

Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis

Background: The best way to prevent allergy symptoms is to treat the allergic condition. Specific immunotherapy with grass allergen tablets 75 000 SQ-T (Grazax[®] *Phleum pratense*, ALK-Abelló) is safe and efficacious in rhinoconjunctivitis patients. As rhinoconjunctivitis often co-exists with asthma, we aimed to confirm safety and efficacy in grass allergic subjects with asthma and rhinoconjunctivitis.

Methods: A randomized, double-blind, placebo-controlled, multicentre trial was performed 10–14 weeks prior to and during the grass pollen season 2004. About 114 subjects were randomized 2 : 1 to grass allergen tablets or placebo. The primary end points were average asthma medication and symptom scores during the grass pollen season, and secondary variables were average rhinoconjunctivitis symptom and medication scores during the grass pollen season. Additionally, number of well days was defined *post hoc*.

Results: Differences in asthma medication and symptom scores between the treatment groups were negligible. The mean difference in asthma medication score was below 0.1 and 0.3 for asthma symptom score [a single inhalation of salbutamol (200 µg) was scored 2]. No serious adverse events were reported. A reduction in rhinoconjunctivitis symptom score of 37% ($P = 0.004$) and a 41% ($P = 0.036$) reduction in medication score was found in the grass pollen season for subjects treated with the grass allergen tablet compared with placebo. Well days increased by 54% ($P = 0.002$).

Conclusions: Self-administration of the grass allergen tablet was safe. The treatment did not impair asthma control and confirmed considerable symptom prevention and reduced medication use. It addresses the allergic condition and represents a baseline treatment for grass pollen allergy.

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Rhinoconjunctivitis is common in western Europe, affecting more than 20% of the adult population (1) and the incidence is increasing (2). Further, allergic rhinoconjunctivitis has been identified as one of the main reasons for visits to primary care clinics, and although usually not regarded as a severe disease it significantly limits the social life, school learning and work productivity (3). Rhinoconjunctivitis often coexists with asthma and is regarded as one of the major risk factors for the development of asthma (4). In a Danish study, 41% of the subjects with pollen-induced rhinitis also had pollen-induced asthma (5), but rhinoconjunctivitis as a comorbidity in asthma may be as high as 80% (3).

Of the different allergies, allergy to grass pollen is one of the most common inhalant allergies. A survey showed that 8–35% of young adults in a wide variety of countries had specific serum antibodies to grass pollen (6). Grass pollen allergy is leading to impaired quality of life and increased expenditures in the health care system (3).

Allergy is a chronic condition that may require lifelong symptomatic treatment. Symptomatic treatments only target the allergic symptoms, and many patients describe their symptom control as partial or poor (7). The best way to prevent symptoms is to treat the allergic condition, and several controlled trials have documented the efficacy of specific immunotherapy (8–12). The documentation is mainly based on immunotherapy given subcutaneously, but immunotherapy given sublingually is facing ongoing development, and is already a widespread application especially in southern Europe (13). Sublingual immunotherapy is generally advantageous because of the convenient administration and the favourable safety profile (14–17). Development of a tablet-based immunotherapy treatment that is easy to administrate and possibly exclude the risk of severe adverse events (AEs) will expand patient's access to specific immunotherapy and may prove to be a baseline treatment of grass pollen allergies.

Because of the high prevalence of coexistent asthma and rhinoconjunctivitis, we decided to test the grass allergen tablet in a population with this comorbidity. The primary aim of this trial was to confirm safe self-administration of the grass allergen tablet in subjects with concomitant mild to moderate grass pollen-induced asthma and grass pollen-induced rhinoconjunctivitis. The secondary aim was to confirm efficacy in terms of significant reduction in rhinoconjunctivitis symptoms and use of medication.

Subjects and methods

Trial design

This was a double-blind, randomized, parallel group, placebo-controlled, multicentre trial conducted 10–14 weeks prior to and during the grass pollen season 2004. A total of 130 subjects suffering from mild to moderate grass pollen-induced asthma as well as rhinoconjunctivitis were screened from 15 sites; 11 in Denmark and four in Sweden. About 114 subjects were randomized 2 : 1 to either grass allergen tablet (Grazax[®], *Phleum pratense*, 75 000 SQ-T, ALK-Abelló A/S, Hørsholm, Denmark) or placebo. The 75 000 SQ-T corresponds to 15 µg Phl p 5. The tablets were administered once daily sublingually as self-medication starting 10–14 weeks before the grass pollen season and continued through out the entire grass pollen season. Written informed consent was obtained before entering the trial and the trial was performed in accordance with the 'Declaration of Helsinki' (18) and Good Clinical Practise. The trial consisted of six visits including a screening visit. About 1 week after the final visit the subjects received a telephone follow-up call.

