SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial

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Background: The main aim of specific immunotherapy is sustained effect due to changes in the immune system that can be demonstrated only in long-term trials.
Objective: To investigate sustained efficacy and disease modification in a 5-year double-blind, placebo-controlled trial, including 2 years of blinded follow-up after completion of a 3-year period of treatment, with the SQ-standardized grass allergy immunotherapy tablet, Grazax (*Phleum pratense* 75,000 SQ-T/2,800 BAU,* ALK, Denmark) or placebo.
Methods: A randomized, double-blind, placebo-controlled, multinational, phase III trial included adults with a history of moderate-to-severe grass pollen–induced allergic rhinoconjunctivitis, with or without asthma, inadequately controlled by symptomatic medications. Two hundred thirty-eight participants completed the trial. End points included rhinoconjunctivitis symptom and medication scores, combined scores, asthma symptom and medication scores, quality of life, days with severe symptoms, immunologic end points, and safety parameters.
Results: The mean rhinoconjunctivitis daily symptom score was reduced by 25% to 36% ($P \leq .004$) in the grass allergy immunotherapy tablet group compared with the placebo group over the 5 grass pollen seasons covered by the trial. The rhinoconjunctivitis DMS was reduced by 20% to 45% ($P \leq .022$ for seasons 1-4; $P = .114$ for season 5), and the weighted rhinoconjunctivitis combined score was reduced by 27% to 41% ($P \leq .003$) in favor of active treatment. The percentage of days with severe symptoms during the peak grass pollen exposure was in all seasons lower in the active group than in the placebo group, with relative differences of 49% to 63% ($P \leq .0001$). Efficacy was supported by long-lasting significant effects on the allergen-specific antibody response. No safety issues were identified.
Conclusion: The results confirm disease modification by SQ-standardized grass allergy immunotherapy tablet in addition to effective symptomatic treatment of allergic rhinoconjunctivitis.
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Key words: *Allergy immunotherapy tablet, disease modification, grass pollen, immunotherapy, sublingual, sustained efficacy, placebo-controlled,* Phleum pratense*, rhinoconjunctivitis, rhinoconjunctivitis quality of life*

The increasing prevalence of atopic diseases such as allergic rhinitis/rhinoconjunctivitis, allergic asthma, and food allergy is a major health issue worldwide. In Western Europe and the United States, up to 20% of the adult population suffers from allergic

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*SQ-T (standardized quality tablet units) and BAU (biological activity units) are quantitative measures of biological activity; ie, the potency of allergen extracts/vaccines. One grass AIT contains 75,000 SQ-T of timothy *(Phleum pratense)* grass pollen extract (measure of total biological potency using ALK in-house reference), equivalent to 2,800 BAU (measure of total biological potency, defined by the FDA).

Abbreviations used
AIT: Allergy immunotherapy tablet
DMS: Daily medication score
DSS: Daily symptom score
RCS: Rhinoconjunctivitis combined score
SQ: Standardized quality

rhinoconjunctivitis.[1-3] Indirect costs such as those due to absenteeism from work and decreased productivity are substantial; estimates suggest 3.5 million lost workdays per year in the United States alone.[4]

The main aim of specific immunotherapy is a sustained significant and clinically relevant disease-modifying effect in posttreatment years.[5] Changes in T-cell reactivity and induction of non-IgE antibodies with blocking capacity are regarded as immunologic markers of the immunomodulation that leads to clinical tolerance.[6,7]

It is generally accepted that the appropriate primary end points for assessing the response of allergic rhinoconjunctivitis to specific immunotherapy are the rhinoconjunctivitis symptom and medication scores, which may be reported separately or as a combined score. Because both symptom and medication scores are reduced by effective treatment of allergic rhinoconjunctivitis, it is now considered advantageous by global regulatory bodies to report the 2 responses as a single combined score.[5,8,9]

The standardized quality standardized grass allergy immunotherapy tablet (AIT) contains an extract of *Phleum pratense* (timothy grass) pollen. The grass AIT is indicated and approved in most of Europe for disease-modifying treatment of grass pollen–induced rhinitis and conjunctivitis in adults and children. The tolerability and efficacy of the tablet has been demonstrated in several randomized, placebo-controlled trials in Europe and North America.[10-16]

This is the first full 5-year double-blind, placebo-controlled trial demonstrating the efficacy of sublingual tablet immunotherapy with 3 years of treatment and 2 years of immunotherapy-free follow-up after the completion of treatment. Symptomatic medications were provided to all participants as needed throughout the trial.

