

Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis

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Background: Specific immunotherapy is widely used to treat allergic rhinitis, but few large-scale clinical trials have been performed.

Objective: We sought to assess the efficacy and safety of specific immunotherapy with 2 doses of Alutard grass pollen in patients with moderately severe seasonal allergic rhinitis inadequately controlled with standard drug therapy.

Methods: We performed a double-blind, randomized, placebo-controlled study of 410 subjects (203 randomized to 100,000 standardized quality units [SQ-U] maintenance, 104 to 10,000 SQ-U, and 103 to placebo). Three hundred forty-seven (85%) completed treatment. Groups were well matched for demographics and symptoms.

Results: Across the whole pollen season, mean symptom and medication scores were 29% and 32% lower, respectively, in the 100,000-SQ-U group compared with those in the placebo group (both $P < .001$). Over the peak pollen season, mean symptom and medication scores were 32% and 41% lower, respectively, than those in the placebo group. The 10,000-SQ-U group had 22% less symptoms than the placebo group over the whole season ($P < .01$), but medication scores reduced by only 16% ($P = .16$). Quality-of-life measures confirmed the superiority of both doses to placebo. Local and delayed side effects were common but generally mild. Clinically significant early and delayed systemic side effects were confined to the

100,000-SQ-U group, but no life-threatening reactions occurred.

Conclusions: One season of immunotherapy with Alutard grass pollen reduced symptoms and medication use and improved the quality of life of subjects with moderately severe hay fever. The 100,000-SQ-U regimen was more effective, but the 10,000-SQ-U regimen caused fewer side effects. (*J Allergy Clin Immunol* 2006;117:319-25.)

Key words: Immunotherapy, allergic rhinitis, efficacy, safety, quality of life, grass pollen

Seasonal allergic rhinoconjunctivitis (SAR) is increasingly common.¹ Although often mild, SAR limits patients' social lives, adversely affects school performance and work productivity,^{1,2} and accounts for approximately 7 times more medical consultations in the United Kingdom than asthma.³ Currently, most patients are treated symptomatically with antihistamines and topical steroids, but in UK general practice less than 40% of patients with SAR report good symptom control.⁴ Specific immunotherapy (SIT) reduces symptoms and medication requirements. However, many SIT trials have included subjects with relatively mild rhinitis, making it difficult to define efficacy in the type of patients with more severe disease who are candidates for SIT in the United Kingdom. Separately, it has been suggested that SIT with lower allergen doses might achieve similar benefit at lower risk of side effects. We therefore conducted a large, 1-year, double-blind, placebo-controlled study of 2 doses of SIT in patients with SAR whose SAR was inadequately controlled with standard medication.

METHODS

Subjects

Male and female subjects aged 18 to 60 years were recruited from clinic referrals and by response to advertisement. For inclusion, they had to have a clinical history of grass pollen-induced SAR that was inadequately controlled in previous years despite using antihistamines, topical steroids, and/or cromoglycate eye drops. Grass pollen allergy was confirmed by means of skin and blood tests (wheal diameter of ≥ 3 mm with Soluprick SQ 10 HEP *Phleum pratense*, ALK-Abelló, Hørsholm, Denmark; grass pollen-specific IgE class ≥ 2 , Pharmacia CAP, Uppsala, Sweden). Patients with additional sensitizations were allowed to participate unless they had significant rhinoconjunctivitis, sinusitis, and/or asthma outside the grass pollen season or daily contact with animals causing symptoms. Patients who had received SIT within the past 5 years were also excluded.

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Abbreviations used

AE: Adverse event
 RQLQ: Rhinoconjunctivitis Quality-of-Life Questionnaire
 SAR: Seasonal allergic rhinoconjunctivitis
 SIT: Specific immunotherapy
 SQ-U: Standardized quality unit
 VAS: Visual analog scale

Study design and assignment

We performed a double-blind, randomized, placebo-controlled study conducted at 26 UK hospital clinics during the winter and spring of 2002. Subjects were randomized in a 1:1:2 ratio to receive placebo, Alutard *P pratense* 10,000 standardized quality units (SQ-U) or 100,000 SQ-U (ALK-Abelló). 200 subjects were included in the 100,000-SQ-U group to increase safety data for this dose.

