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Original article

Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study

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Abbreviations:
AR, allergic rhinitis; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; PET, positron emission tomography; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TSS, total symptom score; QOL, quality of life; AE, adverse event; ADR, adverse drug reaction; ECG, 12-lead electrocardiogram; FAS, full analysis set; SP, safety population; ANCOVA, analysis of covariance; ANOVA, analysis of variance; SD, standard deviation; SE, standard error; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; SAS, statistical analysis software; MCID, minimal clinically important difference

ABSTRACT

Background: Bilastine, a novel non-sedating second-generation H_1 antihistamine, has been approved in most European countries since 2010. This study aimed to evaluate the superiority of bilastine over placebo in Japanese patients with perennial allergic rhinitis (PAR).
Methods: This randomized, double-blind, placebo-controlled, parallel-group, phase III study (trial registration number JapicCTI-142600) evaluated the effect of a 2-week treatment period with bilastine (20 mg once daily), fexofenadine (60 mg twice daily), or a matched placebo (double dummy) in patients with PAR. All patients were instructed to record individual nasal and ocular symptoms in diaries daily. The primary endpoint was the mean change in total nasal symptom scores (TNSS) from baseline to Week 2 (Days 10–13).
Results: A total of 765 patients were randomly allocated to receive bilastine, fexofenadine, or placebo (256, 254, and 255 patients, respectively). The mean change in TNSS from baseline at Week 2 was significantly decreased by bilastine (−0.98) compared to placebo (−0.63, $P = 0.023$). Bilastine and fexofenadine showed no significant difference in the primary endpoint. However, the mean change in TNSS from baseline on Day 1 was more significantly decreased by bilastine (−0.99) than by placebo (−0.28, $P < 0.001$) or fexofenadine (−0.62, $P = 0.032$). The active drugs also improved instantaneous TNSS 1 h after the first and before the second drug administration on Day 1 ($P < 0.05$). The study drugs were well tolerated.
Conclusions: After 2-week treatment period, bilastine 20 mg once daily was effective and tolerable in Japanese patients with PAR, and exhibited a rapid onset of action.

Introduction

Allergic rhinitis (AR) is one of the most common diseases in worldwide. In the Practical Guideline for the Management of Allergic Rhinitis in Japan,[1,2] AR has been classified as seasonal or

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perennial (SAR and PAR, respectively) depending on the temporal pattern of exposure to a triggering aeroallergens and duration of symptoms. SAR is associated with a wide variety of pollen allergens including Japanese cedar pollen and, thus, depends on the geographic location and climatic conditions, whereas PAR is most frequently caused by *Dermatophagoides* allergens (a major antigen in house dust or mites) in Japan.[2,3] AR is a global health problem that affects 10%–30% of the population.[4,5] In 2008, the prevalence rates of PAR, SAR, and AR were 23.4%, 29.8%, and 39.4%, respectively in the Japanese population.[1] The pathological characteristics of both PAR and SAR are a type I allergic disease of the nasal mucosa with associated nasal symptoms such as sneezing and rhinorrhea, as well as nasal congestion or itching. AR symptoms are induced by several chemical mediators released from the mast or inflammatory cells and histamine is a particularly important mediator of AR symptoms, especially sneezing, rhinorrhea, and nasal itching. Oral H_1-antihistamines are symptomatic treatment used to alleviate the symptoms and associated discomfort of AR in everyday life. Newer second-generation H_1-antihistamines are highly selective for the H_1 receptor, and their penetration of the central nervous system is limited. Therefore non-sedating, second-generation H_1-antihistamines are the recommended drug therapy for AR in the present guidelines.[1,5,6] The advantages of oral H_1-antihistamines include rapid onset of action, once-daily dosing, and maintenance of efficacy with regular use.[5]

Bilastine is a novel non-sedating second-generation H_1-antihistamine, which has been approved for the symptomatic treatment of AR and urticaria in numerous countries (Europe, Central/South America, and Africa).[7] It is a potent and highly selective H_1-antihistamine[8] with a good safety profile.[9] Studies in healthy volunteers and patients have shown that bilastine does not affect cardiac conduction[10] or driving ability,[11] satisfied positron emission tomography (PET) criteria to be defined as a non-sedating antihistamine,[12] is not substantially metabolized in humans,[13] and can be safely administered to patients with different degrees of renal insufficiency without the need for dose adjustments.[14] In clinical studies, bilastine 20 mg administered once daily exerted efficacy in AR was comparable to that of cetirizine[15] and desloratadine,[16] while its efficacy in chronic idiopathic urticaria was comparable to that of levocetirizine.[17]

This is the first study to assess the efficacy and safety of once daily bilastine 20 mg versus (vs.) a placebo in Japanese patients with PAR. In addition, the efficacy of bilastine was subsequently compared to that of fexofenadine in a reference group of patients.