Primary safety end points were average daily asthma medication and symptom scores prior to and during the grass pollen season. Efficacy variables were average daily rhinoconjunctivitis symptom and medication scores during the grass pollen season.

Each day the subjects rated their asthma and rhinoconjunctivitis symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). The rated asthma symptoms were: cough, wheeze, chest tightness (dyspnoea) and exercise-induced 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 allergic asthma or rhinoconjunctivitis, subjects had access to rescue medication in a stepwise fashion depending on the persistency and severity of their symptoms. Steps 1, 2 and 3 for rhinoconjunctivitis symptoms and steps A, B and C for asthma symptoms (see Table 1). The final medication and symptom scores were calculated as the mean of the daily scores.

Additional safety variables were average daily peak expiratory flow rate (PEF), average forced expiratory volume in 1 s (FEV₁), number of AE and changes in laboratory assessments, vital signs and physical examinations. Adverse events were reported spontaneously by subjects. The FEV₁ was measured at clinic visits.

Percentage well days in the grass pollen season were *post hoc* defined as additional efficacy variable. A well day was defined as a day with a symptom score no larger than 2 and with no rescue medication taken. Scoring of symptoms, intake of trial medication, intake of rescue medication, presence of AEs and highest of three morning and evening PEF (self-measured using Mini-Wright[™], Clement Clarke International, Harlow, UK) were entered daily into an electronic diary by the subject.

Subjects

The main inclusion criteria were: age 18–65; clinical history of significant grass pollen-induced allergic rhinoconjunctivitis and mild to moderate grass pollen-induced asthma of 2 years or more; well controlled seasonal asthma in accordance with the GINA Guideline (19); a positive skin prick test (Soluprick SQ, ALK-Abelló, Hørsholm, Denmark; wheal diameter ≥3 mm) and specific immunoglobulin E (IgE; ≥CAP allergy class 2) to *P. pratense*. The main exclusion criteria were: significant asthma outside the grass pollen season; FEV₁ < 70% of predicted value; significant allergic rhinitis (requiring medication) caused by allergens other than grass during the planned treatment period; conjunctivitis, rhinitis or asthma at the screening or randomization visits; history of anaphylaxis; immunosuppressive treatment; hypersensitivity to the excipients of the trial medication or rescue medication; having received immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years; pregnancy.

Table 1. Daily scoring of rescue medication

Step	Medication	Score/dose*	Max/day
Rhinoconjunctivitis			
1	Loratadine 10 mg once daily	6	6
1	Levocabastine eye drops (0.5 mg/ml; one drop in each eye twice daily)	2	8
2	Budesonide nasal spray (up to 32 µg; two puffs per nostril twice daily)	1 per puff	8
3	Prednisone (up to 50 mg once daily)†	1.6 per 5 mg	16
	Maximal daily score		38
Asthma			
A	Salbutamol (200 µg per inhalation; 1–2 inhalations twice daily)	2	8
B	Fluticasone (250 µg per inhalation; 1–2 inhalations twice daily)	2	8
C	Prednisone (up to 50 mg once daily)†	1.6 per 5 mg	16
	Maximal daily score		32

*Scoring scale was not seen by the subjects. The maximum score/day was for guidance only; if subjects used more medication than allowed/prescribed, the actual use of medication was scored.

†Counted in the rhinoconjunctivitis score and/or in the asthma score depending on the symptoms.

Definition of grass pollen season

Pollen counts were provided by the European Pollen Information Ltd (Vienna, Austria). The start date of the season was defined as first day of 3 consecutive days with pollen count larger than or equal to 10 grains/m³. The stop date of the season was defined as the first day (after 26 July) followed by 3 consecutive days with pollen count < 10 grains/m³.

Statistics

No formal statistical sample size and power considerations were made, as safety was the primary end point. The full analysis set (FAS) was defined as all randomized subjects. The per-protocol (PP) analysis set was defined as all subjects with: (i) at least 10 weeks of preseasonal treatment, (ii) an intake of at least 80% of the trial medication on days with nonmissing diary data and (iii) an at least 30% filled in diary distributed over at least 50% of the trial weeks. The PP was defined prior to unblinding. Safety data will be presented for FAS, while efficacy will be presented for PP data.

In case of missing values, data were disregarded, i.e. no assumption or replacement of missing information has been performed. Differences between treatment groups in average daily rhinoconjunctivitis symptoms and number of well days in the grass pollen season were tested using an ANOVA model with treatment as fixed effect and the same error in both treatment groups (equivalent to *t*-test). For rhinoconjunctivitis medication score the underlying model assumptions for an ANOVA model were not entirely fulfilled and therefore a Wilcoxon rank sum test was used to test for differences.

