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Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis

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Clinical and Experimental Allergy

Summary

Background The optimal dose of grass pollen tablets for sublingual immunotherapy (SLIT) in allergic rhinoconjunctivitis patients was previously established in a multinational, randomized, double-blind, placebo-controlled study in 628 adults. Patients were randomized to receive once-daily 5-grass pollen sublingual tablets of 100 IR (index of reactivity), 300 IR or 500 IR, or placebo starting 4 months before the pollen season.

Objective The aim of this complementary analysis was to determine whether 300 IR 5-grass pollen SLIT-tablets is effective in different subtypes of patients who are allergic to grass pollen.

Methods Different subgroups could be identified regarding comorbidities (with or without asthma during the grass-pollen season), sensitization (mono/polysensitization) and symptom severity. An additional exploratory analysis was performed within four subgroups based on pre-treatment assessment: Group 1 = high specific IgE; Group 2 = high symptom scores; Group 3 = high skin sensitivity; Group 4 = any of Group 1, 2 or 3.

Results Asthma and sensitization status were not significant covariates as the average Rhinoconjunctivitis Total Symptom Score (RTSS) was identical for patients with and without grass-pollen asthma, as well as for mono- and polysensitized patients. Across the four subgroups, average RTSSs (±SD) for the optimal dosage (300 IR) were 3.91±3.16, 3.83±3.14, 2.55±2.13 and 3.61±2.97, for subgroups 1, 2, 3 and 4, respectively. ANCOVA showed that in Group 1 average RTSS did not differ significantly with different doses of SLIT. In Groups 2, 3 and 4, doses of 300 IR and 500 IR were significantly more effective than 100 IR and placebo ($P \leqslant 0.035$). All doses of SLIT administered in this study can be considered safe in the patients investigated.

Conclusions The risk–benefit ratio validates the use of 300 IR tablets in clinical practice in all of these patient subgroups, regardless of severity profile, sensitization status and presence of asthma.

Keywords allergic asthma, monosensitized, polysensitized, rhinitis, rhinoconjunctivitis, safety, severity, sublingual grass pollen tablets
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Introduction

Allergic rhinitis (AR) is a common inflammatory condition affecting the upper airways and eyes. The main symptoms of AR and conjunctivitis are sneezing, rhinorrhoea, nasal congestion, itchy nose, itchy eyes and watery eyes [1]. The recent Allergic Rhinitis and its Impact on Asthma (ARIA) group classification includes an assessment of the frequency and duration of symptoms [2]. In addition, a severity scale of mild to moderate/severe has been included in the revised classification The severity of rhinitis has a greater impact on quality of life (QOL), sleep, daily activities and work performance than the duration of rhinitis.

The prevalence of self-reported AR in a pan-European survey of an unselected population was between 15% and 22% [3]. In another study, 19% of the population self-identified as having AR and, in this group, 70% reported

having a medical diagnosis of AR [4]. In a recent survey, 3052 patients consulting a general practitioner for AR were classified into one of the four classes of ARIA. Mild intermittent rhinitis was diagnosed in 11% of patients, mild persistent rhinitis in 8%, moderate/severe intermittent rhinitis in 35% and moderate/severe persistent rhinitis in 46%. More than 80% of patients with moderate/severe rhinitis reported impaired activities, compared with only 40% with mild rhinitis [5].

Asthma is more common in subjects with AR than in those without (20% vs. 2–4%, respectively) [3, 6]. In an international cross-sectional study in young adults, 74–81% of subjects with asthma reported symptoms of rhinitis, depending on sensitization to specific allergens. In all countries, bronchial hyperreactivity was also more frequent in subjects with rhinitis than in those without [odds ratio (OR) = 6.63, 95% confidence intervals (CI) 5.44–8.08; and OR = 3.02, 95% CI 2.66–3.43, respectively).

Sensitization to pollen allergens has increased in many areas of Europe where the prevalence of grass pollen sensitization is reported to be around 16.9% [7]. The allergen concentration in the air is an important factor for disease development and outcome. Thus the burden of IgE-mediated grass pollen allergy is related to the length of the pollen season, total pollen counts, the height of the pollen peak and allergen bioavailability. The allergen content within pollen grains of the same taxon has been shown to vary for a number of reasons [8, 9]. Recent birth cohort studies have revealed increased sensitization to at least one allergen, due essentially to the high prevalence of grass pollen exposure [9]. Different and multiple sensitizations are frequent in atopic subjects although clinical symptoms may not always be present [10, 11].

