

BRIEF COMMUNICATION

Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects

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To cite this article: Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy* 2012; DOI: 10.1111/all.12074.

Keywords

grass allergy; *Phleum pratense*; polysensitization; rhinoconjunctivitis; sublingual immunotherapy.

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Accepted for publication 14 October 2012

DOI:10.1111/all.12074

Edited by: Pascal Demoly

Abstract

The efficacy of single-allergen-specific immunotherapy in polysensitized subjects is a matter of debate. We therefore performed a *post hoc* analysis of pooled data from six randomized, double-blind, placebo-controlled trials ($N = 1871$) comparing the efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (*Phleum pratense* 75 000 SQ-T/2800 BAU, ALK, Denmark), in mono- and polysensitized subjects. A statistically significant reduction in the mean total combined symptom/medication score (TCS) of 27% was demonstrated in actively treated subjects compared with placebo ($P < 0.0001$). This was not dependent on sensitization status ($P = 0.5772$), suggesting a similar treatment effect in mono- and polysensitized subjects (i.e. reductions of the TCSs of 28% and 26%, respectively, both $P < 0.0001$). Finally, a comparable and favourable safety profile of grass AIT was demonstrated in the two subgroups. Thus, no difference in efficacy and safety of single-allergen grass AIT was observed between mono- and polysensitized subjects.

Allergen-specific immunotherapy (SIT) represents an important treatment modality for subjects with allergic rhinoconjunctivitis. However, there is a continuing debate concerning the efficacy of *single-allergen* SIT in polysensitized subjects, which requires further delineation considering that the majority of allergic subjects are sensitized to more than one allergen.

In the present investigation, we compared the efficacy and safety of the SQ/BAU-standardized grass allergy immunotherapy tablet (AIT) in mono- and polysensitized subjects. The investigation is based on a *post hoc* analysis of pooled data from six trials including a total of 1871 subjects and thus represents a unique opportunity to establish evidence-based results by circumventing power issues of such subpopulation analysis in individual trials.

Methods

Trials were included provided they had been published; thus, design, patient characteristics and results from the six

included trials have been described previously (1–8). All trials were randomized, double-blind and placebo-controlled and conducted over one grass pollen season (GPS).

Inclusion and exclusion criteria were comparable between trials. Main inclusion criteria were clinical history of grass pollen-induced allergic rhinoconjunctivitis with or without asthma requiring treatment during the GPS; positive skin prick test response to *Phleum pratense* (wheal diameter ≥ 3 –5 mm); and positive specific IgE (≥ 0.7 kU/l) against *Phleum pratense*. Key exclusion criteria were severe asthma and symptomatic allergies, other than grass allergy, during the GPS.

In all trials, subjects were randomized 1 : 1 to receive once-daily sublingual treatment with single-grass AIT (Grazax, *Phleum pratense* 75 000 SQ-T/2800 BAU, ALK, Denmark) or matching placebo for ≥ 8 weeks prior to the GPS and throughout the entire season. Children (parents/guardians) and adults rated 6 rhinoconjunctivitis symptoms (four nasal and two ocular symptoms) daily in electronic diaries during the GPS on a scale from 0–3. Symptomatic medi-

cations were used in a stepwise fashion as needed. The symptomatic medication use was recorded daily in the electronic diary during the GPS and scored according to predefined criteria (European scale: 0–34 for children; 0–30 for adults. North American scale: 0–36 for both children and adults).

Safety was assessed based on adverse event (AE) reporting in terms of type, causality, relationship to treatment, severity and seriousness.

Polysensitized subjects were defined as subjects with more than one sensitization (as determined by skin prick test).

A superiority approach was chosen for all comparisons, using a generalized linear mixed model and two-sided significance levels of 5%. The response variable per subject was the mean total combined symptom/medication score (TCS, i.e. the sum of rhinoconjunctivitis daily symptom score and rhinoconjunctivitis daily medication score averaged over the entire GPS). Treatment groups (grass AIT and placebo) and interaction between treatment group and sensitization status were included as fixed effects. Trial and centre were included as nested random effect to adjust for variation due to the differences in exposure and possible trial and centre effects. Furthermore, estimates were adjusted for different error variation for each treatment group. The model assumed normal distribution of residuals.

Results

For all trials, the majority of subjects (approximately 80%) were polysensitized with equal proportions between treatment groups (Table 1).

In all trials, the mean TCS was lower (i.e. lower degree of symptoms and lower intake of symptomatic medication) in subjects treated with grass AIT compared with placebo and was similar between monosensitized and polysensitized subjects within each treatment group (Table 1).

In the pooled *post hoc* analysis ($N = 1871$), a statistically significant reduction in the mean TCS of 27% was demon-

strated in actively treated subjects compared with placebo ($P < 0.0001$, Table 2). The observed treatment effect was not dependent on sensitization status ($P = 0.5772$), suggesting a similar treatment effect in mono- and polysensitized subjects (Table 2). Reductions in the TCS were found to be similar between mono- and polysensitized subjects, that is, 28% and 26%, respectively (Table 2).

The overall safety profile was similar in mono- and polysensitized subjects; 142 of 196 (72%) monosensitized and 522 of 735 (71%) polysensitized AIT-treated subjects reported treatment-related AEs. In both subgroups, the majority of AEs were mild/moderate local reactions in mouth and throat, that is, the most commonly reported AEs were oral pruritus (reported by 86 (44%) monosensitized and 294 (40%) polysensitized), throat irritation [reported by 44 (22%) monosensitized and 161 (22%) polysensitized], ear pruritus [reported by 31 (16%) monosensitized and 86 (12%) polysensitized], mouth oedema [reported by 25 (13%) monosensitized and 78 (11%) polysensitized]. None of the related AEs were serious. Severe related AEs were rarely reported in both subgroups (overall, 2% of subjects reported severe related AEs) and were mostly local reactions associated with the application site.

