

Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis

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Background: Sublingual immunotherapy is well tolerated and data suggest its effectiveness for the treatment of allergic rhinitis in adults, but it lacks optimum dose definition.

Objective: To assess the efficacy, safety, and optimal dose of grass pollen tablets for immunotherapy of patients with allergic rhinoconjunctivitis.

Methods: In this multinational, randomized, double-blind, placebo-controlled study, 628 adults with grass pollen rhinoconjunctivitis (confirmed by positive skin prick test and serum-specific IgE) received 1 of 3 doses of a standardized 5-grass pollen extract, or placebo, administered sublingually using a once-daily tablet formulation. The treatment was initiated 4 months before the estimated pollen season and continued throughout the season. The primary outcome was Rhinoconjunctivitis Total Symptom Score; secondary outcomes included 6 individual symptom scores, rescue medication use, quality of life, and safety assessments.

Results: Both the 300-index of reactivity (IR) and 500-IR doses significantly reduced mean Rhinoconjunctivitis Total Symptom Score (3.58 ± 3.0 , $P = .0001$; and 3.74 ± 3.1 , $P = .0006$, respectively) compared with placebo (4.93 ± 3.2) in the intent-

to-treat and per-protocol analyses. The 100-IR group (4.70 ± 3.1) score was not significantly different from placebo. Analysis of all secondary efficacy variables (sneezing, runny nose, itchy nose, nasal congestion, watery eyes, itchy eyes, rescue medication usage, and quality of life) confirmed the efficacy of the 300-IR and 500-IR doses. No serious side effects were reported.

Conclusion: In the first pollen season, the efficacy and safety of sublingual immunotherapy with grass tablets was confirmed. The 300-IR and 500-IR doses both demonstrated significant efficacy compared with placebo.

Clinical implications: The risk-benefit ratio favors the use of 300-IR tablets for clinical practice. (J Allergy Clin Immunol ■■■■;■■■;■■■-■■■.)

Key words: Sublingual immunotherapy, grass pollen tablet, grass pollen allergy, allergic rhinoconjunctivitis, allergen, randomized, double-blind, placebo-controlled trial, dose response

Subcutaneous immunotherapy with high-quality allergen vaccines and standardized allergen extracts is effective for the treatment of rhinitis and asthma caused by pollens or mites.^{1,2} However, subcutaneous immunotherapy is hampered by time-consuming treatment modalities and the potential risk of severe adverse reactions.^{1,3}

Although sublingual immunotherapy (SLIT) is now frequently used in many European countries, because of the lack of information on optimal dosing, its use remains controversial.^{4,5} A Cochrane Collaboration meta-analysis of SLIT in rhinitis found significant reduction in symptoms and medications, despite some of the trials being statistically underpowered.⁶ More recent studies on pollen allergy, not included in the meta-analysis, confirm the efficacy of SLIT.⁷⁻⁹

Confirmation of efficacy and safety based on the optimal dose for allergen tablets is still needed. The optimal dose is defined as the dose of allergen extract inducing a clinically relevant effect in most patients without causing unacceptable side effects.^{1,10} Different doses using standardized grass pollen allergens (Stallergènes SA, Antony, France) were assessed in previous clinical trials.¹¹⁻¹³ The phase I study,¹³ performed in 30 patients allergic to grass pollen, confirmed the safety of once-daily 300-index of reactivity (IR) and 500-IR

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Abbreviations used

ANCOVA: Analysis of covariance
 IR: Index of reactivity
 ITT: Intent-to-treat
 PP: Per protocol
 RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
 RTSS: Rhinoconjunctivitis Total Symptom Score
 SIT: Specific immunotherapy
 SLIT: Sublingual immunotherapy

SLIT tablets when using a very short induction phase. Adverse events were most common at the site of administration (sublingual) and resolved rapidly without intervention.

The purpose of the current study was to determine in patients with grass pollen-induced allergic rhinitis the optimal effective and safe dose of tablet-based SLIT.

METHODS

Patients

A large, multinational, randomized, double-blind, placebo-controlled study was performed in 628 patients allergic to grass pollen.

Patients were screened at 42 centers in 10 European countries (Austria, 1 center; Bulgaria, 6; Czech Republic, 7; Denmark, 1; France, 10; Germany, 7; Hungary, 3; Italy, 2; Slovakia, 3; Spain, 2). The first patient was randomized December 16, 2004, and the last visit was September 5, 2005.

