Sleep Medicine 14 (2013) 1085–1091

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Efficacy and safety of rotigotine in Japanese patients with restless legs syndrome: a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study

Yuichi Inoue [a,*], Tetsuo Shimizu [b], Koichi Hirata [c], Naohisa Uchimura [d], Jun Ishigooka [e], Yasunori Oka [f], Junji Ikeda [g], Takayuki Tomida [g], Nobutaka Hattori [h], for the Rotigotine Trial Group

[a] Department of Somnology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan
[b] Department of Neuropsychiatry, Akita University, 1-1 Tegata, Gakuen-machi, Akita 010-8502, Japan
[c] Department of Neurology, Dokkyo Medical University, 880 Kitakobayashi, Shimotsuga-gun, Mibumachi, Tochigi 321-0207, Japan
[d] Department of Neuropsychiatry, Kurume University, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
[e] Department of Psychiatry, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
[f] Department of Sleep Medicine, Ehime University Graduate School of Medicine, Tohon, Japan
[g] Otsuka Pharmaceutical Co., Ltd., 2-9 Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan
[h] Department of Neurology, Juntendo University Hospital, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

ARTICLE INFO

Article history:
Received 3 December 2012
Received in revised form 25 July 2013
Accepted 27 July 2013
Available online 21 August 2013

Keywords:
Restless legs syndrome
Rotigotine
Clinical trial
International Restless Legs Study Group rating scale
Pittsburgh Sleep Quality Index
Japan

ABSTRACT

Objective: We aimed to ascertain the efficacy and safety of transdermal rotigotine (2 and 3 mg/24 h) in Japanese patients with restless legs syndrome (RLS).
Methods: In our double-blind placebo-controlled study, 284 Japanese patients with idiopathic RLS were randomly assigned to receive rotigotine 2 mg/24 h or 3 mg/24 h, or placebo, for 13 weeks. The primary endpoint was the change in International Restless Legs Syndrome Study Group rating scale (IRLS) total score.
Results: The placebo-subtracted decreases in IRLS total score for rotigotine 2 mg/24 h and 3 mg/24 h were −2.8 ± 1.3 and −3.1 ± 1.3, respectively, which were significant ($P < 0.05$). The interaction between baseline Pittsburgh Sleep Quality Index (PSQI) and treatment group for the change in IRLS total score was significant, indicating greater improvements in IRLS total score in patients with severe insomnia. Overall, 80.0%, 86.2%, and 51.6% of patients in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively, experienced adverse events (AEs) including application site reactions in 42.1%, 50.0%, and 7.4% of patients, respectively. None of the AEs were severe.
Conclusions: Our results showed that rotigotine was effective without major safety concerns at doses of up to 3 mg/24 h in Japanese patients with RLS.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder associated with abnormal sensations, particularly in the legs [1,2]. Patients often have a strong desire to move the affected extremities and these sensations are either completely or partially relieved by voluntary movements such as walking. These symptoms are aggravated at rest during the night and often lead to insomnia [3]. Serious RLS can result in daytime sleepiness or malaise associated with nocturnal sleep deprivation, resulting in deteriorated quality of life, depression, and anxiety disorders [4–6]. RLS is also known to be a risk factor for the development of cardiovascular disease [7,8]. Several epidemiologic surveys have been conducted using the International Restless Legs Syndrome Study Group (IRLSSG) and the National Institutes of Health (NIH) criteria [9] and revealed that the morbidity of RLS ranges from 5% to 10% in Western countries [4,10,11] and from 2% to 4% in Japan [12,13].

The four essential criteria for RLS established by the IRLSSG/NIH [9] are as follows: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) an urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) an urge to move or unpleasant sensations are partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues; and (4) an urge to move or

* Corresponding author. Tel.: +81 3 3351 6141.
E-mail address: inoue@somnology.com (Y. Inoue).

1389-9457/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.sleep.2013.07.007

unpleasant sensations that become clearly worse in the evening or at night than during the day or only occur during these periods.

For pharmacotherapy, dopamine receptor agonists are regarded as the first-line treatment of moderate to severe RLS [14–17]. Rotigotine is a non-ergot-derived dopamine agonist for all dopamine receptors (D1–D5), with highest affinity for the D3 dopamine receptor [18,19]. When formulated as a patch, stable plasma concentrations of the drug can be maintained over a 24-h period by continuous delivery [20], allowing control of RLS symptoms during both the daytime and the nighttime [21,22]. To date several clinical trials have been conducted in the United States and Europe to confirm the superiority of the treatment response with rotigotine to that with placebo [21,22]. However, such studies have not yet been conducted in Asian patients. Moreover, the effects of rotigotine on subjective insomnia associated with RLS have not been confirmed. For these reasons, we investigated the efficacy of rotigotine (2 mg/24 h and 3 mg/24 h) on RLS symptoms, the RLS-associated subjective sleep disturbances using an authorized sleep disturbance questionnaire, and the safety of rotigotine (2 mg/24h and 3 mg/24 h) in Japanese patients with idiopathic RLS.