ALK-Abelló generated the randomization sequence, which was retained until all assessments and recordings were completed. Investigators allocated subjects the next randomization number from the randomized sequence. Staff administering medication and assessing outcomes were blinded to the treatment. The study was conducted in accordance with good clinical practice guidelines, with full ethical approval and informed written consent from each subject.

Intervention

Standardized depot preparations of grass pollen extract (Alutard SQ grass pollen, ALK-Abelló) were administered by means of subcutaneous injection. The up dosing phase consisted of 15 injections over 8 weeks (Table I). At each visit, 8 mg of acrivastine was administered 15 minutes before the first injection; the second injection was administered 30 minutes later. Maintenance injections were administered every 6 ± 2 weeks. One hundred thousand SQ-U corresponds to 20 μ g of major allergen (Phl p 5), and 10,000 SQ-U corresponds to 2 μ g. Where appropriate, doses were adjusted following established clinical guidelines.⁵

Study medication was provided as a suspension in vials. Placebo and active medications were identical, except for grass pollen extract. Acrivastine, fluticasone propionate nasal spray, and sodium cromoglycate eye drops were freely available throughout the study. Where necessary, rescue medication was given according to written protocols.

Assessments

Primary outcome measures were symptom scores and medication use during the grass pollen season. Pollen counts were obtained from the National Pollen and Aerobiology Research Unit, Worcester University. Subjects recorded nasal, eye, and lung symptoms on daily diary cards using a 4-point scale (none, mild, moderate, and severe). Medication use was recorded daily. For analysis, drugs were weighted as follows: sodium cromoglycate, 1 per drop; fluticasone propionate nasal spray, 2 per puff; acrivastine (8 mg), 2 per capsule; prednisolone (5 mg), 2 per tablet; and salbutamol (100 μ g), 1 per puff. Rhinoconjunctivitis Quality-of-Life Questionnaires (RQLQs)⁶ were completed before and at the peak of the pollen season. During the pollen season, subjects marked a visual analog scale (VAS) every week to indicate how their hay fever had been.

Adverse events and allergic side effects

Safety data were collected and analyzed separately as local and systemic allergic side effects and other adverse events (AEs). Side effects occurring within 1 hour of injection were documented by

TABLE I. SIT dosage schedules

Week no.	Injection no.	100,000 SQ-U	10,000 SQ-U
1	1	100	0
1	2	1000	100
2	3	1000	100
2	4	1000	100
3	5	2000	200
3	6	3000	300
4	7	5000	500
4	8	5000	500
5	9	10,000	1000
5	10	10,000	1000
6	11	20,000	2000
6	12	20,000	2000
7	13	30,000	3000
7	14	30,000	3000
8	15	100,000	10,000

clinical staff. Side effects 1 to 24 hours after injection were recorded by subjects on preprinted cards and transcribed at the next visit.

Statistical methods

Symptom and medication scores were averaged over the grass pollen season (predefined as June 1 to August 13) and analyzed by means of ANOVA, with treatment group and pollen region as factors. Primary end points were analyzed in a predetermined hierarchy. First, symptoms were compared between the 100,000-SQ-U and placebo groups; if statistically significant, medication scores were analyzed. If these differences were statistically significant, the 10,000-SQ-U group was compared with the placebo group. Finally, 100,000 SQ-U was tested against 10,000 SQ-U. Therefore no adjustments for multiple comparisons were required. Hypothesis testing was 2-sided, with a significance level of a *P* value of less than .05.

The primary analysis included all randomized subjects with adequate diary data. An analysis subset was predefined for explorative efficacy analyses (subjects with ≥ 2 maintenance doses before the grass pollen season and diary card information for $\geq 30\%$ days in $\geq 50\%$ weeks of the pollen season). Safety data include all subjects who received any injections.

For additional efficacy analyses, the peak grass pollen season was predefined as the 3 weeks from June 9th to 30th.