The IgE-mediated immune response differs among sensitized subjects, even when exposed to a common environment; some individuals react towards a limited number of allergens (mono- or pauci-sensitized), whereas others are sensitized to a wide array of allergens (polysensitized). Taking into consideration the cross-reactivity between allergens and panallergens, a minority of symptomatic patients is sensitized to a single allergen [5]. It has been suggested by the ARIA group that patients with multiple sensitivities may not benefit from specific immunotherapy (SIT) as much as patients with a single sensitivity, but more data are needed to confirm this [2].

The aim of this complementary analysis was to determine whether 300 IR (index of reactivity) 5-grass pollen sublingual immunotherapy (SLIT) [12] was equally effective in different subgroups of patients from the original study, including those with particularly severe sensitivity to grass pollen, patients with severe symptoms of AR, those with mild grass-associated asthma and polysensitized patients.

Materials and methods

Participants and setting

Participants of both sexes, aged 18–45 years, with moderate-to-severe grass pollen-induced allergic rhinoconjunctivitis for at least 2 years were included. All patients had a positive skin prick test (SPT; weal diameter $\geqslant$ 3 mm), serum-specific IgE of at least class 2 and a Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) of at least 12 (out of a maximum of 18). The SPT included five grass pollens (*Anthoxanthum odoratum*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense* and *Poa pratensis*), and timothy grass-specific IgE was measured in kU/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 only if these allergens did not induce symptoms during the grass pollen season (symptoms outside the grass pollen season were allowed). Patients with grass pollen-induced asthma requiring treatment with β_2-agonists only were also included. The main exclusion criteria were allergic rhinoconjunctivitis due to a co-sensitization likely to influence the patient's symptoms during the study, or symptoms of rhinoconjunctivitis during the treatment phase due to sensitization to allergens other than grass pollens, previous SIT for grass pollen allergy, and the usual contraindications for SIT. This was a randomized, double-blind, placebo-controlled trial in which a total of 628 patients was enrolled from 42 centres in 10 European countries.

Sublingual immunotherapy

Patients were randomized to receive once-daily sublingual tablets containing either placebo or extracts of 5-grass pollens (*A. odoratum*, *D. glomerata*, *L. perenne*, *P. pratense* and *P. pratensis*) at doses of 100 IR, 300 IR, 500 IR; 300 IR corresponds to 25 μg/tablet of Group 5 major allergens. Treatment began 4 months before the expected start of the pollen season. The pollen season was defined as the first day of three consecutive days with a grass pollen count $>$ 30 grains/m^3 of air to the last day before three consecutive days with a pollen count $<$ 30 grains/m^3. Peak pollen period was defined as the 14-day period with the highest grass pollen count in the area.

Efficacy analysis

The primary efficacy assessment of the study was Rhinitis Total Symptom Score (RTSS) from 0 to 18, corresponding to the sum of the severity of the six rhinoconjunctivitis symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) during the previous 24 h, each symptom assessed on a four-point

scale (0 = absent to 3 = severe). Secondary assessments were the individual rhinoconjunctivitis symptom scores, RTSS at the peak of the pollen season, rescue medication usage and proportion of symptom-free days. Patients' QOL was assessed using the self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire and patients' global evaluation of their condition. In case of severe symptoms, patients could use predefined rescue medication. Patients were instructed to start with an oral antihistamine (cetirizine) and if the symptoms were not alleviated, progress to an intra-nasal corticosteroid (mometasone furoate) and finally an oral corticosteroid.

Safety analysis

Adverse events were monitored throughout the study and graded according to the MedRA dictionary (version 7.1). The safety population included all eligible patients who were randomized and had received a single dose of investigational product.