A *P*-value of <0.05 was considered statistically significant. Reduction in scores and well days were calculated as $100 \times \frac{\text{active} - \text{placebo}}{\text{placebo}}$.

Results

Baseline characteristics

The 114 randomized subjects consisted of 37 females and 77 males with a mean age of 35.7 years (range: 18–64). Trial flow diagram is illustrated in Fig. 1. Subjects in the two groups were comparable with regard to nationality, gender, age, height, weight and relevant clinical history (Table 2). About 94 subjects (82%) showed positive skin prick test towards at least one of nine other allergens (beside *P. pratense*).

Exposure

The mean (\pm SD) preseasonal trial medication exposure endured 84 ± 17 days, while mean (\pm SD) seasonal trial medication exposure endured 53 ± 2 days. There were no differences in trial medication exposure or in compliance between the treatment groups. The pollen season varied from 52 to 60 days between the five regions.

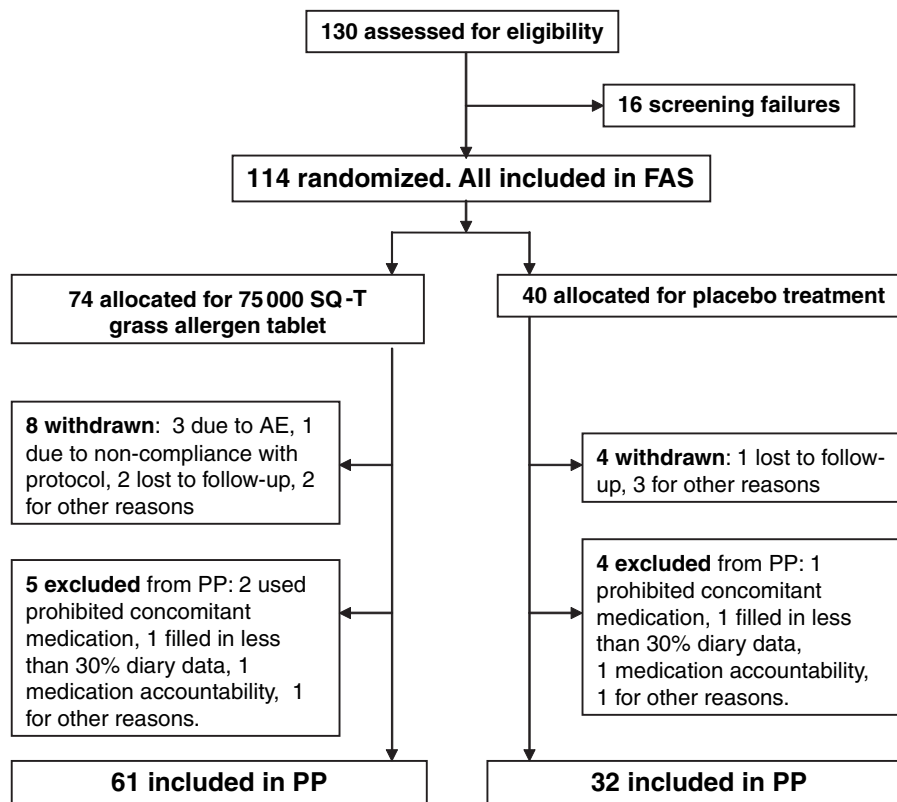


Figure 1. Flow diagram.

Table 2. Subject characteristics and demographics

	Placebo (N = 40)	75 000 SQ-T (N = 74)
Sex, n (%)		
Male	24 (60.0)	53 (71.6)
Female	16 (40.0)	21 (28.4)
Country, n (%)		
Denmark	33 (82.5)	63 (85.1)
Sweden	7 (17.5)	11 (14.9)
Age (years)		
Mean (SD)	34.1 (9.9)	36.5 (10.6)
Minimum–maximum	20–60	18–64
Height (cm)		
Mean (SD)	177 (9.2)	176 (8.8)
Minimum–maximum	161–198	156–196
Weight (kg)		
Mean (SD)	78.5 (17.3)	79.2 (14.8)
Minimum–maximum	45–140	49–138
Grass pollen-induced rhinoconjunctivitis (years)		
Mean (SD)	19.4 (12.5)	19.6 (9.81)
Minimum–maximum	4–51	2–45
Grass pollen-induced asthma (years)		
Mean (SD)	12.5 (8.54)	14.0 (10.8)
Minimum–maximum	2–36	2–45

Asthma medication and symptom score

Prior to the grass pollen season asthma medication and symptom scores were low and similar between treatment groups (Table 3). During the grass pollen season asthma medication and symptom scores were slightly higher but still similar between groups. The difference in seasonal asthma medication score was below 0.1 and for asthma symptom score 0.3. Maximal possible score was 32.