2. Methods

2.1. Patients

Our phase 3, multicenter (44 institutions in Japan), randomized, double-blind, placebo-controlled, parallel-group study of Japanese patients with idiopathic RLS was conducted between February 2010 and December 2010. Patients who fulfilled the following inclusion criteria were enrolled: (1) ages 20 to <80 years at the time of providing informed consent, (2) diagnosis of RLS fulfilling all four items of the IRLSSG/NIH criteria, (3) responsive to prior dopaminergic therapy or no prior treatment for RLS, (4) baseline International Restless Legs Syndrome Study Group rating scale (IRLS) total score $\geqslant$15, and (5) RLS symptoms on $\geqslant$2 days per week for two consecutive weeks before entering the study.

Patients with any of the following criteria were excluded: (1) coexisting sleep disorders other than RLS; (2) somatic conditions that can cause secondary RLS, such as end-stage renal disease or iron deficiency (based on reference values; serum ferritin <18.6 ng/mL [reference range, 18.6–261 ng/mL] in males or <4.0 ng/mL [reference range, 4.0–64.2 ng/mL] in females); (3) concurrent neurologic disease (e.g., polyneuropathy, Parkinson disease, dementia); (4) psychiatric symptoms (e.g., hallucinations, delusions); and (5) symptoms of orthostatic hypertension. The concomitant use of drugs that could possibly affect RLS symptoms, including antiparkinsonian agents, psychoneurotropic agents, hypnotic sedatives, anxiolytic agents, antiepileptic drugs, opioid drugs, gastrointestinal agents with antagonistic effects on dopamine receptors, iron preparations, antihistamines, other central nervous system agents, drugs with opioid-like effects, clonidine, triptans for the treatment of migraine, and magnesium preparations, was prohibited [21,22]. Drugs that could cause QT prolongation (e.g., quinidine, procainamide, amiodarone, sotalol) were also prohibited. Patients were withdrawn from the study if they used any prohibited drugs for any length of time from 14 days before the start of study drug administration to the end of the treatment period. The use of less sedating antihistamines (fexofenadine and loratadine), vitamin B12, and folic acid was permitted during the study, but their dosing regimen was required to remain unchanged from 14 days before starting treatment to the end of the study period.

All patients were provided with an explanation of the study, including its purpose, procedures, and possible risk for adverse reactions or discontinuation, and they gave written informed consent to take part in the study before enrollment. Our study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was reviewed and approved by an institutional review board at each study site. The study was registered with Clinicaltrials.gov (identifier: NCT01084551) and the Japan Pharmaceutical Information Center (identifier, Japic CTI-101053).

2.2. Treatments

The patients were randomly assigned (1:1:1) to receive rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, or placebo. The doses of 2 and 3 mg/24 h were chosen for our study, as a previous dose-finding study in Japan found no significant difference in the efficacy between 1 mg/24 h and placebo (unpublished data; clinicaltrials.gov trial identifier NCT00666965). The study treatment period consisted of a 5-week dose titration period and an 8-week dose-maintenance period, followed by a dose-tapering period at a daily dose of 1 mg/24 h for up to 1 week. We used a fixed-dose titration method [21], in which the rotigotine dose was started at 1 mg/24 h and increased to 2 mg/24 h after 1 week; then the dose was increased to 3 mg/24 h after 2 weeks. After reaching the assigned dose in each group, sham titration was performed. After reaching a dose of 2 mg/24 h or higher, down titration to the previous dose level was permitted only once during the titration period if an intolerable adverse event (AE) occurred.

2.3. Endpoints

The primary endpoint was the change in the IRLS total score (Japanese Version 2.2) [23,24] from baseline to the end of treatment (EOT) at week 13. The proportion of IRLS responders was defined as patients with a $\geqslant$50% improvement in IRLS total score at the EOT compared with the score at baseline as a secondary end point [22]. Other secondary endpoints included improvements in Clinician Global Impression Improvement (CGI-I) and Patient Global Impression Improvement (PGI-I) scores [25], and the total score on the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) manifested the severity of subjective sleep disturbance, mainly insomnia [26,27]. Patients with a CGI-I or PGI-I rating of very much improved or much improved were defined as responders. A PSQI total score $\geqslant$5.5 was defined as pathologic sleep disturbance.

Safety assessments included AEs, and changes in laboratory tests, vital signs, 12-leads electrocardiography, skin irritation assessment [28], the Japanese version of the Epworth Sleepiness Scale completed by the patients to assess safety of sleepiness [29,30], physical and neurologic examinations, and the Japanese version of the modified Minnesota Impulsive Disorders Interview [31] to assess obsessive–compulsive disorders or impulse control disorders. Skin irritation was assessed based on the following six criteria [28]: (1) no reaction; (2) mild erythema; (3) erythema; (4) erythema and edema; (5) erythema plus edema plus papules, seropapules, or small vesicles; and (6) large vesicles.

2.4. Statistical analysis

Based on the results of a previous dose-finding trial of rotigotine in Japanese patients with RLS (unpublished data; clinicaltrials.gov trial identifier NCT00666965), the difference between the rotigotine and placebo groups in the change in IRLS total score from baseline to the EOT was assumed to be 4.5 with a standard deviation (SD) of 9.0 for the change in each group. Under these assumptions, we estimated that we would need a sample size of 80 patients per group to provide an overall power of at least 80% with