Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis

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Background: Allergen immunotherapy (desensitization) by injection is effective for seasonal allergic rhinitis and has been shown to induce long-term disease remission. The sublingual route also has potential, although definitive evidence from large randomized controlled trials has been lacking.
Objective: The aim was to confirm the efficacy of a rapidly dissolving grass allergen tablet (GRAZAX, ALK-Abelló, Hørsholm, Denmark) compared with placebo in patients with seasonal rhinoconjunctivitis.
Methods: A longitudinal, double-blind, placebo-controlled, parallel-group study that included 51 centers from 8 countries. Subjects were randomized (1:1) to receive a grass allergen tablet or placebo once daily. A total of 634 subjects with a history of grass pollen–induced rhinoconjunctivitis for at least 2 years and confirmation of IgE sensitivity (positive skin prick test and serum-specific IgE) were included in the study. Subjects commenced treatment at least 16 weeks before the grass pollen season, and treatment was continued throughout the entire season.
Results: The primary efficacy analysis showed a reduction of 30% in rhinoconjunctivitis symptom score ($P < .0001$) and a reduction of 38% in rhinoconjunctivitis medication score ($P < .0001$) compared with placebo. Side effects mainly comprised mild itching and swelling in the mouth that was in general well tolerated and led to treatment withdrawal in less than 4% of participants. There were no serious local side effects and no severe systemic adverse events.
Conclusion: Sublingual immunotherapy with grass allergen tablets was effective in grass pollen–induced rhinoconjunctivitis. The tablet was well tolerated with minor local side effects.
Clinical implications: The grass allergen tablet represents a safe alternative to injection immunotherapy suitable for home use. (J Allergy Clin Immunol 2006;118:434-40.)

Key words: *Allergy, asthma, grass pollen, immunotherapy, sublingual, rhinoconjunctivitis, tablet-based, double-blind, placebo-controlled,* Phleum pratense

The prevalence of seasonal allergic rhinitis is increasing.[1] At least 20% of the European population has the disease, and approximately half of these people are allergic to grass pollen. A general practice-based community study in United Kingdom revealed that more than 40% of patients receiving usual therapy with antihistamine tablets and/or nasal corticosteroid sprays were dissatisfied with their treatment.[2] In patients with severe hayfever unresponsive to usual therapy, allergen immunotherapy has been shown to be highly effective. Immunotherapy reduces symptoms and use of relief medication and markedly improves patients' quality of life within the first treatment year.[3,4] In contrast with symptomatic treatment with antiallergic drugs, immunotherapy is the only available therapy that treats the underlying cause of the disease, with proven long-term benefits. Thus, immunotherapy has been shown to induce long-term remission for at least 3 years after its discontinuation.[5] In children with seasonal pollinosis, immunotherapy reduced 2-fold to 3-fold the risk of progression of rhinitis to asthma.[6,7] Several studies in children have confirmed that immunotherapy may prevent the onset of new sensitizations to other inhalant allergens.[7-9] A disadvantage of the subcutaneous route is the

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Abbreviations used
SQ-T: Standardized quality tablet
VAS: Visual analog scale

occasional risk of side effects, including systemic allergic reactions, which confines the use of injection immunotherapy to specialist centers with access to adrenaline and other resuscitative measures.

In contrast with the injection route, sublingual immunotherapy has a very favorable safety profile, thereby enhancing the benefit-risk ratio in favor of a broader indication for allergen immunotherapy for use in the patients' home. Although, sublingual immunotherapy has been shown to be effective in a recent meta-analysis, the studies assessed were, in general, small, and there was considerable heterogeneity among studies.[8,10,11] Thus, the efficacy profile for the sublingual route is not as well documented as injection-based immunotherapy, and large controlled studies are needed to define the role of the sublingual approach in allergic rhinitis and asthma as well as in the prevention of asthma.[11,12]