Adverse events

An equal proportion of subjects in both treatment groups reported AEs of which the majority were mild in severity. The most frequently related AEs were: oral pruritus (reported by 53% active, 5% placebo), nasopharyngitis

(36% active, 25% placebo) and throat irritation (32% active, 25% placebo). No serious AEs were reported in this trial.

The number of AEs linked to asthma (chest discomfort, chest pain, asthma, cough, dry throat, dyspnoea, increased bronchial secretion, respiratory disorder, wheezing) was similar between groups and there was no indication of asthma aggravation.

No clinical relevant changes from screening to follow up and no differences between the treatment groups were identified for any of the additional safety variables (PEF, FEV₁, laboratory assessments, vital signs or physical examinations).

Rhinoconjunctivitis medication and symptom score

About 33% of the subjects in each group did not use rescue medication during the pollen season to treat their symptoms even though the subjects suffered from moderate to severe rhinoconjunctivitis. Still the average symptom and medication scores were lower for subjects treated with the grass allergen tablet (Table 4, Fig. 2). The subjects received their rescue medication in steps

Table 4. Average medication scores, symptom scores and percentage well days

Treatment group	Placebo (N = 32)	75 000 SQ-T (N = 61)	Reduction (%)*	P-value
Daily average rhinoconjunctivitis symptom scores				
Mean (SD)	3.3 (2.2)	2.1 (1.7)	–37	0.004
Median	2.9	1.8		
Minimum–maximum	0.1–7.3	0.02–8.1		
Daily average rhinoconjunctivitis medication scores				
Mean (SD)	4.2 (4.1)	2.4 (3.9)	–41	0.036
Median	3.6	1.2		
Minimum–maximum	0–14.1	0–19.9		
Percentage well days				
Mean (SD)	38.2 (32.9)	58.9 (27.6)	54	0.002
Median	34.8	61.4		
Minimum–maximum	0–97.3	0–100		

*Reduction = 100 × $\frac{\text{Active} - \text{Placebo}}{\text{Placebo}}$

Table 3. Average daily asthma medication and symptom score

Treatment group analysis set	Preseason		Grass pollen season	
	Placebo FAS (N = 40)	75 000 SQ-T FAS (N = 73)	Placebo FAS (N = 39)*	75 000 SQ-T FAS (N = 68)*
Asthma medication score				
Mean (SD)	0.09 (0.14)	0.09 (0.23)	0.66 (1.08)	0.71 (1.28)
Median	0.00	0.00	0.07	0.00
Minimum–maximum	0.00–0.49	0.00–1.35	0.00–4.00	0.00–5.33
Asthma symptom score				
Mean (SD)	0.33 (0.33)	0.23 (0.34)	0.74 (0.92)	0.44 (0.68)
Median	0.23	0.10	0.36	0.18
Minimum–maximum	0.00–1.05	0.00–2.00	0.00–3.60	0.00–3.67

*Number of subjects with seasonal diary data were 39 placebo and 68 active. FAS, full analysis set.