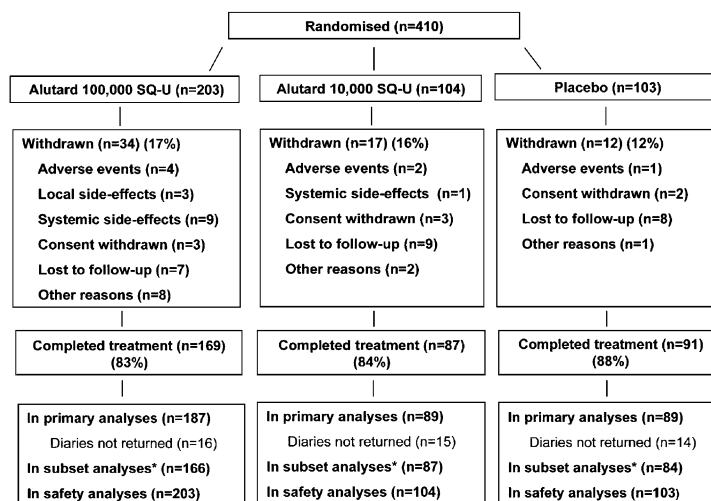
The RQLQ has 28 items in 7 domains, each scored on a 7-point scale (0, no impairment; 6, maximum impairment). Mean overall RQLQ scores and domain scores were calculated for each subject. Change in RQLQ scores from baseline to peak season was analyzed by means of ANOVA, with treatment group and pollen region as factors.

The VAS was averaged over the pollen season for each subject and analyzed as for RQLQ.

With a power of 84%, 100 subjects per treatment were required to detect a 75% relative treatment effect of 10,000 SQ-U versus 100,000 SQ-U.

RESULTS

Four hundred ten subjects were randomized, and 347 (85%) completed treatment (Fig 1). The groups were well balanced for demographics, sensitivity to grass pollen, and symptom duration and received similar numbers of maintenance injections before the pollen season (Table II).



* Subjects with at least two maintenance doses before grass pollen season who provided diaries for $\geq 30\%$ days in $\geq 50\%$ weeks between 1 June and 13 August 2002

FIG 1. Randomization and disposition of subjects participating in the study (consort diagram).

Across the whole season, compared with the placebo group, mean symptom scores for the 100,000-SQ-U group were 29% lower ($P = .0001$), and mean medication scores were 32% lower ($P = .0007$, Fig 2 and Table III). These differences were confirmed and indeed were greater during the peak pollen season (32% and 41%, respectively; both $P < .0001$). Median symptom and medication scores were 34% and 54% lower, respectively, than those in the placebo group across the whole pollen season. The 10,000-SQ-U group showed reduced whole-season symptom scores (22% lower, $P = .013$) but no reduction in medication score (16%, $P = .16$; Table III). This pattern was also observed during the peak pollen season. Median reductions in symptom and medication scores were 26% and 32% lower than those in the placebo group across the whole season. These overall symptom scores were reflected in individual results for nose and eye symptoms, but not lung symptoms, which were very low in both groups (Table III).

Over the whole season, symptom and medication scores were lower in the 100,000-SQ-U group versus those in the 10,000-SQ-U group, but these differences were not statistically significant (Table III). However, significant differences were found in the peak-season subset analysis ($P = .034$ and $P = .001$, respectively; Fig 3, A and B).

Pollen-season RQLQ scores were significantly better with 100,000 SQ-U compared with placebo ($P < .0001$) and with 10,000 SQ-U compared with placebo ($P = .031$; Fig 3, C, and Table III). Changes of 0.5 or greater in RQLQ domains are regarded as clinically relevant⁶ and were observed for 5 of 7 domains comparing 100,000 SQ-U with placebo but in 1 of 7 domains comparing 10,000 SQ-U with placebo.