The study included both men and women, 18 to 45 years old, all of whom had moderate-to-severe seasonal grass pollen-related allergic rhinoconjunctivitis for at least 2 years, confirmed by a positive skin prick test (wheal size greater or equal to 3 mm) and serum specific IgE of at least class 2 (CAP System; Phadia, Uppsala, Sweden) to grass pollen assessed at the screening visit. The skin prick test included 5 grass pollens (orchard [*Dactylis glomerata*], meadow [*Poa pratensis*], perennial rye [*Lolium perenne*], sweet vernal [*Anthoxanthum odoratum*], and timothy [*Phleum pratense*] grasses), and the RAST of timothy grass was reported in kUnit/L. Patients were investigated for sensitization to other allergens by testing with the 10 most common allergens in each country. Patients sensitized to allergens other than grass pollen were included as well as those with asthma requiring treatment only with β_2 -agonists. The main exclusion criteria were allergic rhinoconjunctivitis caused by a cosensitization likely to influence symptoms of the patient throughout the study or symptoms of rhinoconjunctivitis during the treatment phase because of sensitization to allergens other than grass pollens, previous specific immunotherapy (SIT) for grass pollen, and the usual contraindications for SIT.¹

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

Outcomes measures

The primary outcome was the efficacy of SLIT on the Rhinoconjunctivitis Total Symptom Score (RTSS), which included the 6 most common symptoms of pollinosis (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). A score ranging from 0 to 3, according to the Center for Drug

Evaluation and Research guidance (April 2000),¹⁴ was used for each individual symptom: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of bothersome but tolerable symptoms), and 3 = severe symptoms (symptoms hard to tolerate and/or cause interference with activities of daily living and/or sleeping).

From approximately a month before and during the pollen season, patients completed a daily diary card to score nasal and ocular symptoms using the RTSS. The average RTSS was calculated during the entire pollen season.

In addition, the effect of immunotherapy on the 6 individual symptom scores (sneezing, runny nose, itchy nose, nasal congestion, watery eyes, and itchy eyes) was analyzed as secondary outcomes.

The proportion of symptom-free days (%) during the pollen season was also assessed. A symptom-free day was a day on which "0 = absent" was recorded for each of the 6 individual rhinoconjunctivitis symptoms.

In case of severe symptoms, patients could use rescue medication. Patients were instructed to start with an oral antihistamine (cetirizine) and, if the symptoms were not alleviated, progress to an intranasal corticosteroid (mometasone furoate). Thus, the proportion of days with rescue medication could be calculated and compared between treatment groups.

Patients' quality of life was assessed using the self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).¹⁵ Individual items within the RQLQ were equally weighted. The patients' global evaluation of the treatment was also assessed.

Blood samples were taken before and at the end of the pollen season to measure serum grass allergen-specific IgE (RAST CAP System; Pharmacia Diagnostics, Uppsala, Sweden) and IgG₄ (radioimmunoassay; Pharmacia Diagnostics).

Immunotherapy

Each SLIT tablet contained a mixture of equal proportions of 5 grass pollens: orchard, meadow, perennial rye, sweet vernal, and timothy grasses. Tablet formulations are more stable, allow more precise dosage, and are easier to take than liquid formulations.^{12,16} Patients were given 1 of 3 daily doses (100 IR, 300 IR, or 500 IR) of the SLIT tablets (IR is a measure of biological potency [skin reactivity] used to describe the strength of an allergen extract). The mean dosage of 300 IR/mL corresponded to approximately 25 μ g/mL of the group 5 major allergens.

The placebo tablet matched the active treatment in size, shape, and color but contained no pollen allergens or other active ingredients.¹³ Allergen or placebo tablets were taken sublingually once daily in the morning before eating or drinking. The patient was instructed to keep the tablet under the tongue until complete dissolution before swallowing.

Study design

In November 2004, approximately 5 months before the expected start of the pollen season, patients were screened for eligibility and randomized 1:1:1:1 to 1 of the 4 treatment groups (100 IR, 300 IR, 500 IR, or placebo) by using a computer-generated randomization list.

The first dose was administered under the investigator's supervision 4 months before the expected start of the grass pollen season.