In the complementary and exploratory sensitivity analysis, four subgroups of patients with severe disease profiles were evaluated: (i) Group 1: patients with baseline specific (timothy grass) IgE > 17.5 kU/L (≥ class 4); (ii) Group 2: patients with a RRTSS greater than the third quartile (≥ 15); (iii) Group 3: patients who had a baseline SPT to the 5-grass pollen extracts (Stallergènes, Antony, France) with a weal diameter greater than the third quartile (≥ 10.5 mm); and (iv) Group 4: patients falling in any of these three subgroups.

Statistical methods

Clinical efficacy assessed by the RTSS was examined using an ANCOVA model with treatment and pooled site as main effects, and RRTSS, presence or absence of grass pollen-induced asthma and sensitization (mono/polysensitized) status as covariates. Non-parametric methods were also used on the primary efficacy variable as a supportive analysis. All data are given as means±SD. For the primary outcome, the difference between each active and placebo group was estimated by the difference in adjusted means together with the 95% CI for this difference. In order to control the overall type I error rate of 5%, a step-down approach was used, from highest to lowest dose.

Results

Demographic characteristics

Of the 628 randomized patients, 569 comprised the Intent-to-Treat (ITT) population, and 559 of these completed the study. The baseline characteristics of the patients included in each treatment group (active and placebo) were identical. The mean RRTSS was 14.2±1.75, with no statistical significance between the groups.

The proportion of the overall population with mild intermittent asthma (GINA 1) was 8.8–11.0% of patients and the proportion of polysensitized patients was 51.5–57.4%.

At baseline, the patients who were sensitized to more than one allergen (polysensitized) were well matched across the treatment groups. The most common allergens were birch, ash, mugwort, ragweed and cat.

The mean treatment duration before the pollen season was similar in the four 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.

Similarly, the four subgroups of patients with severe grass pollen allergy were well represented in the three active treatment and placebo groups (Table 1).

Table 1. Distribution of patients in the four sensitivity subgroups

Population	Treatment group	IgE ≥ 17.5 kU/L (Group 1)		RRTSS ≥ 15 (Group 2)		SPT weal diameter ≥ 10.5 mm (Group 3)		Any of Group 1, 2 or 3 (Group 4)	
		n	%	*n*	%	*n*	%	*n*	%
Safety population (*n* = 628)	100 IR	62	22.2	67	27.5	37	23.6	117	25.5
	300 IR	69	24.7	52	21.3	36	22.9	112	24.5
	500 IR	66	23.7	66	27.0	44	28.0	117	25.5
	Placebo	82	29.4	59	24.2	40	25.5	112	24.5
	All	279	100.0	244	100.0	157	100.0	458	100.0
ITT population (*n* = 569)	100 IR	55	21.9	61	27.2	34	23.9	105	25.4
	300 IR	59	23.5	47	21.0	32	22.5	100	24.2
	500 IR	57	22.7	60	26.8	39	27.5	103	24.9
	Placebo	80	31.9	56	25.0	37	26.1	105	25.4
	All	251	100.0	224	100.0	142	100.0	413	100.0

IR, index of reactivity; ITT, Intent-to-Treat; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

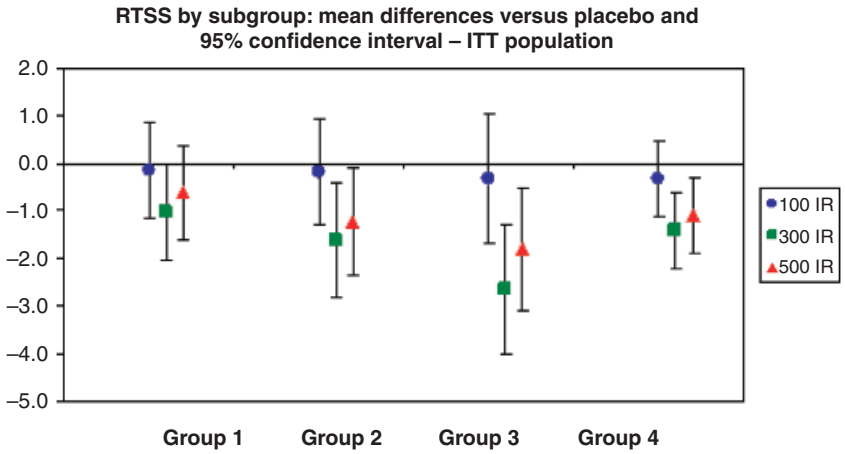

Fig. 1. Average Rhinoconjunctivitis Total Symptom Score (RTSS) (mean±SD) during the pollen season according to sensitivity subgroup [Intent-to-Treat (ITT) population].

