Allergology International 64 (2015) 60–65

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Safety and efficacy of fluticasone furoate nasal spray in Japanese children 2 to <15 years of age with perennial allergic rhinitis: A multicentre, open-label trial

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ARTICLE INFO

Article history:
Received 24 April 2014
Received in revised form
22 June 2014
Accepted 3 July 2014
Available online 26 November 2014

Keywords:
Children
Fluticasone furoate
Perennial allergic rhinitis
Pharmacokinetics
Safety

ABSTRACT

Background: Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of allergic rhinitis (AR). This study aimed to assess the safety, efficacy, and systemic exposure of FFNS in Japanese children with perennial AR (PAR).

Methods: In this multicentre, open-label, phase 3 study, 61 children aged 2 to <15 years were treated with FFNS 55 μg, once daily for 12 weeks. Nasal and ocular symptoms were scored by parents/guardians/patients and recorded in a patient's daily diary. In addition, rhinoscopy findings, including mucosal swelling, were scored by the investigators as an efficacy measure. As a safety measure, adverse events and clinical laboratory data were evaluated.

Results: An adverse event was reported by 67% of patients during the treatment and follow-up period, all of which were mild in intensity. The most commonly reported adverse events were nasopharyngitis and acute sinusitis (acute rhinosinusitis). There were no serious adverse events. FFNS 55 μg improved nasal symptom scores and rhinoscopy findings compared with the baseline. Ocular symptom scores were also improved compared with the baseline in FFNS 55 μg in a sub-group of patients with any ocular symptoms at baseline. FFNS 55 μg was shown to be well tolerated over the 12-week treatment period. Majority of patients receiving FFNS 55 μg had unquantifiable plasma levels of fluticasone furoate (FF).

Conclusions: Twelve-week treatment with FFNS 55 μg, once daily, is well tolerated and effective with low systemic exposure in Japanese children aged 2 to <15 years with PAR.

Introduction

Allergic rhinitis (AR) is the most common chronic condition in children, and its prevalence has been increasing in most countries.[1] The prevalence of AR in children in Japan is approximately 30%,[2,3] which is similar to that in adults. In younger age children, aged 0–4 years, prevalence of AR is low but significant proportion, especially in perennial AR (PAR) (i.e., 4.0%). AR is characterized by symptoms of sneezing, rhinorrhea, nasal congestion, and nasal itching,[2,3] and is often associated with ocular symptoms.[1] According to the allergic rhinitis and its impact on asthma (ARIA) guidelines,[1] AR is intermittent or persistent in duration and mild or moderate/severe in intensity. The Japanese guidelines[2,3] classify AR as PAR or seasonal AR (SAR) depending on the timing and duration of symptoms. Common allergens of PAR include dust mites, animal dander, molds, and cockroaches, and allergens of SAR include Japanese cedar pollens, ragweed, and orchard grass.[4] The Japanese guidelines use a unique scoring system based on frequency of symptoms in a day, including episodes of paroxysmal sneezing and episodes of nose blowing, to rate AR severity (mild, moderate, severe, and most severe).[2,3] This scoring system was used as an efficacy measure in this study.

AR in children has a significant impact on the quality of life (QOL), sleep, and school performance.[5] Cognitive dysfunction related to AR itself can impair the performance of school children with AR[6]. Some studies have shown that ocular symptoms also deteriorate patients' QOL, and some patients consider ocular symptoms to be more annoying than nasal symptoms.[7,8] In addition, if left untreated, comorbid conditions associated with AR, including asthma and otitis media, can be problematic in children.[9]

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2014.07.002

Another important issue associated with AR is the cost of the disease.[1,10] In Germany, the average annual cost of SAR is 1089 € per child or adolescent and 1543 € per adult.[1]

Anti-inflammatory therapy with corticosteroids to effectively control the nasal symptoms of AR is well established, and international guidelines recommend intranasal corticosteroids (INS) as first-line therapy for patients with all but the mildest symptoms.[1] The Japanese guidelines recommend INS as the most effective medication to improve symptoms of AR[2,3]. INS has a broad spectrum of efficacy for a range of nasal symptoms, including congestion, rhinorrhea, and sneezing.[1–3] In addition, INS has been reported to improve eye symptoms accompanying AR.[11,12]

Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of AR, and is administered using a unique, side-actuated device.[13] This delivery system was designed for ease of self-administration, as well as for convenient parent or caregiver administration to children.[14] As a treatment for AR, FFNS is currently approved for use in more than 100 countries including Europe and United States. FFNS is approved for use in patients as young as 2 years of age with AR in the United States and 6 years of age in Europe.