During the first 5 days of treatment, doses were increased by 100 IR until the final dose was achieved. To maintain the blinding, patients took 2 tablets per day during the first 5 days of titration and 1 tablet per day from day 6 until the end of treatment. For each patient, 8 visits were scheduled: screening, randomization, 2 weeks after randomization, 4 weeks before the estimated start of the pollen, at the

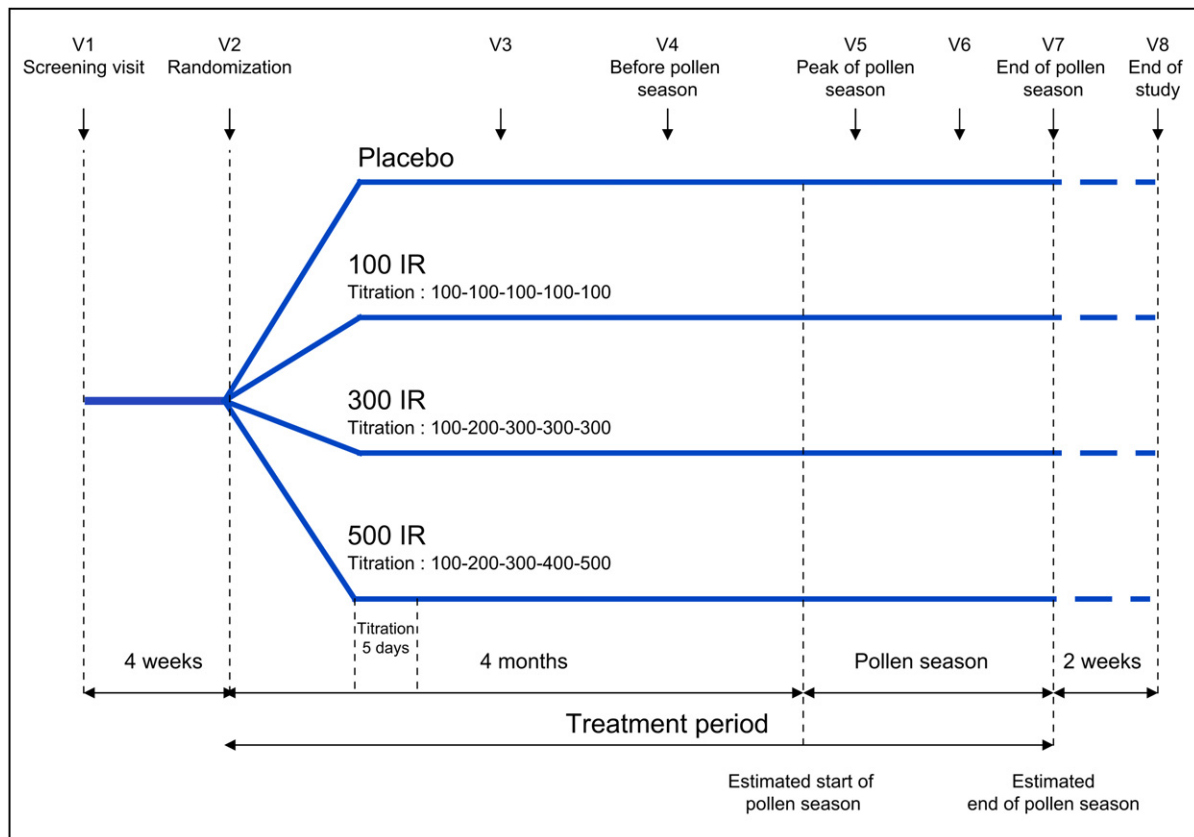


FIG 1. Study design.

peak and at the end of the pollen season, at the end of treatment, and a follow-up visit 2 weeks later (Fig 1). Any adverse events and use of concomitant medication were noted in diary cards.

Patients were considered treatment-compliant if the number of tablets they took (number dispensed – number returned) was at least 75% of the number of tablets they should have taken.

Safety

Adverse events were monitored throughout the study and graded according to the MedDRA dictionary (version 7.1; <http://meddrams.com>). The safety population included all eligible patients who were randomized and had received a single dose of investigational product.

Pollen count

For each center, the beginning, the peak, and the end of the pollen season were based on the estimated average pollen season over the past 5 to 10 years, according to the data collected by the European Aeroallergen Network (available at <http://www.univie.ac.at/ean>). The pollen season was defined as the first day of 3 consecutive days with a grass pollen count above 30 grass pollen grains/m³ of air to the last day before 3 consecutive days with a pollen count below 30 grains/m³.

Daily pollen counts were recorded using the Hirst-type volumetric pollen traps in all but 2 centers, where the Durham samplers were used.¹⁷

Statistics

The primary analyses were performed for the intent-to-treat (ITT) and per protocol (PP) populations. The secondary analyses were performed for the ITT population alone.

