Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen–induced rhinoconjunctivitis

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Background: Seasonal allergic rhinoconjunctivitis affects millions of persons. The efficacy of allergen sublingual immunotherapy (SLIT) was demonstrated in previous short-term studies.

Objectives: We sought to evaluate the sustained efficacy of 2 dosing regimens of a pre- and coseasonal treatment with 300 IR (index of reactivity) 5-grass-pollen SLIT tablets (Oralair) compared with placebo assessed by using the average adjusted symptom score (AAdSS) at season 3 in adults with grass pollen–induced rhinoconjunctivitis.

Methods: Six hundred thirty-three patients were treated for either 2 or 4 months before and then during the grass pollen season with active or placebo treatment for 3 consecutive seasons. The primary outcome was the AAdSS, a symptom score adjusted for rescue medication use, after 3 consecutive treatment seasons. Secondary outcomes were symptoms and rescue medication score, quality-of-life, and safety assessments.

Results: The mean AAdSS was reduced by 36.0% and 34.5% at season 3 in the 2- and 4-month pre- and coseasonal active treatment groups, respectively, compared with that in the placebo group ($P < .0001$ for both). Reductions were observed in total symptom scores and ISSs and the medication score, with a marked improvement in quality of life for both active groups compared with the placebo group at season 3. Most treatment-emergent adverse events were local reactions expected with SLIT, decreasing in number and intensity in each treatment season.

Conclusions: Sustained efficacy of 2- and 4-month pre- and coseasonal treatment with the 300 IR tablet over 3 pollen seasons was demonstrated, with reduction in symptoms and rescue medication use. The treatment was well tolerated. Adverse events decreased in number and intensity over the 3 seasons. (J Allergy Clin Immunol 2011;128:559-66.)

Key words: *Rhinoconjunctivitis, sublingual immunotherapy, grass pollen, allergen, pre- and coseasonal treatment*

Respiratory allergy occurs in more than 500 million persons around the world.[1,2] In developed countries allergic rhinitis affects between 10% and 25% of the general population,[3] with an average of 23% in European countries.[4] The risk of asthma is higher in patients with rhinitis.[5] Allergies to grass, weed, and tree pollen characteristically result in seasonal rhinitis symptoms, which correlate with the presence of allergen exposure in the environment. The primary approach to the control of symptoms is the identification and avoidance of the causal allergens, which is often impossible for pollen. Pharmacotherapy and immunotherapy are the main treatment modalities.

Allergen immunotherapy is considered appropriate when allergic rhinitis symptoms cannot be controlled sufficiently by avoidance of the allergen or an optimal symptomatic medication regimen. Allergen immunotherapy acts on the main cause of the allergic reaction by modifying or downregulating the immune response. Sublingual immunotherapy (SLIT) tablets containing freeze-dried allergen extracts of 5 grasses (cocksfoot *[Dactylis glomerata]*, meadow grass *[Poa pratensis]*, rye grass *[Lolium perenne]*, sweet vernal grass *[Anthoxanthum odoratum]*, and timothy grass *[Phleum pratense]*) have been developed by Stallergenes S.A. (Antony, France) and approved for use in 23 European countries under the trade name Oralair.

Short-term studies in adult and pediatric patients demonstrated the efficacy in the first pollen season after starting therapy with Oralair.[6,7] This study evaluated the sustained efficacy and the safety of pre- and coseasonal treatments with a 300 IR (index of reactivity) 5-grass SLIT tablet in patients with grass pollen–induced rhinoconjunctivitis compared with that of placebo, as assessed by the average adjusted symptom score (AAdSS)[8,9] over 3 consecutive pollen seasons. Efficacy parameters were reported at each season.

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Abbreviations used

AAdSS: Average adjusted symptom score
AdSS: Adjusted symptom score
AE: Adverse event
ANCOVA: Analysis of covariance
ARMS: Average rescue medication score
ARTSS: Average rhinoconjunctivitis total symptom score
ISS: Individual symptom score
LS: Least squares
RMS: Rescue medication score
RTSS: Rhinoconjunctivitis total symptom score
SLIT: Sublingual immunotherapy
TEAE: Treatment-emergent adverse event

METHODS

Study design

We performed a randomized, multicenter, double-blind, placebo-controlled, 5-year, ongoing phase III study with 3-season treatment and 2-year follow-up phases. Six hundred thirty-three men and women 18 to 50 years of age with seasonal grass pollen–induced allergic rhinoconjunctivitis for at least the 2 previous pollen seasons were enrolled. The study was conducted in Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, and Slovakia. The use of antihistamines, nasal corticosteroids, and oral corticosteroids as rescue medication was allowed by using a stepwise regimen defined in the study protocol. The protocol was reviewed and approved by local regulatory authorities and independent ethics committees in each country and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice–International Conference on Harmonisation guidelines. Written informed consent was obtained from all patients before starting any study procedure.