Methods

Study design

We conducted a multicenter, randomized, double-blind, placebo controlled, parallel-group, pivotal Phase III study at four centers in Japan between September 2014 and January 2015. The study design, which is shown in Figure 1 consisted of observation and treatment periods. The eligible patients commenced a 2-week observational period and received placebo twice a day for at least 7 days to assess their baseline symptoms under single-blind conditions before their registration. A total of 750 patients were eventually randomly allocated (1:1:1) to one of three treatment groups, bilastine 20 mg, fexofenadine 60 mg, or placebo (double dummy). A non-deterministic minimization method with a stochastic-biased coin was used in the randomization of patients. The sum of the total nasal symptom scores (TNSS) over the 3 days before the randomization ($\geq$16, $\leq$23, and $\geq$24 points) were used as stratification factors of minimization to ensure a balance existed between the treatment groups. Furthermore, the randomization was performed centrally using a computer (ADJUST Co., Ltd., Sapporo, Japan).

The study drugs were supplied by Taiho Pharmaceutical and were administered twice a day, in the morning 1 h before or 2 h after breakfast and in the evening before or after dinner during the observation and treatment periods (Supplementary Table 1). A follow-up visit was scheduled 4–7 days after the end of the treatment. The patients who completed all of their visits were considered to have completed the study while those who were assigned to a treatment and discontinued the study before the completion had an early withdrawal visit to assess the safety and efficacy at the end of the treatment.

Patients

Patients were considered eligible for inclusion in the study if they met the following eligibility criteria: aged 18–74 years, diagnosed with a 2-year or longer history of PAR, and had a positive nasal provocation test with house dust disc and specific

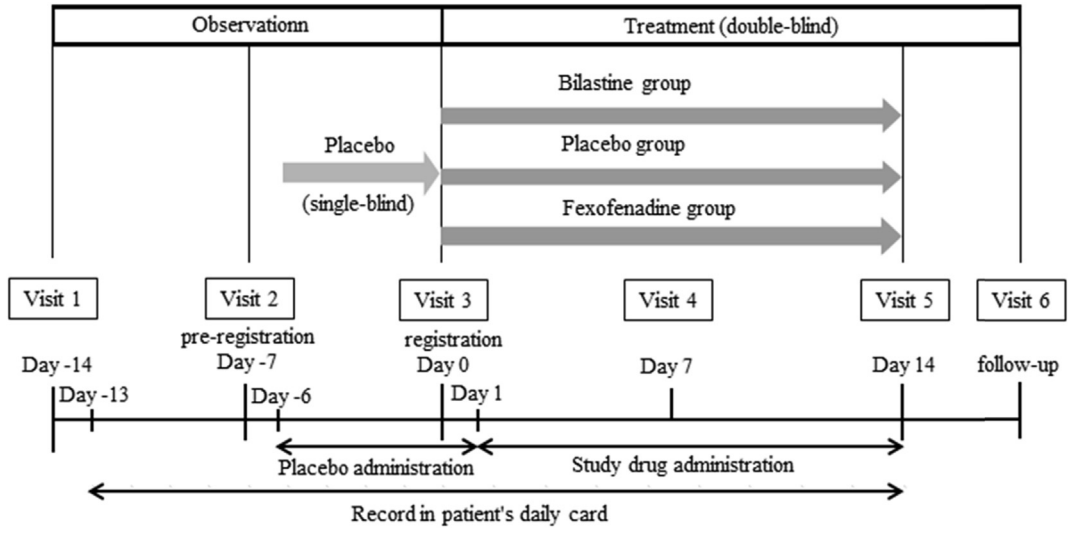

Fig. 1. Study design.