Previous studies¹¹ indicated that a sample size of 137 patients per group would have a 90% power to detect a difference between placebo and 300 IR in the mean RTSS, assuming an overall α value of 0.05 and a common SD of 2.1. Assuming a 10% dropout rate, target recruitment was for 150 patients in each group. For the analysis of the RTSS, a step-down approach (from highest to lowest dose) was used for the primary comparison of the 3 active treatment groups versus placebo to control the overall type I error rate of 5%. The clinical efficacy using the RTSS was examined by an analysis of covariance (ANCOVA) model with treatment and pooled site as main effects and presence or absence of asthma and sensitization (mono- or polysensitized) of patients¹⁸ as covariates. The normality of the residuals was tested using the Shapiro-Wilk test. Because the data were skewed, nonparametric methods were also used on the primary efficacy variable as a supportive analysis. All data are given as means $\pm$ SDs and medians. For the primary outcome, the difference between each active and placebo groups was estimated by the difference in adjusted means together with the 95% CI for this difference.

Proportion of days with rescue medication calculated during the pollen season was analyzed by using the Wilcoxon 2-sample test.

Safety data were analyzed descriptively. All patients who received at least 1 dose of the investigational product were included in the safety analysis.

RESULTS

A total of 749 patients were screened, and 628 patients were randomized to the study and valid for inclusion in the safety protocol. Fifty-nine patients were excluded from the

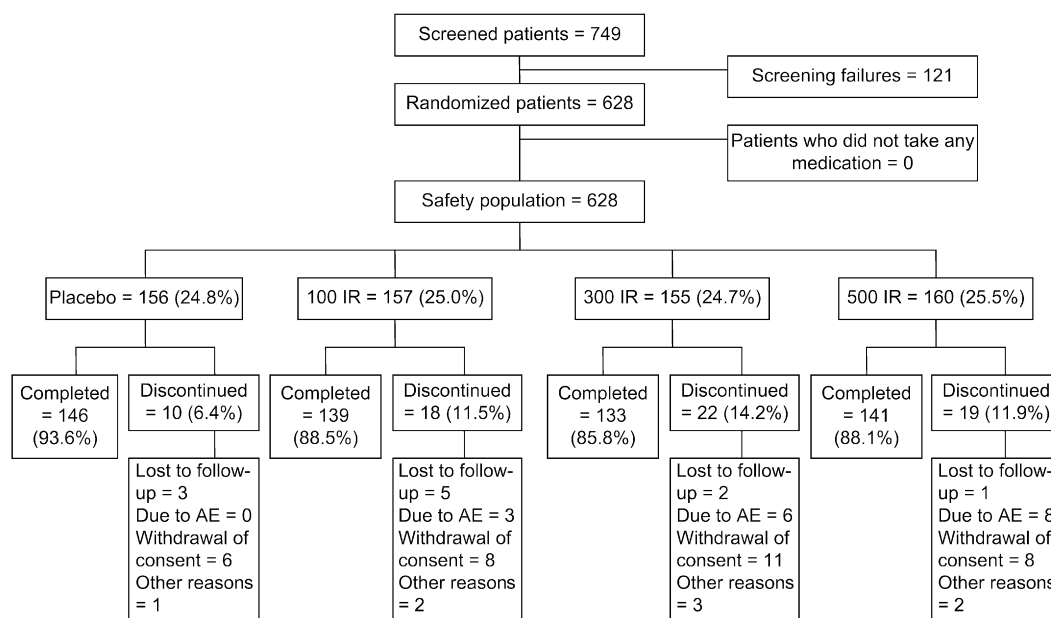


FIG 2. Flow chart. AE, Adverse events.

ITT population because the RTSS was unavailable for the pollen season, and 104 patients were excluded from the PP analysis due to poor compliance, use of prohibited medications, and unavailability of RTSS, or withdrawal for a reason other than adverse event or lack of efficacy. A total of 559 patients completed the study. Fig 2 describes the overall participant flow for the study.

The baseline demographic and clinical characteristics of each group are presented in Table I. No differences were observed for the baseline characteristics. The mean treatment duration before the pollen season was similar in the 4 treatment groups (121.4 ± 31.1 to 128.6 ± 15.4 days in the safety population). The mean duration of the pollen season was 29.5 ± 9.5 days.

Efficacy

For the ITT population, rhinoconjunctivitis symptoms (RTSS) were lower in the 300-IR and 500-IR groups during the pollen season than in the 100-IR and placebo groups (Table II). The treatment effect, assessed by the mean difference in RTSS between each active group and the placebo group (including the 95% CI), was highly significant for the 300-IR (-1.39 [-2.09 , -0.69]; $P = .0001$) and 500-IR groups (-1.22 [-1.91 , -0.53]; $P = .0006$) but not significant for the 100-IR group (-0.26 [-0.95 , 0.43]; $P = .46$). Throughout the pollen season, daily mean RTSS was lower in the 300-IR and 500-IR groups than the placebo or 100-IR groups (Fig 3).

