

Short communication

Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy

Background: Sublingual immunotherapy treatment with grass allergen tablets (Grazax[®]) is initiated preseasonally without up-dosing and treatment is continued throughout the entire grass pollen season.

Aims of the study: The influence of the duration of preseasonal treatment on clinical efficacy obtained within the grass pollen season was investigated.

Methods: Data from three randomized, double-blind, placebo-controlled, multi-centre trials with varying preseasonal treatment periods were analysed. In the grass pollen season, symptom and medication score reductions relative to placebo were calculated and correlated with the duration of the preseasonal treatment period.

Results: The analysis was based on data from 934 patients. A significant reduction in seasonal daily rhinoconjunctivitis symptom and medication scores (17%, CI: 1–33% and 23%, CI: 1–47%, $P < 0.05$) was observed for patients treated with Grazax[®] compared with placebo after approximately 8 weeks of pretreatment. The magnitude of the reductions in rhinoconjunctivitis symptom and medication scores increased with longer duration of preseasonal treatment ($P < 0.0001$).

Conclusions: Sublingual immunotherapy with Grazax[®] must be initiated at least 8 weeks prior to the grass pollen season to provide a significant clinical efficacy. A longer preseasonal treatment period (> 8 weeks) improves the clinical efficacy (relative to placebo) during the grass pollen season.

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Introduction

Sublingual immunotherapy is now recognized as a viable alternative to subcutaneous immunotherapy (1–3). An initial up-dosing treatment phase is an important element of subcutaneous immunotherapy, to optimize treatment to the tolerance of each patient and thus minimizing the risk of systemic side effects. As a result, subcutaneous immunotherapy is a relatively complicated treatment regimen with the need for frequent clinic visits for the first 8–16 weeks. By tradition, the up-dosing concept used in subcutaneous immunotherapy has also been adopted in sublingual immunotherapy (4). However, the favourable safety profile of sublingual immunotherapy suggested the possibility of simplifying the treatment regimen by eliminating the up-dosing phase, thereby providing a simple and convenient one-dose-a-day only treatment regimen. The use of sublingual grass allergen tablets (Grazax[®]; *Phleum pratense*, 75 000 SQ-T, ALK-Abelló A/S, Hørsholm, Denmark) to treat grass pollen induced rhinoconjunctivitis without an up-dosing phase has been shown to

be efficacious and free of significant systemic side effects in patients with rhinoconjunctivitis. To investigate how the duration of preseasonal treatment (prior to the grass pollen season) might influence clinical efficacy observed during continued co-seasonal administration, the combined data from three clinical trials (5–7) conducted with the grass allergen tablet (Grazax[®]) were analysed.

Material and methods

Data from three randomized, double-blind, placebo-controlled, multi-centre trials (5–7) with varying duration of preseasonal treatment were combined and analysed using a mixed regression model with symptom and medication scores as dependent variables. The analysis included a total of 934 patients suffering from grass pollen induced rhinoconjunctivitis, with or without mild to moderate asthma, receiving Grazax[®] (480 patients) or corresponding placebo (454 patients). 75 000 SQ-T corresponds to approximately 15 µg Phl p 5. A tablet was administered once daily sublingually as self-administration starting prior to the grass pollen season and continuing throughout the entire grass pollen season. The length of

the treatment period prior to the start of the grass pollen season (the preseasonal treatment period) varied between 4 and 35 weeks. Because of the 'no up-dosing' concept and the one-dose-once-daily administration, the number of treatment days \times dose is equal to the cumulative dose of Grazax[®] administered.

Efficacy variables upon which the analysis is based were average daily rhinoconjunctivitis symptom and medication scores during the grass pollen season. Each day the patients rated their rhinoconjunctivitis symptoms on a scale from 0 to 3 (0, no symptoms; 1, slight symptoms; 2, moderate symptoms and 3, severe symptoms). The rated rhinoconjunctivitis nose and eye symptoms were: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes. In case of symptoms of rhinoconjunctivitis, patients had access to rescue medication in a stepwise manner [loratadine/desloratadine tablets, levocabastine eye drops (only for one of the three trials), budesonide nasal spray and prednisone/prednisolone tablets] depending on the persistence and severity of their symptoms. The final symptom and medication scores were calculated as the average of the daily scores during the whole grass pollen season.