Subjective evaluations of symptoms were reported as “better” or “a lot better” than previous years by 68% in the 100,000-SQ-U group, 57% in the 10,000-SQ-U

TABLE II. Demographics and symptom duration for the 3 treatment groups

Treatment group	100,000 SQ	10,000 SQ	Placebo
Age (y)			
Mean (SD)	38.3 (9.1)	36.9 (9.0)	37.9 (9.1)
Range	18.4-59.7	19.7-58.2	18.9-59.2
Sex			
Male	110 (54.2%)	59 (56.7%)	62 (60.2%)
Female	93 (45.8%)	45 (43.3%)	41 (39.8%)
Years with symptoms (mean, SD)			
Eye-nose	20.6 (11.0)	20.2 (10.8)	19.9 (10.0)
Lung	16.8 (11.3)	16.8 (12.3)	16.2 (10.9)
Skin test to <i>Phleum pratense</i> (mm diameter), mean (SD)	8.8 (3.0)	9.9 (6.8)	9.4 (3.5)
Grass pollen-specific IgE (mean RAST class)	3.8	3.8	4.0
No. of maintenance doses given before pollen season, mean (SD)	6.4 (1.33)	6.5 (1.07)	6.3 (1.27)
5%-95% range	4-8	5-8	3-8

group, and 48% in the placebo group. Mean VAS scores were 25% lower after 100,000 SQ-U compared with those after placebo ($P = .0006$). VAS showed no statistically significant difference between the 10,000-SQ-U and placebo groups (Table III).

Two hundred seventy-six of the 347 subjects were polysensitized, as judged on the basis of skin tests. This group showed a similar degree of improvement in symptoms, medication use, RQLQ, and VAS scores compared with the whole study group. Specifically, in the polysensitized subjects who received 100,000 SQ-U, symptom

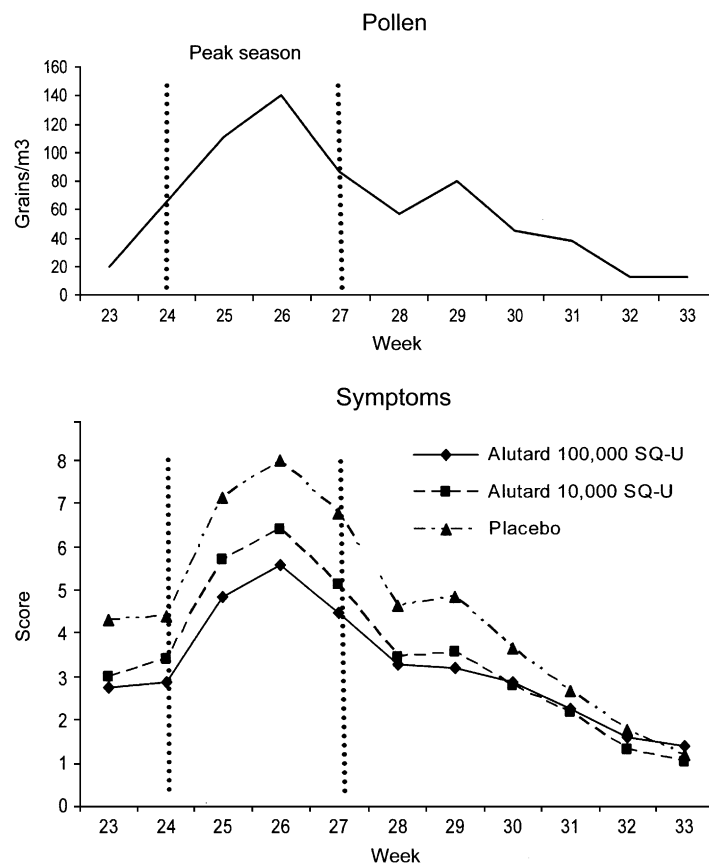


FIG 2. The weekly average symptom scores for each treatment group and grass pollen exposure. The peak grass pollen season (the 3 weeks representing the highest pollen exposure) is indicated by the vertical dotted lines.

scores across the whole season were 34% less and medication scores were 40% less than in the equivalent placebo-treated group (compared with 29% and 32%, respectively, for the whole study group). In the 10,000-SQ-U group polysensitized subjects had 26% less symptoms and 21% less medication than the placebo-treated group (22% and 16% in the whole group).