Compared with placebo, median RTSS in the 300-IR group demonstrated 37% improvement, whereas patients taking 500 IR had 35% improvement. Results for the PP population were similar and confirm those for the ITT population.

In the 300-IR and 500-IR groups, all individual symptoms (Table II) were significantly improved compared

with placebo. The median proportion of symptom-free days was 15.65% in the 300-IR group, 11.11% in the 500-IR group, 3.33% in the 100-IR group, and 2.93% in the placebo group.

The proportions of patients with asthma and of those who were monosensitized to any of the grass pollen allergens only and polysensitized (all other allergens) were similar across the 4 dose groups. Between 8.8% (placebo group) and 11.0% (300-IR group) of patients had asthma. Between 42.6% (placebo group) and 48.5% (300-IR group) of patients were monosensitized, and between 51.5% (300-IR group) and 57.4% (placebo group) were polysensitized. Asthma and sensitization status were not significant covariates, indicating that the average RTSS was similar for patients with and without asthma as well as for monosensitized and polysensitized patients.

The proportions of days with rescue medication usage were lower in the 300-IR and 500-IR groups than in the 100-IR and the placebo groups (Table II). Patients in the 300-IR group reported significantly less rescue medication use (46%) compared with those taking placebo ($P = .019$).

The overall RQLQ score was highly significantly different between the 300-IR and 500-IR groups versus the placebo group at peak ($P < .0001$) and at the end ($P \leq .0031$) of the pollen season.

The trends were similar for the 7 individual domains: activities, sleep, nonnose/eye symptoms, eye symptoms, emotional, practical problems, and nasal symptoms. The eye symptoms domain had the highest mean overall scores, and the emotional domain had the lowest.

For the safety population, compliance during the escalation period was between 81.3% (300-IR group) and 87.9% (100-IR group). Overall treatment compliance¹⁹ was between 87.7% (300-IR group) and 95.5% (placebo group) and was similar for all treatment groups.

TABLE I. Demographic characteristics of the patients*

		Placebo	100 IR	300 IR	500 IR
No. of subjects	Randomized	156	157	155	160
	ITT	148	142	136	143
	PP	136	132	123	133
Age (y)		29.1 ± 7.60	29.3 ± 6.90	28.7 ± 7.34	30.4 ± 7.45
Sex (% male)		59.5	51.4	54.4	62.2
Body mass index (kg/m ²)		23.7 ± 3.54	23.8 ± 3.59	24.5 ± 4.13	24.0 ± 3.91
Polysensitized patients (%)		57.4	54.9	51.5	54.5
Patients with asthma (%)		8.8	9.9	11.0	10.5

*Results for the ITT population in percentages or means ± SDs. Polysensitized patients: patients with positive skin tests to a wide array of allergens, including grass pollen.

TABLE II. Study outcomes*

Entire pollen season	Placebo	100 IR	300 IR	500 IR	P values§	
					Placebo vs 300 IR	Placebo vs 500 IR
Total RTSS (ITT)						
Mean ± SD	4.93 ± 3.229	4.72 ± 3.141	3.58 ± 2.976	3.74 ± 3.142	.0001†	.0006†
Median (P25-P75)	4.62 (2.06-7.42)	4.44 (2.27-6.78)	2.91 (1.43-5.06)	3.00 (1.43-5.00)	.0002‡	.0029‡
Percent median improvement¶		3.9	37.0	35.1		
Sneezing						
Mean ± SD	1.00 ± 0.647	0.99 ± 0.678	0.82 ± 0.592	0.85 ± 0.702	.0102†	.0309†
Median (P25-P75)	0.91 (0.44-1.44)	0.95 (0.41-1.47)	0.79 (0.37-1.07)	0.71 (0.31-1.26)	.0171‡	.0143‡
Runny nose						
Mean ± SD	0.95 ± 0.672	0.94 ± 0.686	0.73 ± 0.654	0.75 ± 0.688	.0033†	.0064†
Median (P25-P75)	0.82 (0.38-1.44)	0.90 (0.33-1.48)	0.61 (0.13-1.10)	0.57 (0.19-1.18)	.0014‡	.0020‡
Itchy nose						
Mean ± SD	0.83 ± 0.657	0.82 ± 0.652	0.60 ± 0.592	0.63 ± 0.632	.0016†	.0044†
Median (P25-P75)	0.71 (0.26-1.26)	0.75 (0.23-1.23)	0.47 (0.07-0.98)	0.45 (0.13-1.00)	.0018‡	.0035‡
Watery eyes						
Mean ± SD	0.59 ± 0.627	0.51 ± 0.570	0.39 ± 0.554	0.40 ± 0.545	.0016†	.0032†
Median (P25-P75)	0.36 (0.05-1.00)	0.31 (0.03-0.82)	0.18 (0.00-0.52)	0.24 (0.00-0.55)	.0014‡	.0051‡
Itchy eyes						
Mean ± SD	0.80 ± 0.706	0.71 ± 0.628	0.56 ± 0.610	0.59 ± 0.650	.0012†	.0038†
Median (P25-P75)	0.60 (0.20-1.21)	0.62 (0.15-1.07)	0.42 (0.04-0.86)	0.36 (0.04-0.95)	.0013‡	.0017‡
Nasal congestion						
Mean ± SD	0.75 ± 0.652	0.75 ± 0.720	0.48 ± 0.607	0.53 ± 0.613	.0003†	.0021†
Median (P25-P75)	0.61 (0.20-1.15)	0.60 (0.05-1.23)	0.25 (0.00-0.78)	0.26 (0.03-0.88)	.0001‡	.0007‡
Percent days with rescue medication						
Median (P25-P75)	19.72 (0.00-46.67)	15.19 (0.00-42.75)	10.62 (0.0-29.77)	10.53 (0.0-40.63)	.0194	0.1611