Although well studied in healthy volunteers and patients with AR, including non-Japanese children aged 2–11 years with PAR or SAR,[15,16] the clinical efficacy, safety, and systemic exposure of FFNS in Asian children, including Japanese children, have, to our knowledge, not been investigated. Therefore, we conducted two clinical studies to evaluate the efficacy and safety of FFNS 55 μg in Japanese children. One study was a two-week, randomized, phase III study to assess the efficacy and safety of once-daily FFNS 55 μg compared with placebo in Japanese children aged 6 to <15 years with PAR, which has been reported in this journal.[17] (The ClinicalTrials.gov Identifier: NCT01630135, GlaxoSmithKline protocol number: FFR116364.) In this article, we report the results of the other study, a twelve-week, open-label, phase III study to assess the safety, efficacy, and systemic exposure of once-daily FFNS 55 μg in Japanese children aged 2 to <15 years with PAR.

Methods

Study design

This phase 3, multicenter, open-label study was conducted in 6 centers in Japan. Eligible patients entered a 1–2-week screening period and those meeting the criteria were assigned to the treatment, FFNS 55 μg. Treatment was administered once daily in the morning for 12 weeks, and patients attended a clinic every 4 weeks. A follow-up visit/phone call was scheduled one week after the end of the treatment. Patients who completed all of their visits including the follow-up were deemed to have completed the study. Patients who were assigned to a treatment and discontinued study before the completion had early withdrawal visit to assess safety and efficacy at the end the treatment.

Patients

Eligible patients were aged 2 to <15 years with ≥6 months history of PAR, and had positive specific immunoglobulin E (IgE) antibody tests to PAR allergens (i.e., positive to at least one house dust mite or house dust allergen), elevated nasal eosinophil counts, and a 3 total nasal symptom scores (3TNSS) of ≥3 at baseline.

Patients were excluded from the study if they had symptoms of SAR due to pollen present in their geographic area during the study participation, had a co-morbid disorder that could affect the result of the study (e.g., acute/chronic sinusitis, nasal polyps, upper respiratory or eye infection), had a co-morbid disease that could threaten their safety (e.g., tuberculosis, infection without effective antibacterials, serious hepatic/renal/cardiac/pulmonary dysfunction or hematopoietic disorder, uncontrolled hypertension/diabetes mellitus, or asthma [except for mild intermittent cases]), or used medications that could affect the efficacy outcome of the study (e.g., systemic corticosteroids within 8 weeks of the study).

Use of any medication for allergic rhinitis, other than the study medication, and any concomitant medication that could affect the efficacy outcome of the study (e.g., corticosteroids) was prohibited during the screening and treatment periods.

Safety assessments

The primary safety endpoints were frequency and severity of adverse events. Adverse events were monitored during the treatment and follow up periods. Safety of FFNS was also assessed by laboratory tests (hematology and clinical chemistry). Blood samples (e.g. hematology, clinical chemistry, IgE) were analyzed at central laboratories. Treatment compliance was assessed through patient diary cards.

Efficacy assessments

Efficacy values included 3TNSS, 4TNSS, total ocular symptom scores (TOSS), individual nasal and ocular symptom scores, troubles with daily life score, rhinoscopy findings, and overall evaluation of response to therapy. Parents/guardians/patients were instructed to record patients' symptom scores (individual nasal and ocular symptoms and troubles with daily life) in a diary every day during the screening and treatment periods. Each baseline value was an average of values obtained on 4 consecutive days prior to randomization. Investigators scored rhinoscopy findings at baseline (randomization) and at each visit during the treatment period. Parents/guardians/patients and investigators evaluated the overall response to therapy at the end of the treatment period.

3TNSS is the sum of individual 4-point scores for sneezing (number of episodes of paroxysmal sneezing in a day: 0 = 0 time; 1 = 1–5 times; 2 = 6–10 times; 3 = ≥11 times), rhinorrhea (number of episodes of nose blowing in a day: 0 = 0 time; 1 = 1–5 times; 2 = 6–10 times; 3 = ≥11 times), and nasal congestion (0 = none; 1 = nasal congestion without oral breathing; 2 = severe nasal congestion causing occasional oral breathing in a day; 3 = severe nasal congestion causing prolonged oral breathing in a day). 4TNSS is the sum of individual 4-point scores for sneezing, rhinorrhea, nasal congestion, and nasal itching (0 = none; 1 = minimal awareness of the symptom; 2 = definite awareness of symptom that is tolerable [between 3 and 1]; 3 = severe symptom that causes interference with activities of daily living). TOSS is the sum of individual 4-point scores for eye itching, tearing, and eye redness, which were scored as follows: 0 = none; 1 = minimal awareness of the symptom; 2 = definite awareness of symptom that is tolerable (between 3 and 1); 3 = severe symptom that causes interference with activities of daily living. Troubles with daily life score was scored as follows: 0 = no trouble; 1 = few troubles with daily life; 2 = Intermediate between 3 and 1; 3 = painful and complicating daily life. Rhinoscopy findings included swelling of the inferior turbinate mucosa (0 = none; 1 = possible to see the center of the middle turbinate; 2 = between 3 and 1; 3 = impossible to see the middle turbinate) and quantity of nasal discharge (0 = none; 1 = small amount adhered; 2 = between 3 and 1; 3 = filled). Overall evaluation of response to therapy assessed the change in AR symptoms from the baseline on a 7-point score (7 = significantly worse; 4 = no change; 0 = significantly improved). The nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and