Efficacy outcomes

For the RTSS in the overall ITT population, the mean differences for the active treatment group compared to placebo during the entire pollen season achieved significance for the 300 IR ($P = 0.0001$) and 500 IR ($P = 0.0006$) doses, but not the 100 IR dose (Fig. 1). Furthermore, a significant treatment effect for these doses ($P = 0.0005$ for 300 IR and $P = 0.0014$ for 500 IR), but not the 100 IR dose, was also seen during the peak of the pollen season. Non-parametric methods, used as supportive analyses, led to similar conclusions. Average RTSS showed that symptoms were reduced by 27.4% and medication use by 46.1% in patients allocated the 300 IR grass pollen tablets compared with those allocated placebo.

Asthma and co-sensitization

For the ITT population, the average RTSS score was always lower with the 300 IR and 500 IR doses than with the 100 IR dose and placebo, regardless of asthma and sensitization status (Table 2). Asthma and sensitization status were not significant baseline covariates, indicating that the average RTSS was similar for patients with and without asthma, as well as for mono- and polysensitized patients (Table 2).

Sensitivity subgroups

In the ITT population, patients in the 300 IR treatment group had the lowest average RTSS and those in the placebo group or 100 IR treatment group the highest average score across the four subgroups (Table 3). The within-subgroup exploratory ANCOVA of the average RTSS, with treatment and pooled sites as factors, and RRTSS, asthma and polysensitization as covariates, showed a statistically significant difference between the 300 IR and 500 IR treatment groups vs. placebo ($P \leqslant 0.0346$) in Groups 2, 3 and 4. However, for Group 1, the overall treatment effect was not statistically significant ($P = 0.2032$). Comparison of each dose with the placebo group showed that patients treated with 300 IR achieved a statistically significant effect in all four sensitivity subgroups ($P < 0.05$), and that the 500 IR dose was significantly effective in all subgroups except those with IgE class $\geqslant 4$.

Table 2. Average Rhinoconjunctivitis Total Symptom Score (mean±SD) according to asthma and sensitization status during the pollen season (Intent-to-Treat population)

	Placebo	100 IR	300 IR	500 IR
Asthma	4.30±2.74	4.66±2.39	3.92±3.08	3.13±2.71
No asthma	4.99±3.28	4.72±3.22	3.54±2.97	3.81±3.19
Monosensitized	4.59±3.06	4.87±3.31	3.93±3.01	3.74±2.90
Polysensitized	5.18±3.34	4.59±3.01	3.25±2.93	3.74±3.35
Overall	4.93±3.23	4.72±3.14	3.58±2.98	3.74±3.14

IR, index of reactivity.

Safety and tolerability

The majority of treatment-emergent adverse events (TEAEs) were mild-to-moderate in severity, did not require any action and had resolved by the end of the study. No serious systemic events or anaphylactic shock were observed. Three patients reported serious adverse events, none of these were attributed to the study treatment.

Most adverse events were local reactions such as oral pruritus or throat irritation. The duration of events was highly variable; the median duration of related TEAEs was 3, 6, 5 and 8 days for patients taking placebo, 100 IR,

Table 3. Average Rhinoconjunctivitis Total Symptom Score (mean±SD) during the pollen season according to sensitivity subgroup (Intent-to-Treat population)

	Placebo	100 IR	300 IR	500 IR
G1 = Specific IgE ⩾ 17.5 kU/L	4.86±3.25	4.48±2.77	3.91±3.16	4.01±3.27
G2 = RRTSS ⩾ 15	5.32±3.13	5.34±3.05	3.83±3.14	4.00±3.32
G3 = Weal diameter ⩾ 10.5 mm	5.56±3.07	4.86±3.31	2.55±2.13	3.64±2.86
G4 = G1, or G2, or G3	4.94±3.19	4.71±2.96	3.61±2.97	3.87±3.27
Overall study population	4.93±3.23	4.72±3.14	3.58±2.98	3.74±3.14

IR, index of reactivity; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

300 IR and 500 IR, respectively. For oral pruritus the median duration was 1, 24, 12.5 and 5.5 days for placebo, 100 IR, 300 IR and 500 IR, respectively. Between 1.9% (placebo) and 6.4% (100 IR) of the patients reported severe adverse events, usually oral pruritus, or more rarely, gastrointestinal pain.