*Total symptom score includes sneezing, runny nose, itchy nose, nasal congestion, watery eyes, and itchy eyes. Total score = total of the 6 individual symptom scores, each assessed on a 4-point scale (from 0 = absent to 3 = severe).

†ANCOVA with treatment group and pooled center as factors and asthma and sensitization as covariates.

‡Nonparametric analysis: Wilcoxon 2-sample test.

§ANCOVA with treatment group and pooled center as factors and overall RQLQ score at V2, asthma and sensitization as covariates.

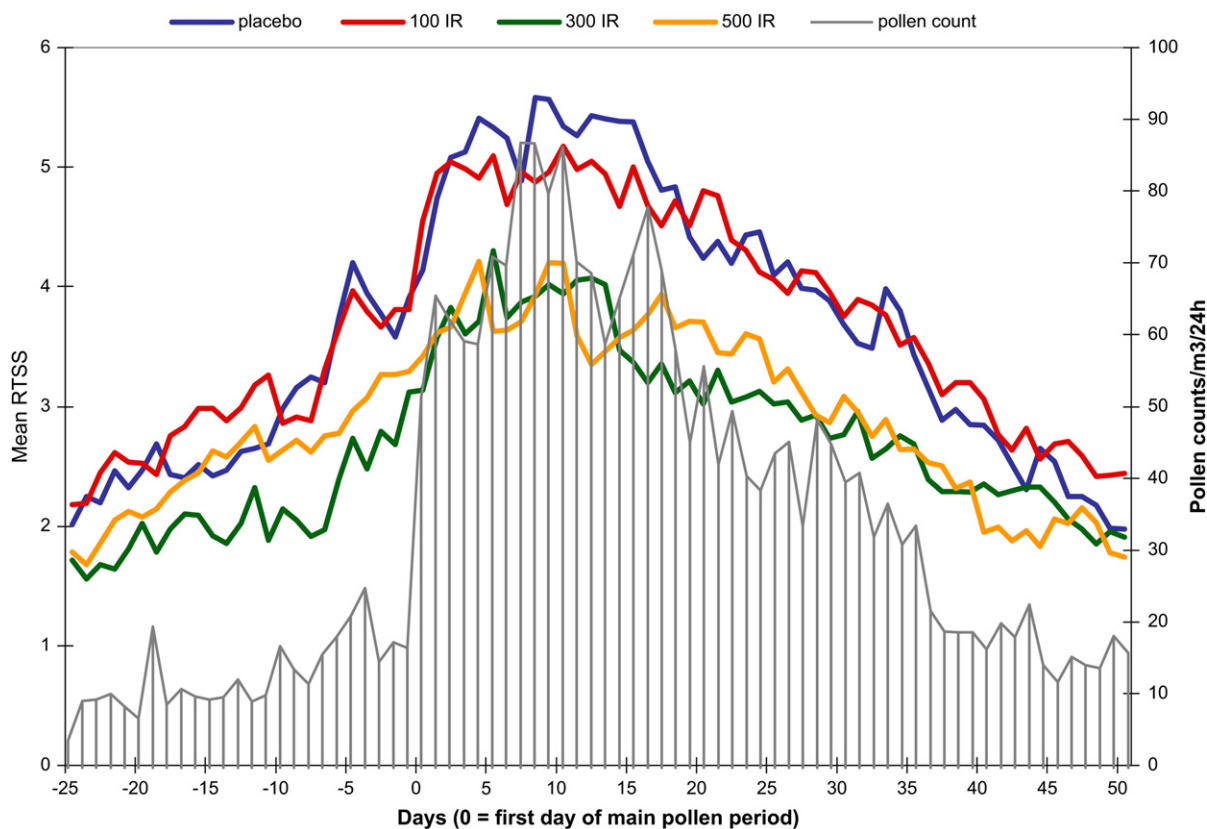
||Wilcoxon 2-sample test for the overall difference in proportion of days with ≥1 rescue medications between active treatment and placebo. NS, Not significant at .05 level.