Written informed consent was obtained before entering the trials and all three trials were performed in accordance with current Good Clinical Practice (GCP) standards and the Declaration of Helsinki.

Patients

The main inclusion criteria in all three trials were: age 18–65; clinical history of significant, troublesome symptoms, of seasonal allergic rhinoconjunctivitis of a duration of at least 2 years with/without mild–moderate grass pollen induced asthma during the grass pollen season; positive (wheal diameter ≥ 3 mm) skin prick test to *P. pratense* (Soluprick[®] SQ, ALK-Abelló A/S, Hørsholm, Denmark) and with positive specific immunoglobulin E (IgE) (\geq CAP allergy class 2) to *P. pratense*. The main criteria for exclusion included the following: significant asthma outside the grass pollen season; forced expiratory volume in 1 s $< 70\%$ of predicted value; significant allergic rhinitis (requiring medication) caused by other allergens than grass pollen during the planned treatment period; significant recurrent acute sinusitis or chronic sinusitis; conjunctivitis, rhinitis or asthma at the screening or randomization visits; history of anaphylaxis or angioedema; presence of serious underlying conditions; immunosuppressive treatment; hypersensitivity to excipients of trial medications or rescue medications; having received immunotherapy with grass pollen allergen within the previous 5–10 years or any other allergen within the previous 5 years; or pregnancy.

Statistical analysis

Data from three trials (5–7) were combined and a mixed regression model using Proc Mixed in SAS[®] version 8.02 (SAS Institute Inc., Cary, NC, USA) was developed with symptom and medication score as dependent variables and duration of preseasonal treatment as independent variable. In the model, a separate intercept term for treatment and placebo as well as a separate slope for treatment and placebo were included as fixed effects. In addition, pollen region within trial was included as a nested random effect. Separate variance estimates for the treatment groups were used.

Results

The analysis was based on the data from 934 patients with a mean age of 34.7 years. The majority of patients

Table 1. Patient characteristics and demographics

	Total analysis population (N = 934)
Male population; n (%)	569 (60.9)
Age (years); mean (SD)	34.7 (9.7)
Grass pollen induced rhinoconjunctivitis duration (years); mean (SD)	16.9 (10.7)
Associated grass pollen induced asthma*; n (%)	276 (29.6)
Proportion of smokers; n (%)	156 (16.7)
History of severity of rhinoconjunctivitis symptoms †; n (%)	
Mild/slight	28 (3.0)
Moderate	459 (49.1)
Severe	445 (47.6)
Additional positive skin prick tests to other allergens; n (%)	753 (80.6)
Duration of preseasonal treatment (weeks); mean (SD)	19.7 (8.5)
Duration of grass pollen season (days); mean (SD)	52.3 (16.0)

Details of demography can be found in (5–7).

*Asthma was defined according to the patients' medical history.

†The severity of rhinoconjunctivitis symptoms was defined by the investigator based on the patients' allergic disease history. Severity of rhinoconjunctivitis symptoms is missing for two patients.

had a history of moderate–severe rhinoconjunctivitis symptoms and approximately 30% of the patients had grass pollen induced asthma (Table 1).

A statistically significant reduction in the average daily rhinoconjunctivitis symptom and medication scores in the grass pollen season for patients treated with Grazax[®] relative to patients treated with placebo was obtained with approximately 8 weeks of preseasonal treatment (17%, CI: 1–33% and 23%, CI: 1–47%, $P < 0.05$). The reduction in the average daily rhinoconjunctivitis symptom and medication score increased with longer preseasonal treatment, which is reflected in the P -value approaching zero ($P < 0.0001$) (Fig. 1).

Discussion

A new tablet-based sublingual immunotherapy, Grazax[®], has been shown to be efficacious and well tolerated (5–9) without up-dosing in patients with grass pollen induced seasonal allergic rhinoconjunctivitis.

