus away from L-dopa and towards dopamine agonists [23]. Some dopaminergic agents, however, for example the ergot-based agonists such as pergolide, while demonstrating efficacy in improving the symptoms of RLS [24–26], may be associated with cardiac complications such as valvular heart disease [27] and fibrosis [28]. The dopamine agonists ropinirole and pramipexole are not ergot-derived and both have shown efficacy in RLS [29–33]. To date, pramipexole has been studied only in small or open-label clinical trials [32–35]. In contrast, ropinirole has been the most extensively studied dopamine agonist. Large, randomised, controlled trials have demonstrated the effectiveness of ropinirole over a 12-week period in alleviating the symptoms of idiopathic RLS (TREAT RLS 1, TREAT RLS 2 and TREAT RLS US) [29,30,36], including motor symptoms (RESET PLM) [31], with benefits observed within two nights of initiation of treatment [37]. The reduction in RLS symptoms and improvement in sleep parameters found with ropinirole, which are maintained during treatment up to 36 weeks [38], have the potential to provide patients with improved daytime function and quality of life [29,30]. However, aside from the 36-week study mentioned above, only short-term treatment effects have been investigated to this point. As RLS is a chronic disorder, patients may require long-term treatment. Thus, it is imperative to evaluate the long-term safety and tolerability of treatment, as well as efficacy.

The goal of the current study was to examine over 1 year the long-term safety of ropinirole in patients with RLS. Secondary objectives included investigating the effectiveness of ropinirole in improving sleep parameters and disease-specific and generic quality-of-life parameters.

2. Methods

2.1. Study design

This was a multicentre, 52-week, open-label continuation study (protocol: 101468/192) of the long-term safety of ropinirole in patients with idiopathic RLS. It was conducted at 57 centres in 11 countries (Australia, Austria, Belgium, Canada, France, Germany, Italy, South Africa, Spain, Sweden, and the United Kingdom).

Subjects completing the following parent studies were eligible for this continuation study: Study 188 (36-week maintenance-of-effect study) [38], Study 190 (TREAT RLS 1; 12-week efficacy study) [29], Study 194 (TREAT RLS 2; 12-week efficacy study [non-US subjects only]) [30] and Study 218 (7-week pharmacokinetic study) [39]. In addition, subjects who met the definition of relapse during the double-blind phase of Study 188 (defined as an increase [worsening] of at least 6 points in the patient's IRLS total score compared with the start of the double-blind treatment phase, or withdrawal of the patient because of lack of