¶Percent median improvement, Improvement compared with placebo (if active RTSS < placebo RTSS), according to Mallings definition = (1-(active/placebo))*100, based on the medians. A symptom-free day is a day with "0 = absent" recorded for the corresponding symptom. A totally symptom-free day is a day with "0 = absent" recorded for all the 6 symptoms.

During the study, IgG₄ (μg/L) levels increased 2.7-fold in the 100-IR group, 3.2-fold in the 300-IR group, and 3.7-fold in the 500-IR group compared with the placebo group. The progressive mean IgG₄ level elevations

corresponded with increasing SLIT dose, which suggests a dose-effect for IgG₄.

The IgE (kU/L) levels increased by a factor of 2.0 for the 100-IR group, 2.1 for the 300-IR, group and 2.2 for the



Daily mean symptom scores are plotted as one curve by treatment group with the corresponding scale on the left vertical axis. Daily mean grass pollen counts are plotted as vertical lines and the corresponding scale is on the right vertical axis.

FIG 3. Daily mean RTSS and grass pollen counts (2005).

500-IR group, whereas for the placebo group, the geometric means were remained constant at the 2 visits (a ratio of 1.0).

Safety

The allergen tablets were generally well tolerated. A total of 384 patients reported treatment-emergent adverse events (Table III). Compared with patients receiving active treatment, there were fewer adverse events in subjects receiving placebo. The proportions of patients with treatment-emergent adverse events were 48.7%, 68.8%, 62.6%, and 64.4% in the placebo, 100-IR, 300-IR, and 500-IR groups, respectively. Most adverse events were mild or moderate, such as mild oral pruritus or throat irritation. The duration of events was highly variable; the median duration of oral pruritus was 1, 12, 12.5, and 5 days for patients taking placebo, 100 IR, 300 IR and 500 IR, respectively.

Between 1.9% and 6.4% of the patients reported severe adverse events, usually oral pruritus, or more rarely, gastrointestinal pain. Three patients reported serious adverse events: 1 taking 300 IR had back pain, and in the 500-IR group, 1 developed suspected appendicitis and another an intervertebral disc protrusion. None of these were attributed to the study treatment.

A comparison of the frequency of patients who experienced at least 1 adverse event showed statistical differences

for global comparison ($P = .002$) and compared with placebo in the 500-IR ($P = .0064$), 300-IR ($P = .0165$), and 100-IR ($P = .0004$) groups. According to recommendations for immunotherapy trials, in this study the systemic reactions possibly, probably, and certainly related to the treatment included 8 episodes of rhinitis (2 in the 100-IR group, 4 in the 300-IR group, and 2 in the 500-IR group) and 2 episodes of urticaria in the 100-IR group. No serious systemic events or anaphylactic shock were observed.

Adverse events led to the discontinuation of the study treatment in 3.8% (100-IR group), 5.2% (300-IR group), and 6.9% (500-IR group) of the patients.

DISCUSSION

The current study shows that SLIT with an extract of 5 grass pollens is well-tolerated and effective for the treatment of patients sensitized to grass pollens. Compared with placebo, patients treated with the 300-IR and 500-IR grass pollen tablets showed highly significant improvements for all efficacy endpoints tested.

A dose-response effect was observed because the 100-IR dose was more effective than placebo but less effective than the 300-IR and 500-IR doses. With 300 IR, the

TABLE III. Adverse events during treatment (safety population)