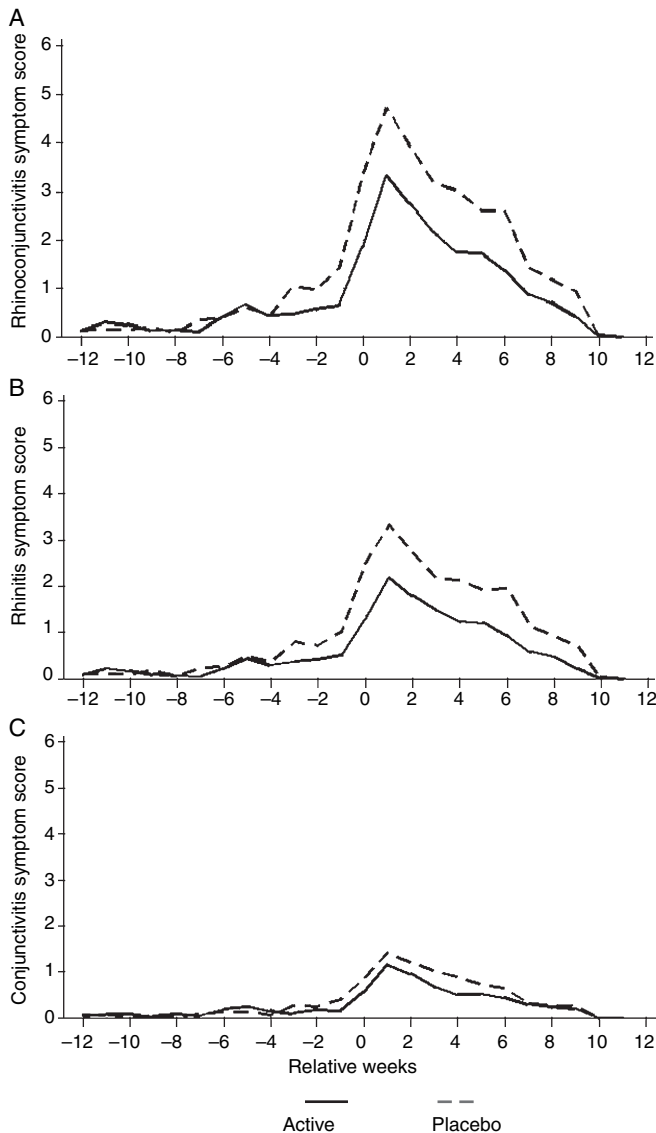


Figure 2. Average daily symptom score for (A) rhinoconjunctivitis, (B), rhinitis, (C) conjunctivitis. Relative week, start of pollen season = 0.

and the far majority of actively treated subjects were able to stay on the first step of rescue medication (loratadine tablets and levocabastine eye drops). About 59% of the placebo subjects reached the intermediate step (budesonide), compared with 28% of the actively treated subjects.

The observed differences between treatment groups in the efficacy variables were statistically significant. A mean reduction of 37% in rhinoconjunctivitis symptom score and 41% in rhinoconjunctivitis medication score was found. In addition, the mean percentage of well days in the grass pollen season was 54% higher in the subjects treated with the grass allergen tablet.

Discussion

Outside the grass pollen season asthma medication and symptom scores were similar between treatment groups. This suggests that the grass allergen tablet itself did not provoke asthma. In the grass pollen season asthma medication and symptom scores also stayed low in both treatment groups and the mean difference in asthma medication score was below 0.1. In proportion, a single inhalation of salbutamol (200 µg) was scored 2. Asthma symptom score differed 0.3 between groups. Thus, the coexisting exposure of the grass allergen tablet and airborne grass pollen did not worsen the asthmatic condition of the subjects. This finding is essential as comorbidity between rhinoconjunctivitis and asthma is high. The low overall asthma medication and symptoms scores may be caused by the low pollen exposure present in Denmark and southern Sweden in 2004. Accordingly, the possibility of reduction in asthma medication and symptoms scores was limited.

In a review on sublingual immunotherapy for allergic rhinitis including 22 studies, all studies reported a complete absence of systemic AEs, while minor local AEs consisting of itching and swelling of the oral mucosa were almost universally reported but rarely of significance (20). In this trial the three most frequent-related AEs were oral pruritus, nasopharyngitis and throat irritation. These were overall mild and did not lead to withdrawals. The incidence of these events should be taken with caution because of a considerable placebo effect, i.e. a large number of placebo subjects experienced especially nasopharyngitis and throat irritation but also oral pruritus. Thus, the local AEs reported in this trial were expected and did not influence adherence to the grass allergen tablet.

Sublingual immunotherapy is generally advantageous because of the convenient administration and the favourable safety profile, but the self-administration normally requires careful instruction and detailed follow up (14). The present trial raised no safety concern in relation to the self-administration. There were no serious AEs, AEs were generally mild and only three subjects (4%) withdrew from the trial because of AEs.

A considerable and clinically relevant reduction in both rhinoconjunctivitis symptom and medication score was found in this trial. Also fewer patients treated with the grass allergen tablet required treatment with the nasal steroid budesonide. This is the main reason for the difference in medication score. Symptom prevention by use of nasal steroids is well established and effective; still long-term treatment with nasal steroid may have significant side-effects especially in children and asthmatics receiving inhaled steroids (21). Subcutaneous and sublingual-specific immunotherapy of subjects with rhinoconjunctivitis has in previous long-term studies been shown to decrease or prevent the development of asthma (4, 22, 23). These benefits may also be valid for the grass allergen

tablet used in the present trial and thereby enable grass allergic patients to avoid both nasal steroids and worsening of their allergic disease.

In conclusion, self-administration of the grass allergen tablet was safe and well-tolerated, did not provoke asthma and caused considerable rhinoconjunctivitis symptom prevention and reduced medication use. It addresses the allergic condition and may represent a baseline treatment for grass pollen allergy.

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