Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: The importance of allergen-specific serum IgE

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Background: Previous trials have demonstrated the efficacy, safety, and optimal dosage of the 5-grass pollen sublingual tablet for adults and children with grass pollen–induced allergic rhinoconjunctivitis.
Objectives: We sought to evaluate the efficacy and safety of 300 index of reactivity (IR) 5-grass pollen sublingual tablet in US adults.
Methods: Adults with grass pollen allergy and Rhinoconjunctivitis Total Symptom Scores of 12 or greater (scale, 0-18) during the previous grass pollen season were randomized in a double-blind, placebo-controlled study to receive 300IR 5-grass pollen sublingual tablet or placebo starting 4 months before and continuing through the pollen season. The primary efficacy end point was the daily Combined Score (CS; scale, 0-3), which integrates symptoms and rescue medication use.
Results: Four hundred seventy-three participants were randomized. The mean daily CS over the pollen period was significantly lower in the active treatment group versus the placebo group (least-squares mean difference: −0.13; 95% CI, −0.19 to −0.06; $P = .0003$; relative reduction: 28.2%; 95% CI, 13.0% to 43.4%). In placebo-treated participants, the daily CS least-squares mean was 0.32 in the subgroup with baseline timothy grass–specific serum IgE of less than 0.1 kU/L (n = 23) and 0.46 in those with baseline timothy grass–specific serum IgE of 0.1 kU/L or greater (n = 204). The most frequent reported adverse events were oral pruritus, throat irritation, and nasopharyngitis. There were no reports of anaphylaxis, and no actively treated participant received epinephrine.
Conclusion: In US adults with grass pollen–induced allergic rhinoconjunctivitis, preseasonal and coseasonal treatment with 300IR 5-grass pollen sublingual tablet demonstrated clinically meaningful efficacy, especially in study subjects with measurable timothy grass–specific serum IgE. Use of 300IR 5-grass pollen sublingual tablet was safe and well tolerated. A requirement for a measurable level of allergen-specific serum IgE should be considered in future studies in this field. (J Allergy Clin Immunol 2012;130:1327-34.)

Key words: *Double-blind, placebo-controlled trial, allergy, allergic rhinoconjunctivitis, grass pollen, specific immunotherapy, sublingual immunotherapy tablet, combined score, grass-specific IgE*

Approximately 30 million Americans have allergic rhinoconjunctivitis (ARC),[1] much of which is caused by grass pollen allergy.[2] Untreated or inadequately treated ARC can cause sleep[3] and mood disorders[4] and impair social functioning[5] and work performance.[6]

Current treatment options include antihistamines and intranasal corticosteroids. These provide temporary relief of allergy symptoms but are not disease modifying. A large proportion of patients are "not very satisfied" with pharmacologic therapies, and the most common reasons for stopping treatment include lack of efficacy (37%), effectiveness beginning to wear off (35%), lack of 24-hour relief (32%), and bothersome side effects (25%).[7] Subcutaneous immunotherapy (SCIT) is a guideline-recommended therapeutic option for patients in whom symptomatic medications are ineffective, unwanted, or contraindicated.[8] Despite the clear benefits of SCIT, only 5% of the US population with allergic rhinitis, asthma, or both receive this treatment.[9] Its use is limited by the risk of near-fatal or fatal anaphylaxis, as well as the discomfort and inconvenience of frequent injections.[10-12]

The favorable safety profile and convenience of sublingual immunotherapy (SLIT) are likely factors for the substantial and growing increase in its use in Europe.[12,13] Recent studies have demonstrated the efficacy of SLIT tablet in the treatment of grass pollen–associated ARC in adults and children.[14-19] The purpose of this trial was to assess the efficacy and safety profile of 300 index of reactivity (IR) 5-grass pollen sublingual tablet in US adults with grass pollen–induced ARC.

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Abbreviations used
AdSS: Adjusted Symptom Score
ARC: Allergic rhinoconjunctivitis
CS: Combined Score
FAS: Full analysis set
IR: Index of reactivity
LS: Least-squares
RMS: Rescue Medication Score
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RSS: Individual Rhinoconjunctivitis Symptom Score
RTSS: Rhinoconjunctivitis Total Symptom Score
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SPT: Skin prick test
TEAE: Treatment-emergent adverse event
WAO: World Allergy Organization

METHODS

Study design

This was a double-blind, placebo-controlled, parallel-group, randomized, multicenter study conducted at 51 sites in the United States (ClinicalTrials.gov no. NCT00955825). Written informed consent was obtained from all participants before study entry. The study was conducted in accordance with International Conference on Harmonisation good clinical practice and approved by the appropriate institutional review boards and the US Food and Drug Administration.

Study subjects were enrolled between December 2008 and August 2009 for a 6-month preseasonal and coseasonal treatment phase and a 2-week follow-up phase (Fig 1).