		Placebo		100 IR		300 IR		500 IR	
TEAE	No.	76 (48.7%)		108 (68.8%)		97 (62.6%)		103 (64.4%)	
	Mild	55 (35.3%)		82 (52.2%)		74 (47.7%)		78 (48.8%)	
	Moderate	40 (25.6%)		50 (31.8%)		52 (33.5%)		58 (36.3%)	
	Severe	3 (1.9%)		10 (6.4%)		8 (5.2%)		10 (6.3%)	
	Discontinued study medication	0 (0%)		6 (3.8%)		8 (5.2%)		11 (6.9%)	
Most common AEs with an incidence of $\geq 5\%$ in at least 1 treatment group	Preferred term	No. (Percent)	AEs	No. (Percent)	AEs	No. (Percent)	AEs	No. (Percent)	AEs
	Oral pruritus	8 (5.1)	9	31 (19.7)	50	40 (25.8)	56	41 (25.6)	73
	Headache	21 (13.5)	41	23 (14.6)	46	22 (14.2)	54	14 (8.8)	30
	Throat irritation	5 (3.2)	9	18 (11.5)	22	14 (9.0)	20	23 (14.4)	31
	Nasopharyngitis	11 (7.1)	11	16 (10.2)	21	13 (8.4)	13	12 (7.5)	15
	Edema mouth	0	0	5 (3.2)	7	7 (4.5)	8	10 (6.3)	16
	Ear pruritus	1 (0.6)	1	8 (5.1)	14	5 (3.2)	5	7 (4.4)	12
	Tongue edema	0	0	5 (3.2)	5	4 (2.6)	5	9 (5.6)	9
	Pruritus*	1 (0.6)	1	10 (6.4)	12	3 (1.9)	4	3 (1.9)	4
Serious adverse events		0 (0%)		0 (0%)		1 (0.6%)		2 (1.3%)	
Serious adverse events related to study medication		0 (0%)		0 (0%)		0 (0%)		0 (0%)	

AEs, Number of AEs; TEAE, treatment emergent adverse event coded using MedDRA 7.1.

*Pruritus of any part of the body.

plateau of efficacy was reached, because 500 IR did not increase the clinical efficacy further. This dose-response effect has already been reported with subcutaneous immunotherapy² and SLIT.^{6,20,21}

In this study, efficacy was obtained after only a short preseasonal (4 months before the season) allergen administration. Moreover, clinical efficacy was observed from the beginning and throughout the pollen season, including the peak season.

The improvement in RTSS scores of 37% in the 300-IR group and 35% in the 500-IR group is considered clinically meaningful.²² This magnitude of effect is similar to recent studies using SLIT tablets^{8,23} and occurred despite use of rescue medication.

All individual nasal and ocular symptoms were improved with the 2 highest doses of active treatment, including congestion, which is a nasal symptom not normally relieved by antihistamines.²

The rescue medication usage (percentage of days with rescue medication) was significantly lower in the 300-IR group versus placebo. An assessment of rescue medication score (based on the rescue drugs and weightings: 0.5 = topical antihistamines, 1 = oral antihistamines, 2 = nasal corticosteroids, 3 = oral corticosteroids) showed a significantly reduced score for the 300-IR group versus placebo ($P < .006$) with a median reduction of 63% during the pollen season.

The improvement in RQLQ score was comparable to a recent SLIT clinical study,²⁰ with a difference between the placebo and 300-IR and 500-IR groups of 20%. All 3 doses of allergens were well tolerated. The rate and the severity of side effects observed in this study were similar to those reported in other tablet-based SLIT studies.^{8,12,20,24,25} There were no serious side effects reported. These data are in agreement with the well established safety profile of SLIT according to systematic reviews,

meta-analyses, clinical trials,^{6,26,27} and postmarketing surveillance.²⁸ This study reports 1 year's preseasonal and seasonal treatment, but the treatment needs to be assessed in a long-term, placebo-controlled trial.

In this study, both patients allergic only to grass pollens (monosensitized) and patients allergic to grass pollen plus other allergens (polysensitized) were studied. Although some guidelines^{1,2} do not recommend the use of SIT for polysensitized patients, this is not the conclusion of all previous articles,^{18,29} some of which agree with the current study and suggest use of SIT in polysensitized patients because of evidence of comparable improvement for both polysensitized and monosensitized patients. This is of importance in clinical practice because the majority of patients with allergy are polysensitized. These data extend the possibility of the use of SIT to a wider population of patients with allergies in countries where its use is restricted to monosensitized patients.

The current study shows that the 300-IR SLIT tablet containing 5 grass pollens was well tolerated and effective in reducing the symptoms of rhinitis and conjunctivitis caused by grass pollens. The highest dose (500 IR) was no more effective but induced more adverse events. The 100-IR dose was not effective; this dose was on the slope of the dose-response curve, in contrast with the 300-IR and 500-IR doses, which were on the plateau of the curve. Thus, the optimal dose of allergen (300 IR) for SLIT has been found in this study. These benefits for adults after 1 year's preseasonal and seasonal treatment need to be confirmed in a long-term, placebo-controlled trial and in a pediatric population.

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