Results from one of the trials (5) suggested that the duration of the preseasonal treatment period might influence the magnitude of the clinical effect, since patients who received more than 8 weeks therapy prior to the grass pollen season improved more than those who received < 8 weeks preseasonal treatment. Furthermore, another trial (8) showed that treatment with Grazax[®] induced a time-dependent increase in allergen specific IgE, IgG and IgA antibody responses during the preseasonal treatment

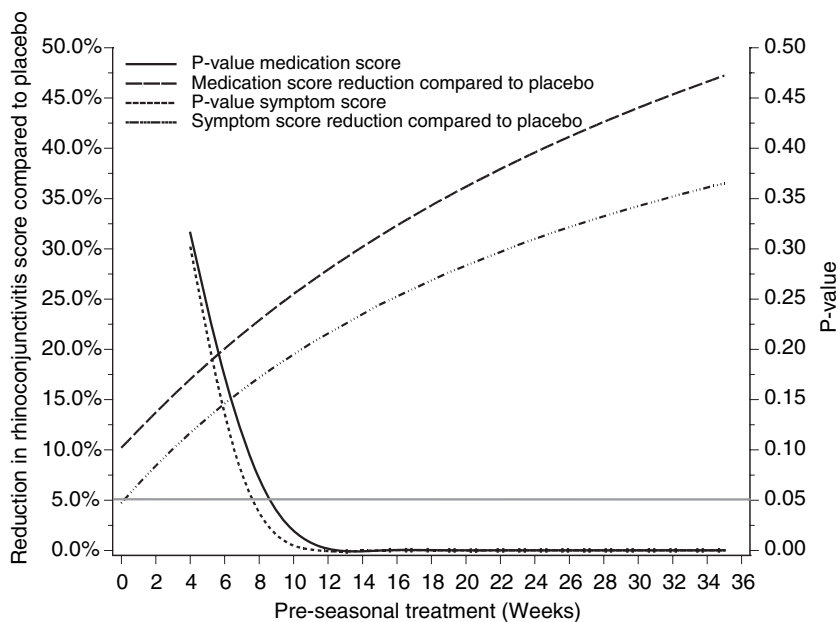


Figure 1. Duration of pre-seasonal treatment in relation to average symptom and medication score reductions in the grass pollen season.

period (8 weeks). This suggested that the treatment had a significant effect on the immune system in an allergen specific manner, and that the duration of pre-seasonal treatment potentially could influence the clinical efficacy.

Symptom and medication score reductions during the season were statistically significantly different from placebo after approximately 8 weeks of pre-seasonal treatment with reductions of 17–23% over placebo (Fig. 1). The model indicates that increasing reductions could be obtained with longer pre-seasonal treatment (Fig. 1). Reductions in symptom and medication scores of a similar magnitude have previously been observed with subcutaneous immunotherapy in a large randomized, double-blind, placebo-controlled, multi-centre trial (10). However, it should be noted that the patient population included in the subcutaneous trial was slightly different in disease severity from the populations in the trials included in this analysis.

We believe that this is the first evaluation of the impact of duration of pre-seasonal treatment on clinical efficacy of sublingual immunotherapy during the pollen season. Clinical trials of dose regimens, the need for up-dosing and on timing of optimal initiation of sublingual immunotherapy treatment in seasonal allergy has been lacking. For Grazax® the optimal dose has been verified without up-dosing in large clinical trials (5, 7). The results obtained here indicate that pre-seasonal treatment of approximately 8 weeks or more is necessary to obtain clinical efficacy in the grass pollen season. However, the increasing clinical effect with prolonged pre-seasonal treatment leave room for flexibility in the treatment regimen with the option to obtain better clinical effect in

the grass pollen season if treatment is initiated earlier. From a clinical and practical point of view, treatment could possibly be initiated as early as soon after the preceding grass pollen season. At this time, the pre-seasonal treatment is maximized to obtain an optimal clinical effect in the next grass pollen season and the patient’s motivation and thereby compliance is likely to be higher.

It cannot be concluded whether the observed increased efficacy is due to the longer pre-seasonal treatment duration or possibly because of a greater cumulative pre-seasonal dose during this period. For example double the dose over half the period could potentially give the same optimal efficacy. However, it is documented that a once daily dose of 75 000 SQ-T provides optimal benefit/risk profile for patients (6, 9) such that a doubling of the daily dose to investigate this possibility may not be appropriate.

In conclusion, sublingual immunotherapy with Grazax® must be initiated at least 8 weeks prior to the grass pollen season to provide a significant clinical efficacy in the first treatment season. A longer pre-seasonal treatment period (>8 weeks) improves the clinical efficacy by lowering the patients’ symptom load and reducing their medication needs during the grass pollen season.

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