In the four-subgroup safety population, the adverse event with the highest incidence in all subgroups (and in the overall study population) was oral pruritus. Few patients reported severe adverse events (Table 4). The relative safety profiles of the four treatment groups were similar across all four sensitivity subgroups of patients.

One hundred and sixty-eight (60%) patients in Group 1, with baseline-specific timothy IgE ⩾ 17.5 kU/L, reported a total of 585 TEAEs. The TEAEs with the highest incidence (observed in more than 10% of patients) were oral pruritus (23%, 26% and 30% of patients in the 100 IR, 500 IR and 300 IR treatment groups, respectively), tongue oedema (12% in the 500 IR treatment group), throat irritation (13% and 23% of patients in the 100 IR and 500 IR treatment groups, respectively) and headache (11% and 13% of patients in the placebo and 300 IR treatment groups, respectively). For those patients reporting oral pruritus, the majority of events were considered mild in severity although some patients (between 0% and 13%) did report moderate oral pruritus. No patients presented with severe oral pruritus. Tongue oedema events were considered mild to moderate with one patient in the 300 IR treatment group reporting a severe event.

One hundred and forty-four (59%) patients with a RRTSS greater than the third quartile (⩾15) reported a total of 498 TEAEs. The placebo group had the lowest percentage of patients with TEAEs (46%) and the 300 IR treatment group the highest (67%). The majority of TEAEs were mild to moderate in severity, did not require any action and had resolved by the end of the study. The TEAEs with the highest incidence (observed in more than 10% of patients) in this group were oral pruritus (16%, 19% and 20% of patients in the 100 IR, 300 IR and 500 IR treatment groups, respectively), nasopharyngitis (12% of patients in the 300 IR treatment group), throat irritation (10% and 12% of patients in the 100 IR and 500 IR treatment groups, respectively) and headache (10%, 11%, 15% and 19% of patients in the placebo, 500 IR, 300 IR and 100 IR treatment groups, respectively).

Table 4. Proportion of patients reporting severe treatment-emergent adverse events according to sensitivity subgroup (safety population)

	Placebo	100 IR	300 IR	500 IR
G1 = Specific IgE ⩾ 17.5 kU/L	1.2	3.2	7.2	7.6
G2 = RRTSS ⩾ 15	3.4	3.0	3.8	0.0
G3 = Weal diameter ⩾ 10.5 mm	2.5	2.7	0.0	6.8
G4 = G1, or G2, or G3	1.8	2.6	5.4	6.0
Overall study population	1.9	6.4	5.2	6.3

IR, index of reactivity; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

One hundred and two (65%) patients with a baseline SPT weal diameter to 5-grass pollens greater than the third quartile (⩾10.5 mm) reported a total of 356 TEAEs. The percentage of patients with TEAEs was similar across treatment groups, ranging between 63% (placebo) and 70% (100 IR). The TEAEs with the highest incidence (observed in more than 10% of patients) in Group 3 were oral pruritus (16%, 23% and 25% of patients in the 100 IR, 500 IR and 300 IR treatment groups, respectively), nasopharyngitis (16% of patients in the 100 IR treatment group), throat irritation (11% of patients in both the 100 IR and 300 IR treatment groups), pharyngolaryngeal pain (11% of patients in the 300 IR treatment group) and headache (14%, 19% and 20% of patients in the 300 IR, 100 IR and placebo groups, respectively).