There were no differences in AE frequency among the 3 treatment groups. Overall, 270 (65.9%) subjects reported AEs. Most AEs were mild or moderate and not related to treatment. The most frequent AEs were headache and nasopharyngitis, which were reported equally often in all groups (Table IV).

In all 3 groups, the most common local side effects were redness, swelling, and discomfort at injection sites. Overall, 36 (9%) subjects had early local side effects, and 171 (42%) subjects had delayed local side effects, which were more often reported in the 100,000-SQ-U group. In general, these were mild and did not require treatment.

Individual early systemic side effects were reported by less than 10% of subjects in each group (Table IV). Early systemic side effects were reported by 105 (25.6%) subjects: 32.5% in the 100,000-SQ-U group, 21.2% in the 10,000-SQ-U group, and 16.5% in the placebo group. By using the grading scheme of the European Academy

of Allergy and Clinical Immunology (EAACI) SIT guidelines,⁵ most early systemic side effects were nonspecific or mild (grade 1 to 2). Nine (4.4%) subjects receiving 100,000 SQ-U had non-life-threatening grade 3 reactions (urticaria or asthma; ie, 2.7/1000 injections). These subjects were allowed to continue in the study at the discretion of the investigator if they wished to do so. No grade 4 (anaphylactic) reactions occurred.

Delayed systemic side effects were mostly mild and were reported by 230 (56.1%) subjects (67% in the 100,000-SQ-U group, 51% in the 10,000-SQ-U group, and 40% in the placebo group). Symptoms were similar to the early systemic side effects but also included asthma, headache, conjunctivitis, and pruritus. Fatigue was the most common systemic side effect, affecting more than 20% in each group. Delayed systemic side effects were defined as clinically significant if they were moderate or severe or treatment related and involved angioedema, asthma, or urticaria. By using these criteria, 35 subjects reported moderate side effects: 14% in the 100,000-SQ-U group, 4% in the 10,000-SQ-U group, and 2% in the placebo group. Severe side effects were reported by 4 (2%) subjects in the 100,000-SQ-U group, representing 1 in 1000 injections. These 4 subjects included 1 with urticaria, 1 with wheezing and urticaria, 1 with

TABLE III. Effect during the first season of SIT on symptom and medication scores, RQLQ scores, and hay fever VAS scores