Treatment was initiated 4 months before the expected start of the pollen season. Patients received either placebo or 300 IR 5-grass-pollen tablets (Oralair) sublingually once daily for 2 months or 4 months before and then during the pollen season (the 2-month and 4-month groups, respectively) for 3 consecutive pollen seasons in years 1 to 3 (2007, 2008, and 2009 seasons). The 2-month group also received placebo for 2 months before the start of active treatment during the time that the 4-month group was receiving active treatment to maintain the blinding. The primary end point was the AAdSS assessed for the third pollen season. The fourth and fifth pollen seasons (years 4 and 5) are treatment free, with follow-up periods currently ongoing (Fig 1). The secondary end points discussed in this publication were symptom and medication scores, individual symptom scores (ISSs), symptom and medication-free days, quality of life, and safety.

Baseline characteristics

Sensitization status to either 5-grass-pollen allergens only (monosensitization) or to 5-grass-pollen allergens and at least another allergen (polysensitization) was derived from a skin prick test at screening. Asthma status and severity were recorded at every visit. A retrospective rhinoconjunctivitis total symptom score (RTSS) was calculated from the most severe rhinoconjunctivitis symptoms of the previous pollen season, as reported by the patient.

Symptom and medication scores

Symptom and medication scores have been discussed previously.[8,10] The following 6 rhinoconjunctivitis symptoms were assessed daily by the patient over each pollen season: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. The severity of these symptoms was evaluated by using a 4-level descriptive scale: 0, absent (no sign/symptom evident); 1, mild (sign/symptom clearly present but minimal awareness and easily tolerated); 2, moderate (definite awareness of sign/symptom, bothersome but tolerable); and 3, severe (sign/symptom hard to tolerate and causes interference with daily activities, sleeping, or both).

For each of the 6 ISSs, an average for each pollen season was calculated, resulting in ISSs per pollen season. The sum of the daily 6 ISSs provided the daily RTSSs, which ranged from 0 to 18. The average rhinoconjunctivitis total symptom score (ARTSS) was defined as the average of the daily RTSSs for the considered pollen period during treatment (for study years 1, 2, and 3).

The rescue medication score (RMS) was recorded daily by the patients. The following scale was used: 0, no rescue medication; 1, antihistamine (oral and/or eye drops); 2, nasal corticosteroid; and 3, oral corticosteroid. If a patient took 2 or more categories on the same day, the higher score was used for the RMS. The RMS on a particular day was only valid if the RTSS was valid for that same day. Daily RMSs were summarized as the average rescue medication score (ARMS) during a pollen season while receiving treatment (for study years 1, 2, and 3).

The daily adjusted symptom score (AdSS) corresponds to adjustment of the daily RTSS for rescue medication use. When a patient takes rescue medication on a particular day, the observed symptom severity is biased. To adjust for rescue medication use, we assume that the true severity of the symptoms is at least as high as on the preceding rescue medication–free day. Because rescue medication can be taken early in the morning or late in the evening on a particular day, the adjustment applies to the day of rescue medication use and the following day. The AdSS is defined by using the following algorithm:

1. On the first day, AdSS and RTSS are equal:

$$\mathrm{AdSS}_1 = \mathrm{RTSS}_1.$$

2. If a patient did not take rescue medication on day *(d-1)* and day *d*, then:

$$\mathrm{AdSS}_d = \mathrm{RTSS}_d.$$

3. If a patient took rescue medication on day *d*, then:

$$\begin{aligned}\mathrm{AdSS}_d &= \text{maximum}\,(\mathrm{RTSS}_d,\ \mathrm{AdSS}_{d-1}) \text{ and } \mathrm{AdSS}_{d+1}\\ &= \text{maximum}\,(\mathrm{RTSS}_{d+1},\ \mathrm{AdSS}_d).\end{aligned}$$

If RTSS_d was missing, AdSS_d was missing. If a patient took rescue medication at day *d* and RTSS_{d-1} was missing, then:

$$\mathrm{AdSS}_d = \mathrm{RTSS}_d.$$

The AAdSS is the average of the nonmissing daily AdSSs over the pollen season and ranges from 0 to 18.

The proportion of symptom and medication-free days, defined as days on which the patient had no symptoms and did not take any symptomatic medication, was calculated as follows:

$$\begin{aligned}&100 \times (\text{number of symptom} - \text{ and medication} - \text{free days})/\\ &\qquad(\text{number of days in the considered pollen period}).\end{aligned}$$

The patient's quality of life was assessed by using the self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire.[11]

Pollen season measurements

The expected site-specific start and end dates of the 2007, 2008, and 2009 grass pollen seasons were determined before the study's start by Dr S. Jäger (ENT University Clinic, Vienna, Austria), taking into account historical pollen data, pollen counts, and pollen graphs during the previous pollen seasons for the various study sites. The expected dates were used to define when to start and end treatment at the site level. The actual start and end dates for the grass pollen period of each study year were established based on the pollen counts measured at pollen traps in the regions where sites were located during each pollen season.

The pollen period for statistical analysis was defined as starting on the first of 3 consecutive days with a grass pollen count of at least 30 grass pollen grains per cubic meter of air and the end as the last day of 3 consecutive days with a grass pollen count of 30 grass pollen grains or above per cubic meter of air. The daily pollen counts were available at the end of each grass pollen season during the study in all 3 years, so that the start, end, duration, and intensity of the various pollen seasons at each site could be discriminated according to the definition detailed above.