Two hundred and seventy-eight (61%) patients in Group 4 (any of Group 1, 2 or 3) reported a total of 972 TEAEs. The placebo group had the lowest percentage of patients with TEAEs (49%) and the 100 IR treatment group the highest (67%). The TEAEs with the highest incidence (observed in more than 10% of patients) in Group 4 were oral pruritus (21%, 28% and 25% of patients in the 100 IR, 300 IR and 500 IR treatment groups, respectively), nasopharyngitis (10% of patients in the 100 IR treatment group), throat irritation (12% and 15% of patients in the 100 IR and 500 IR treatment groups, respectively) and headache (12%, 13% and 15% of patients in the

Table 5. Proportion of patients with treatment-emergent adverse events according to sensitivity subgroup (safety population)

	Placebo	100 IR	300 IR	500 IR
G1 = Specific IgE ⩾ 17.5 kU/L	46	68	61	70
G2 = RRTSS ⩾ 15	46	64	67	59
G3 = Weal diameter ⩾ 10.5 mm	63	70	64	64
G4 = G1, or G2, or G3	49	67	63	63
Overall study population	49	69	63	64

IR, index of reactivity; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

placebo, 300 IR and 100 IR treatment groups, respectively) (Table 5).

Discussion

It has recently been demonstrated that patients treated with either the 300 IR or 500 IR doses (but not the 100 IR dose) of this 5-grass pollen SLIT tablet achieved significantly improved RTSS scores (the primary efficacy measure of the study) compared with placebo [12]. Based on these efficacy data, together with the safety profile, the Data Safety Monitoring Board recommended the 300 IR dose as the optimal dose for SLIT with grass allergens.

The percentage mean improvement in RTSS scores compared with placebo of 27% in the 300 IR group and 24% in the 500 IR group is considered clinically meaningful [13]. This magnitude of effect is similar to other recent studies using grass allergen SLIT tablets [14, 15].

Because immunotherapy is specific for the allergen, rather than for the disease, its use in polysensitized patients is still a matter of debate and no clinical trial has been designed to dissect the response of SLIT in patients with single vs. multiple sensitizations. In this study, we included patients who were allergic only to grass pollens (monosensitized) and patients who were allergic to grass pollen and to other tested allergens with symptoms outside the grass pollen season (polysensitized). No differences in terms of efficacy or safety were observed in patients who were polysensitized. This is of importance in clinical practice because the majority of allergic patients are polysensitized. Similar results were observed in a previous open-label study in patients sensitized to grass and birch, where SLIT with both allergens gave the best clinical results [16]. It is important to confirm these results so that SLIT can be offered to a wider population of patients in countries where its use is currently restricted to monosensitized patients [17].

Furthermore analysis showed that efficacy was achieved with the 300 IR dose regardless of the presence of underlying asthma. These results are important in terms of efficacy and safety of adequate treatment of AR in patients with concomitant asthma. The absence of significant systemic reactions in this group of patients with intermittent mild asthma emphasizes the safety of this approach [18]. Additionally, no subject with concomitant asthma was withdrawn from immunotherapy as a result of adverse events or perceived lack of efficacy.

In patients with severe rhinoconjunctivitis (as assessed by IgE class, SPT weal size or RRTSS), the 300 IR dose achieved a statistically significant treatment effect compared with placebo. The intensity of symptoms and consequences on QOL seem to be more important than a comprehensive list of symptoms of rhinitis. It is now well known that intensity and chronology can both be evaluated by symptoms. However, it seems to be more efficient for both practitioner and patient to talk about the impact of the disease rather than to simply list symptoms using medical words which are usually incomprehensible to the patient. The proposal of the ARIA expert panel defining the severity of AR based on QOL parameters is likely to simplify daily physician practice [2].

In these subgroups, the 300 IR dose had a similar safety profile as in the overall study population. In comparison with placebo, patients treated with the 300 IR dose achieved a statistically significant effect in all four sensitivity subgroups ($P < 0.05$).

Conclusions

Regardless of sensitization (monosensitized/polysensitized) or concomitant mild asthma, both the 300 IR and 500 IR doses resulted in a significantly improved RTSS compared with placebo. Similarly in patients with severe rhinoconjunctivitis (as assessed by IgE level, RRTSS and SPT weal size), the 300 IR dose achieved a statistically significant treatment effect compared with placebo. The data also indicate that the relative safety profiles of the treatment were similar across all four sensitivity subgroups of patients, suggesting that the doses of SLIT administered in this study were well tolerated in all four subgroups of patients investigated. All these complementary analyses support the use of 300 IR tablets in grass pollen-allergic patients in clinical practice.

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