Treatment group	N	Adjusted Mean (SE)	Difference vs placebo (95% CI)	Difference of 100,000 SQ-U vs 10,000 SQ-U (95% CI)
Symptom score during season				
Alutard 100,000 SQ-U	187	3.13 (0.25)	-1.26 (-1.89 to -0.62), $P = .0001$	-0.31 (-0.95 to 0.33), $P = .34$
Alutard 10,000 SQ-U	89	3.44 (0.31)	-0.94 (-1.69 to -0.20), $P = .013$	
Placebo	89	4.39 (0.32)		
Medication score during season				
Alutard 100,000 SQ-U	187	2.85 (0.31)	-1.36 (-2.14 to -0.58), $P = .0007$	-0.70 (-1.48 to 0.08), $P = .079$
Alutard 10,000 SQ-U	89	3.55 (0.38)	-0.66 (-1.57 to 0.26), $P = .16$	
Placebo	89	4.21 (0.40)		
Symptom score during peak season				
Alutard 100,000 SQ-U	187	4.44 (0.33)	-2.09 (-2.94 to -1.23), $P \leq .0001$	-0.83 (-1.68 to 0.03), $P = .058$
Alutard 10,000 SQ-U	89	5.27 (0.41)	-1.26 (-2.26 to -0.26), $P = .014$	
Placebo	89	6.53 (0.43)		
Medication score during peak season				
Alutard 100,000 SQ-U	187	3.61 (0.40)	-2.51 (-3.54 to -1.48), $P \leq .0001$	-1.65 (-2.68 to -0.61), $P = .0019$
Alutard 10,000 SQ-U	89	5.26 (0.49)	-0.87 (-2.07 to 0.34), $P = .16$	
Placebo	89	6.13 (0.52)		
Nose symptom score during season				
Alutard 100,000 SQ-U	187	1.88 (0.16)	-0.86 (-1.28 to -0.44), $P \leq .0001$	-0.30 (-0.72 to 0.12), $P = .16$
Alutard 10,000 SQ-U	89	2.19 (0.20)	-0.56 (-1.05 to -0.07), $P = .025$	
Placebo	89	2.75 (0.21)		
Eye symptom score during season				
Alutard 100,000 SQ-U	186	0.87 (0.09)	-0.50 (-0.72 to -0.28), $P \leq .0001$	-0.09 (-0.31 to 0.13), $P = .43$
Alutard 10,000 SQ-U	89	0.96 (0.11)	-0.41 (-0.67 to -0.15), $P = .0019$	
Placebo	89	1.37 (0.11)		
Lung symptom score during season				
Alutard 100,000 SQ-U	186	0.43 (0.09)	-0.07 (-0.31 to 0.16), $P = .54$	0.09 (-0.14 to 0.32), $P = .44$
Alutard 10,000 SQ-U	89	0.33 (0.11)	-0.16 (-0.44 to 0.11), $P = .24$	
Placebo	89	0.50 (0.12)		
Change from baseline in RQLQ score				
Alutard 100,000 SQ-U	183	1.31 (0.14)	-0.88 (-1.23 to -0.54), $P \leq .0001$	-0.44 (-0.79 to -0.09), $P = .013$
Alutard 10,000 SQ-U	88	1.75 (0.17)	-0.44 (-0.84 to -0.04), $P = .031$	
Placebo	92	2.19 (0.17)		
Allergic symptoms measured by VAS				
Alutard 100,000 SQ-U	185	2.21 (0.16)	-0.72 (-1.14 to -0.31), $P = .0006$	-0.32 (-0.73 to 0.10), $P = .13$
Alutard 10,000 SQ-U	89	2.52 (0.20)	-0.41 (-0.89 to 0.08), $P = .098$	
Placebo	89	2.93 (0.21)		

Statistical comparison by means of ANOVA, including adjustment for pollen exposure. Reductions compared with placebo are shown for means and for medians.

angioedema and urticaria, and 1 with wheezing, angioedema, and urticaria. No delayed anaphylactic or life-threatening systemic reactions were reported.

DISCUSSION

In the first season of therapy, SIT with single-species grass pollen extract reduced symptoms and medication requirements in subjects with SAR inadequately controlled with standard drug therapy. These effects were even more marked in the peak pollen season. The beneficial effects of grass pollen SIT have been reported previously.^{7,8} This is the first large-scale, randomized, controlled SIT study performed and is confined to subjects meeting current UK guidelines for SIT, including polysensitized subjects, provided grass pollen was the principal

cause of symptoms. This means that our results are also applicable to polysensitized patients whose main symptoms are due to grass pollen, a common group in clinical practice.

Most previous SIT studies have restricted concomitant medication use, but our participants were allowed free use of conventional antiallergic medication. Thus our study shows that SIT confers clinical benefit over and above that achievable with standard drug therapy.

Both active doses were effective, but 100,000 SQ-U was more effective than 10,000 SQ-U, as confirmed by greater reductions in symptom scores, medication scores, and VAS scores and less seasonal change in RQLQ score. This dose-response effect is consistent with earlier findings with house dust mite SIT.⁹

For optimal outcome, it is normally recommended to continue SIT maintenance treatment for 3 years.^{5,8,10-12}

