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Long-term safety and efficacy of bilastine following up to 12 weeks or 52 weeks of treatment in Japanese patients with allergic rhinitis: Results of an open-label trial

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ABSTRACT

Objective: Bilastine is a novel second-generation antihistamine. This open-label, single-arm, phase III study evaluated the safety and efficacy of long-term treatment with bilastine in Japanese patients with seasonal (SAR) or perennial allergic rhinitis (PAR).

Methods: Patients with SAR or PAR who met the registration criteria and did not violate the exclusion criteria received bilastine (20 mg, once daily) for 12 weeks (treatment period). Patients with PAR who met the transition criteria could elect to continue the bilastine treatment for an additional 40 weeks (continuous treatment period: a total of 52 weeks). Safety and tolerability were the primary outcomes, and the main secondary endpoint was to evaluate changes in efficacy variables from baseline measurements.

Results: Fifty-eight patients with SAR and 64 patients with PAR received bilastine (20 mg/day) for 12 weeks. Fifty-five patients with PAR transitioned to the continuous treatment period. Adverse events (AEs) were reported by 17.2% of patients with SAR and by 31.3% of patients with PAR, and adverse drug reactions (ADRs) were reported by 6.3% of patients with PAR but by no patients with SAR during the 12-week treatment period. All of the ADRs were mild in severity. During the 52-week treatment period, AEs and ADRs were reported by 73.4% and 6.3% of patients with PAR, respectively. All of the ADRs occurred during the 12-week treatment period, and none during the continuous treatment period. The AEs were categorized using the System Organ Class of nervous system disorders; 4.7% of patients reported headache, but none reported somnolence. One serious AE was reported, but it was considered to be unrelated to the bilastine treatment. There were no deaths, and no patients withdrew from the study because of AEs. In patients with SAR, bilastine significantly decreased the total nasal symptom score (TNSS), total ocular symptom score (TOSS), and total symptom score (TSS) relative to baseline. Prolonged treatment with bilastine resulted in the maintenance of a significant reduction in TNSS, TOSS, and TSS from the baseline in patients with PAR. Improvement of quality of life was also observed in patients with SAR and PAR.

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Conclusion: Bilastine was safe, well tolerated, and effective for patients with SAR and PAR. The observed improvement was maintained for the duration of the study, with no loss of drug efficacy (registration number JapicCTI-142622).

1. Introduction

Allergic rhinitis (AR) is a global health problem that affects 10–30% of adults and up to 40% of children [1]. AR is classified as seasonal (SAR) or perennial (PAR) depending on the temporal pattern of exposure to triggering aeroallergens and the duration of symptoms [2]. In Japan, SAR can be triggered by a wide variety of pollen allergens, including cedar, cypress, and grass pollen. The morbidity of SAR depends on the geographic region, the pollen season, and the local climate. Approximately 26.5% of the Japanese population is known to suffer from Japanese cedar (JC) pollinosis in Japan [2]. JC or cypress pollen dispersal starts in early February, reaches a peak in March–April, and finishes in May. Consequently, individuals with JC pollinosis endure allergic symptoms for at least 12 weeks. PAR is most frequently caused by dust mites and animal dander. Patients with PAR endure allergic symptoms throughout the year; 23.4% of the Japanese population was reported to suffer with PAR in 2008 [2].

In the Practical Guideline for the Management of Allergic Rhinitis in Japan [2], the severity of AR is classified as mild, moderate, and severe/very severe. In addition, nasal symptoms are classified as sneezing/nasal discharge, nasal obstruction, or complete, based on the severity of the respective nasal symptoms. The severity and duration of the symptoms of AR vary in different patients. The most effective first-line drugs for AR are second-generation antihistamines and intranasal corticosteroids [2,3]. Second-generation antihistamines are recommended for relief of sneezing and rhinorrhea symptoms in both SAR and PAR. For relief of nasal blockage or combined symptoms, leukotriene receptor antagonists or prostaglandin D_2/thromboxane A_2 receptor antagonists are recommended. Concomitant use with intranasal corticosteroids is also recommended, as needed, for both types of symptoms regarding the severity. To determine the short-term and long-term prognoses of patients receiving drug therapy, observation periods of at least 2–4 weeks and 1–3 months, respectively, are required [4].

Second-generation antihistamines are H_1-receptor antagonists with high efficacy (rapid onset of action for AR symptoms, sometimes even for nasal congestion, improvement of quality of life [QOL], and additional anti-allergic effects) and safety (low sedation rates) [5]. Because antihistamines are used to treat non-life threatening conditions, these medications should be very well tolerated and free of serious and potential safety issues for use in long-term treatment [6,7].

Bilastine, a novel second-generation antihistamine, has been granted marketing authorization for adults and adolescents (≥12 years) in most European countries since 2010. The recommended dose is 20 mg once a day for symptomatic treatment of allergic rhinoconjunctivitis and urticaria [8]. We previously conducted a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the effect of a 2-week treatment period with bilastine in Japanese patients with PAR. We demonstrated that bilastine (20 mg, once daily) was effective and well tolerated in Japanese patients with PAR, and exhibited a rapid onset of action [9]. The International Conference on Harmonisation (ICH) guidelines state that long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year [10]. Accordingly, long-term safety data on treatment with bilastine at 20 mg/day for 1 year were obtained in an overseas clinical trial [11]; however, the safety and efficacy of long-term treatment with bilastine have not been elucidated in Japanese patients with SAR or PAR. To this end, we conducted this open-label phase III study to assess the long-term safety and efficacy of bilastine following 12 or 52 weeks of treatment in Japanese patients with SAR or PAR, respectively.

2. Subjects and methods

2.1. Patients

Patients with SAR (JC pollinosis) were considered eligible for inclusion in the study at the screening visit if they met the following criteria: aged 18–74 years, with at least a 2-year history of JC pollinosis during the JC or cypress pollen season. The inclusion criteria for registration were as follows: positive for specific immunoglobulin E (IgE) antibodies to both JC and cypress allergens, a total nasal symptom score (TNSS) of ≥24 (up to 45 points), and a sum of rhinorrhea or sneezing scores of ≥6 (up to 12 points) for 3 days before registration.

The inclusion criteria for patients with PAR at the screening visit were as follows: aged 18–74 years, with at least a 2-year history of PAR, and a positive nasal provocation test with a house dust disc. The inclusion criteria for registration were: positive for specific IgE antibodies to PAR allergens (i.e., positive for at least one house dust mite, *Dermatophagoides pteronyssinus* or *D. farinae*), a TNSS sum of ≥16 (up to 45 points) and a sum of rhinorrhea or sneezing scores of ≥5 (up to 12 points) for 3 days before registration.

Patients (PAR and SAR) were excluded from the study if they had active infections; nasal septal ulcers or polyps, asthma, or any other nasal, ocular, or ear disorders that could interfere with the efficacy evaluation; had undergone specific immunotherapy or non-specific modulation therapy in the previous 3 years; had undergone immunotherapy or received corticosteroid injections or treatment with humanized anti-IgE antibody (omalizumab) in the previous 180 days; taken other investigational drugs in the previous 90 days; received corticosteroids or P-glycoprotein inhibitors in the previous 30 days; or taken anti-allergic, antihistamine, anticholinergic,

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