Historically, an initial up-dosing treatment phase has been an important element of injection immunotherapy to optimize treatment to the tolerance of each patient while minimizing any untoward effects. However, up-dosing complicates the treatment regimen with the need for frequent clinic visits for the first 8 to 16 weeks. A new tablet-based sublingual immunotherapy (GRAZAX, ALK-Abelló, Hørsholm, Denmark) without up-dosing has recently been investigated in subjects with grass pollen allergy.[13] In a preliminary dose-finding study of 855 patients, there was a dose-dependent efficacy with a reduction in symptoms of 16% and decrease in relief medication of 29% with the 75,000 standardized quality tablet (SQ-T) daily dose (GRAZAX) given from approximately 8 weeks before the season compared with placebo therapy.[14] The results suggested that the length of the preseasonal treatment period might influence the magnitude of the clinical effect, because those subjects who received more than 8 weeks of therapy improved more than subjects who received less than 8 weeks. For this reason and on the basis of the favorable safety profile for the 75,000 SQ-T dose, this dose was selected for the current study in which the preseasonal treatment period was extended to a minimum of 16 weeks before the onset of the pollen season.

METHODS

The study was initiated in the autumn 2004 and was randomized, parallel-grouped, double-blinded, and placebo-controlled. A total of 634 patients from 51 centers in 8 countries (Austria, Denmark, Germany, Italy, The Netherlands, Spain, Sweden, and United Kingdom) were randomized 1 to 1 receiving either an orodispersible grass allergen tablet 75,000 SQ-T (GRAZAX; approximately 15 μg major allergen *Phleum* p 5) or a placebo tablet similar in taste, smell, and appearance once daily. The placebo tablet did not contain histamine or other active ingredients. The treatment started 16 weeks before the expected start of the grass pollen season and continued throughout the grass pollen season 2005. Double-blind treatment continued for another 2 years, followed by 2 years of follow-up. Results from the first treatment season are presented here.

TABLE I. Daily scoring of rescue medication

Step	Rhinoconjunctivitis	Score/dose
1	Desloratadine 5 mg once daily	6
2	Budesonide nasal spray (as much as 32 μg; 2 puffs per nostril twice daily)	1 per spray
3	Prednisone (as much as 50 mg once daily)	1.6 per 5 mg

Written informed consent was obtained before entering the study, and the study was performed in accordance with the Declaration of Helsinki[15] and Good Clinical Practice. The ethics committees in each of the participating countries approved the study.

Inclusion criteria were as follows: 18 to 65 years old; at least 2-year clinical history of significant grass pollen–induced allergic rhinoconjunctivitis; specific IgE against *Phleum pratense* CAP class ≥2; positive skin prick test against *Phleum pratense* (Soluprick SQ, ALK-Abelló), wheal diameter ≥3 mm; and FEV_1 higher than 70% of predicted value. Exclusion criteria were as follows: significant asthma outside the grass pollen season; FEV_1 lower than 70% of predicted value; allergic rhinitis requiring medication caused by allergens other than grass during the treatment period (patients with positive skin tests to other allergens in the absence of symptoms were permitted); conjunctivitis, rhinitis, or asthma at the screening or randomization visits; history of anaphylaxis; immunosuppressive treatment; receipt of immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years; and pregnancy.

Each day the subjects rated their rhinoconjunctivitis symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). The symptoms rated were runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. In case of allergic symptoms, subjects had free access to relief medication (desloratadine, budesonide nasal spray, and oral prednisone) in a stepwise fashion depending on the persistence and severity of their symptoms. Relief medication was scored according to predetermined criteria (Table I). The scoring scale was not seen by the subjects. The final medication and symptom scores were calculated as the mean of the total daily scores recorded throughout the whole 2005 pollen season.

Well days, defined as days without intake of rescue medication and a symptom score of 2 or less, were calculated for the entire grass pollen season. Rhinoconjunctivitis symptoms were also evaluated through daily scoring on a visual analog scale (VAS). Throughout the grass pollen season, the subjects registered their overall severity of rhinoconjunctivitis symptoms daily by answering the question, "How has your hay fever been today?" by indicating a point on a continuous VAS ranging from no symptoms (0) to severe symptoms (100).

Finally, rhinoconjunctivitis symptoms were globally evaluated by asking the subjects the following question: "Compared to your symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season?" The possible response categories were much better, better, the same, worse, or much worse. For the statistically analysis, categorical data were pooled into a binary endpoint of improved or not improved (improved = much better/better, and not improved = the same/worse/much worse). This analysis permitted the computation of a responder analysis because the observations were within-subject and based on the patients' retrospective comparison with their previous baseline seasons. All