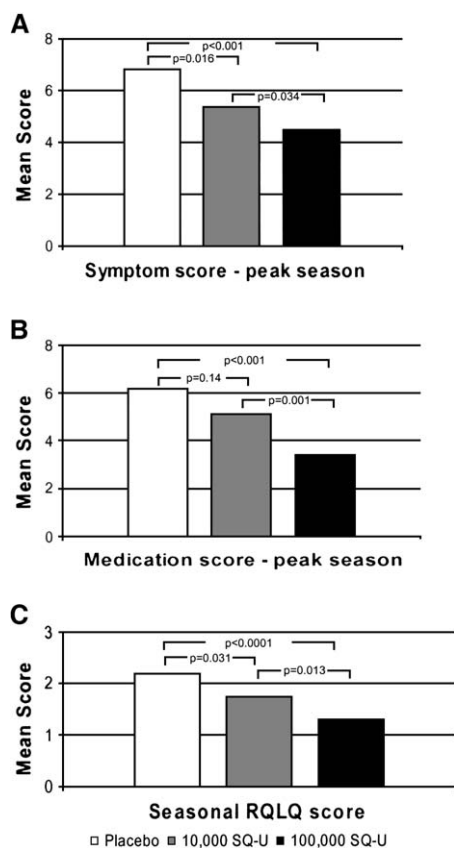


FIG 3. Mean symptom score (**A**) and medication score (**B**) during the peak grass pollen season for subjects who received at least 2 preseasonal maintenance injections and contributed with sufficient diary data. **C**, Mean seasonal RQLQ scores (change from baseline) for the full analysis set.

Ideally, we should have continued the placebo-controlled phase for 3 years, but this was impractical because of the size of the study population and the impracticality of long-term placebo injections.

Particular attention was paid to safety in this study, with extra efforts to capture all side effects, many of which might have been ignored in earlier SIT studies. Formally defined AEs were equally frequent in all groups, and no fatal or life-threatening reactions were reported. Local side effects to SIT injections are common and not generally regarded as AEs, even in clinical studies. As expected, local and systemic side effects occurred more often in the 100,000–SQ-U group. Where antiallergic treatment was needed, the subjects responded well. Systemic side effects occurring 1 to 24 hours after injection were reported by almost 40% of placebo-treated subjects, possibly because of the antihistamine premedication, their underlying disease, or both. Four subjects experienced urticaria, angioedema, or wheeze some hours after injection, despite having been asymptomatic during the initial observation period. None of these episodes was regarded as clinically significant.

Given the clinical benefits of SIT and the tolerable nature of side effects, we consider that the risk/benefit ratio

TABLE IV. Frequency of AEs and side effects reported after SIT injections

	100,000 SQ-U (n = 203), n (%)	10,000 SQ-U (n = 104), n (%)	Placebo (n = 103), n (%)
AEs (>5% of subjects in any group)			
Headache	69 (14.7)	19 (9.1)	36 (14.5)
Nasopharyngitis	59 (12.6)	26 (12.4)	29 (11.7)
Early systemic side effects (>5% of subjects in any group)			
Fatigue	16 (7.9)	10 (9.6)	4 (3.9)
Urticaria	17 (8.4)	0	0
Wheezing	13 (6.4)	0	0
Chest tightness	12 (5.9)	3 (2.9)	2 (1.9)
Flushing	12 (5.9)	1 (1.0)	1 (1.0)
Early systemic side effects, graded according to EAACI			
1 (nonspecific)	22 (10.8)	10 (9.6)	9 (8.7)
2 (mild)	35 (17.2)	12 (11.5)	8 (7.8)
3 (non-life threatening)	9 (4.4)	0	0
4 (anaphylactic shock)	0	0	0

EAACI, European Academy of Allergology and Clinical Immunology.

of SIT favors treating patients with SAR who have not responded to standard drugs, provided potential risks and benefits are properly assessed and explained to the patient and that staff are trained to recognize and treat reactions appropriately.

In summary, Alutard SQ grass pollen was effective and well tolerated in subjects with rhinoconjunctivitis and grass pollen allergy inadequately controlled by standard antiallergic drugs. The 100,000–SQ-U dose was more effective than 10,000–SQ-U dose but was associated with a higher frequency of side effects. SIT is the only effective alternative to drug therapy in severe hay fever. Renewed interest in SIT is timely because recent studies suggest that SIT not only induces long-term disease remission¹³ but also can reduce the onset of new atopic sensitizations^{14–16} and, at least in children, prevents the progression of rhinitis to asthma.¹⁷

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