METHODS

Clinical trial design

Details of the randomized, double-blind, placebo-controlled trial, conducted according to the Declaration of Helsinki,[17] have been published previously[11,12,14] (ClinicalTrials.gov number: NCT00227279). From original 1 year of treatment, the trial was extended to cover in total 3 years of active treatment and 2 years of follow-up to investigate long-term and sustained efficacy of grass AIT (extension implemented in April 2005). The ethics committees in each country approved the trial as well as the extension, and participants gave written informed consent and reconsented to the extension prior to its inception. Enrollment of participants commenced in September 2004. A total of 51 sites in 8 European countries participated in the trial. Data collection, management, statistics, and results reporting upon trial completion were performed by the sponsor.

Trial population

The main inclusion criteria were males or females; age 18 to 65 years; a clinical history of grass pollen–induced allergic rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season, with rhinoconjunctivitis symptoms interfering with usual daily activities or sleep and remaining troublesome despite treatment with symptomatic medications; and positive skin prick test result (wheal diameter ≥ 3 mm) and serum specific IgE (IgE CAP class ≥2) to *P pratense*. The main exclusion criteria were $FEV_1 < 70\%$ of predicted value, a clinical history of symptomatic seasonal allergic rhinitis/asthma due to tree or weed pollen potentially overlapping the grass pollen season, a clinical history of significant active perennial allergic rhinitis/asthma caused by an allergen to which the participant was regularly exposed, previous immunotherapy within the last 5 years, and a history of anaphylaxis or angioedema.

Assignment and treatment

Block randomization randomly assigned participants to daily treatment with grass AIT (Grazax, *P pratense* 75,000 SQ-T/2,800 BAU, ALK, Denmark) or placebo (1:1). Randomization was performed by ALK (by a statistician not otherwise involved in the trial) by using the SAS system for Windows, version 8e (SAS Institute, Cary, NC).

The tablets were supplied as fast-dissolving, neutral-tasting oral lyophilisates for sublingual application. Excipients included gelatin, mannitol, and sodium hydroxide. Placebo was indistinguishable from the active tablet in appearance but contained no grass pollen extract. Investigational treatment was initiated 4 to 8 months prior to the anticipated start of the grass pollen season 2005 and per the extension continued in a double-blinded manner until the end of the season 2007. The additional 2 years of follow-up without investigational treatment was continuously double-blinded. During each grass pollen season, all participants had free access to open-labeled symptomatic medications in case of rhinoconjunctivitis or asthma symptoms. The participants attended the clinics at least twice a year, 2 weeks before the anticipated start and 1 week after the grass pollen season.

Grass pollen season

Grass pollen counts were obtained from regional pollen stations in each country. The season was defined with start as the first day of 3 consecutive days with grass pollen count of 10 grains/m^3 or more and stop as the last day in the last occurrence of 3 consecutive days with pollen count of more than 10 grains/m^3. The peak pollen season was defined as the 15-day period with the highest average pollen count. Cumulated pollen loads were calculated after 3 and 10 weeks of each season.

Outcomes

The main objective was to evaluate sustained efficacy 2 years after the completion of a 3-year period with active treatment compared with placebo. The ranked coprimary end points each year were average rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) within the grass pollen seasons. The scores were registered daily from the preseasonal visit and until the postseasonal visit in an electronic diary (LogPad, PHT Corporation, Boston, Mass). A weighted rhinoconjunctivitis combined score (RCS) was calculated on the basis of primary end points (please refer to this article's Online Repository at www.jacionline.org for details).

Further secondary end points included rhinoconjunctivitis quality of life[18] during the peak grass pollen seasons, percentages days with severe symptoms (defined as a symptom score of 3 in any of the 6 rhinoconjunctivitis symptoms), change from baseline in specific IgG_4 levels and IgE-blocking factor (ie, the presence of components blocking IgE-allergen binding), change from baseline in facilitated allergen presentation inhibition (for details on immunologic methods, see this article's Online Repository at www.jacionline.org), and safety and tolerability (adverse events and serum and urine safety parameters).

Asthma DSS and asthma DMS were analyzed in the subgroup of participants having asthma at randomization (see this article's Online Repository at www.jacionline.org for details). Post hoc, the asthma combined score was calculated on the basis of the same principle as the RCS.