Eligible participants were randomized 1:1 to active treatment or placebo by using a computer-generated list (block size of 4; for details on randomization, see the Methods section in this article's Online Repository at www.jacionline.org).

Participants

The study enrolled men and women aged 18 to 65 years with documented grass pollen–related ARC for at least the 2 previous grass pollen seasons, a positive skin prick test (SPT) response to timothy grass (mean wheal diameter of 5 mm or greater than that elicited by the negative control; longest flare dimension, ≥10 mm), a Retrospective Rhinoconjunctivitis Total Symptom Score (RTSS; scale, 0-18) of 12 or greater during the previous grass pollen season, and an FEV_1 of 80% or greater of predicted value.

A panel of seasonal and perennial aeroallergens (including timothy and other grasses [Bermuda, Bahia, and Johnson grasses], trees and weeds, dust mites, molds, and dog and cat dander; Hollister-Stier Laboratories, Spokane, Wash), along with any other aeroallergens considered relevant by the investigator, was tested by SPT.

Participants were excluded from the study if they had (1) a positive SPT response to any other endemic grass allergens present in their region during the grass pollen period (including Bermuda, Bahia, and Johnson grasses); (2) clinically significant, confounding symptoms of allergy to other allergens that potentially overlapped the grass pollen period (eg, tree allergens, dust mites, and molds); or (3) asthma requiring treatment with medications other than inhaled β_2-agonists.

Study treatment and rescue medication

Active treatment consisted of 300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*). For details on the active treatment, see the Methods section in this article's Online Repository). Active and placebo tablets were identical in appearance and taste to ensure blinding.

Treatment was initiated approximately 4 months before the expected start of the grass pollen period at each study center and continued for its duration. One 300IR or placebo tablet was to be taken sublingually at the same time every day from the randomization visit to the end of the treatment period. Participants were instructed to leave the tablet under the tongue until it had completely dissolved before swallowing. The first 3 doses were taken at the study site, and the participants were monitored for 30 minutes. The remainder of the treatment was taken at home. Self-injectable epinephrine was provided for use in the event of a severe systemic reaction, and study subjects were given instructions in its use. Rescue medications (oral and eye drop antihistamines and nasal corticosteroids) were supplied to participants who were instructed to use them according to a stepwise regimen for the management of severe or intolerable ARC symptoms. Participants were to consult the investigator if they remained symptomatic despite these treatments. Investigators could then provide study subjects with oral corticosteroids.

Participants were considered treatment compliant if the number of tablets taken was between 80% and 120% (inclusive) of the expected value.

Grass pollen season

Pollen counts were monitored and recorded at each study center during the 2009 grass pollen season. The pollen period was defined as starting on the first of 3 consecutive days with a grass pollen count (7-day moving average) of 10 grains/m^3 of air or greater and ending on the last day of 3 consecutive days with a grass pollen count (7-day moving average) of 10 grains/m^3 of air or greater. Pollen period start and end dates were determined before unblinding the data.

Outcome

Participants were provided with a daily record card for recording the 6 individual Rhinoconjunctivitis Symptom Scores (RSSs; sneezing, runny nose, itchy nose, nasal congestion, itchy eyes, and watery eyes) and rescue medication use during the previous 24 hours. The diary cards were to be completed at the same time every evening from approximately 3 weeks before the pollen season until its end by using a 4-point descriptor scale for each symptom: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The daily RTSS was the sum of the 6 individual RSSs. The daily Rescue Medication Score (RMS) was derived as follows: 0, no rescue medication taken; 1, use of antihistamine (oral drops, eye drops, or both); 2, use of nasal corticosteroid; and 3, use of oral corticosteroid. If a study subject took 2 or more rescue medications on the same day, the highest score was used for the RMS.

The primary efficacy criterion was the daily Combined Score (CS), a patient-specific measure that combines symptom (RTSS) and medication (RMS) scores per the World Allergy Organization (WAO) taskforce recommendations for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy.[20] The daily CS was calculated as follows:

$$CS = [(RTSS/6)+RMS]/2$$

and ranged from 0 to 3. Secondary efficacy criteria included the daily RTSS, the daily RMS, the daily Adjusted Symptom Score (AdSS; which adjusts the RTSS according to rescue medication use),[21] each of the daily RSSs, quality of life, and patient's global evaluation of treatment efficacy. Quality of life was evaluated by using the overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.[22] The questionnaire was administered at screening and at the expected middle of the grass pollen period (visit 5). The RQLQ consists of 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). In the patient global evaluation of treatment efficacy, which was completed at the end of the grass pollen season, each participant was asked to rate their overall symptoms relative to those of the previous season by using a 5–point Likert scale (1, marked worsening; 2, slight to moderate worsening; 3, no change; 4, slight to moderate improvement; and 5, marked improvement).

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