Discussion

Most allergic subjects are polysensitized and polysensitization is often associated with more severe disease (9). This emphasizes the importance of research in this group of subjects.

It is often suggested that polysensitized subjects may not benefit from single-allergen SIT as much as monosensitized subjects. This is not supported by the present investigation where we observed no significant difference in efficacy of grass AIT between mono- and polysensitized subjects in terms of a statistically significant reduction in the TCS in actively treated subjects regardless of sensitization status.

Table 1 Summary statistics and mean total combined scores for each trial

Trial ID (region)	Number of subjects and % polysensitized				Mean total combined score			
	Active		Placebo		Active		Placebo	
	N	% Poly	N	% Poly	Mono	Poly	Mono	Poly
Adult trials								
GT-02 (EU, NA)	131	73%	129	75%	3.94	3.86	5.59	4.78
GT-07 (EU)	68	81%	39	82%	6.59	4.41	9.14	6.30
GT-08 (EU)	282	72%	286	72%	4.97	4.73	6.75	7.30
P05238 (NA)	184	85%	207	85%	5.81	5.25	7.73	6.51
Paediatric trials								
GT-12 (EU)	117	82%	121	83%	4.32	4.91	6.40	5.56
P05239 (NA)	149	87%	158	91%	5.08	5.21	8.13	6.60
All	931	79%	940	80%	4.95	4.81	6.87	6.39

For each trial, the table summarizes the number of subjects treated with grass AIT and placebo, respectively, as well as the per cent of polysensitized subjects in each treatment group. In addition, mean total combined symptom/medication scores are given for monosensitized and polysensitized subjects for both treatment groups. Active = SQ-standardized grass AIT 75 000 SQ-T/2800 BAU; Poly, polysensitized; Mono, monosensitized; EU, European; NA, North American.

Table 2 Pooled *Post hoc* analysis of mean total combined scores

Treatment	N	Mean total combined score (SE)	CI ₉₅	P-value
Overall	1871			
Placebo	940	6.05 (0.30)		
Grass AIT	931	4.44 (0.31)		
Difference		1.61 (0.19)	[1.23–1.99]	<0.0001
Difference/placebo (%)		27%	[21–32%]	
Interaction between treatment and sensitization status				0.5772
Monosensitized	381			
Placebo	185	6.58 (0.47)		
Grass AIT	196	4.71 (0.45)		
Difference		1.87 (0.44)	[1.01–2.74]	<0.0001
Difference/placebo (%)		28%	[18;38]	
Polysensitized	1490			
Placebo	755	6.02 (0.31)		
Grass AIT	735	4.47 (0.31)		
Difference		1.55 (0.22)	[1.12–1.98]	<0.0001
Difference/placebo (%)		26%	[20;31]	

Pooled *post hoc* analysis of mean total combined score. SE, standard error; CI₉₅, 95% confidence interval.

It would have been relevant to investigate the relationship between increasing number of sensitizations and efficacy of therapy; however, this was not possible in the present analysis because the skin prick test panel varied between the different trials in terms of number of allergens included. This in turn causes a different probability of having positive sensitizations between trials making pooling of skin prick test results unacceptable. This issue thus remains to be investigated.

A favourable and similar safety profile in mono- and polysensitized subjects was demonstrated, and thus, the overall benefit/risk ratio of grass AIT treatment was found to be equal in the two subgroups. These present results support other studies suggesting equal effectiveness and safety of single-allergen sublingual SIT in mono- and polysensitized subjects (10–15).

In summary, this *post hoc* analysis suggests that efficacy and safety of grass AIT is similar in mono- and polysensitized subjects, thus supporting the use of grass AIT in both of these subgroups.

Acknowledgments

We thank all participating investigators in individual trials for their contribution of data to permit this analysis.

Authors contributions

Nelson H, Blaiss M and Durham SR were investigators contributing to data collection in at least one of the trials. In addition, these authors have contributed to the enclosed manuscript from the draft stage by outlining, data analysis and reviewing the manuscript.

Würtz SØ and Andersen JS are employed by ALK. Andersen JS was the statistician, performing the statistical analyses.

Würtz SØ was the medical writer, drafting and finalizing the manuscript and providing input to the analyses. Both authors have contributed to the enclosed manuscript from the draft stage by outlining, data analysis and reviewing the manuscript.

Nolte H is employed by Merck and was involved in the US Grazax trials with regard to study design, study conduct, data review, data interpretation and authoring the study reports. In addition, Nolte H contributed to the enclosed manuscript from the draft stage by outlining, data analysis and reviewing the manuscript.

Submission of the final manuscript was endorsed by all authors.

Conflict of interest

Nelson H is a consultant to Merck, Sunovion, Reigel, Circassia and Sanofi-US and has received research support from Lincoln Diagnostics and the National Institutes of Health.

Blaiss M has provided consultant services for Merck, Alcon, Sunovion, JDP Therapeutics, Allergan, Pfizer, PMD Healthcare, Nycomed, Proctor & Gamble and Sanofi-Aventis and has received honorarium from AstraZeneca, Merck, GlaxoSmithKline, Sunovion, Nycomed, Genentech, Nestles and Allergan.

Nolte H is employed by Merck.

Würtz SØ and Andersen JS are both employed by ALK-Abelló.

Durham SR has received research funding via imperial College from ALK Abello, Novartis and Glaxo Smith Kline and honoraria for lectures/consultancy fees from ALK Abello, Merck, Glaxo Smith Kline, Circassia and Boehringer Ingelheim.

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