

ORIGINAL ARTICLE

Sustained effects of grass pollen AIT

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Abstract

We report the sustained efficacy of the SQ-standardized grass allergy immunotherapy tablet Grazax[®] (*Phleum pratense* 75 000 SQ-T/2,800 BAU, ALK, Denmark) from a 5-year randomized, double-blind, placebo-controlled phase III trial. Adults with moderate-to-severe grass pollen allergy inadequately controlled by symptomatic medications were followed for 2 years after the completion of 3 years of treatment. The active group demonstrated a 31% reduction in median rhinoconjunctivitis symptom score over the season compared with placebo. Individual symptom scores favoured active treatment. Combined symptom and medication scores demonstrated a 33% reduction in medians with active treatment. Persistent clinical efficacy was accompanied by prolonged increases in allergen-specific IgG₄ antibodies and IgE-blocking factor, confirming clinical and immunological tolerance for at least 2 years after the treatment completion. No safety issues were identified during follow-up.

Three published double-blind placebo-controlled (DBPC) trials have addressed the sustained effects of allergy-specific immunotherapy (SIT) (1–4). One used high-dose, i.e. 100 000 SQ-U, Alutard SQ[®] *Phleum pratense* and covered 7 years, of which three were postwithdrawal. Although a small study, results were supported by skin, eye and nose provocation testing that paralleled clinical response to treatment, changes in serum antibody measurements and late skin responses (1). All parameters indicated persistence of response with no difference in the SIT maintenance and discontinuation groups.

Naclerio et al. (2) examined patients who underwent ragweed subcutaneous immunotherapy (SCIT) with withdrawal over 1 year. No difference was seen between the withdrawal and continued treatment groups. This was an equivocal result, however, because the trial lacked power to detect differences. The comprehensive Ott study (3, 4) used a sublingual liquid extract for 1-year baseline, 3-year treatment and 1-year follow-up. The follow-up showed a trend for differences between the sublingual immunotherapy (SLIT) and placebo group that failed to reach significance. The groups were markedly mismatched at baseline, making interpretation difficult; nonetheless, the data show a suggestive trend.

GT-08 study on sustained effects of SIT

The GT-08 study (5) examined the sustained effect of Grazax[®] grass allergy tablets. The basis of the study (6) was

the need to perform a definitive DBPC analysis of the sustained effects of treatment over 3 years with 2 years of follow-up. The study covered 43 sites in seven European Union countries. Grazax[®] tablets were taken daily for 3 years, with a 2-year follow-up that remained double-blinded.

All subjects had moderate-to-severe rhinoconjunctivitis with free access to standard-of-care modern symptomatic medication such as antihistamines or nasal steroids, with access to rescue medication, if necessary. Inclusion criteria were age – 18–65, grass pollen-induced rhinoconjunctivitis for at least 2 years, a history of moderate-to-severe symptoms interfering with quality of life despite standard treatment, with objective confirmation by skin prick test sensitivity and specific IgE. Symptoms were largely confined to the grass pollen season. Initially, over 600 patients were recruited and treated during year 1, after which the decision was made to extend the trial and continue treatment for two additional years and follow-up for 2 years. Consent was requested across participating sites and individuals. After the first year, 350 patients continued into the second year. The patients remaining in the trial were identically matched with no survivor effect. Subsequent withdrawal rate was approximately 10% per year, which is acceptable for a large, multiyear trial. Immunotherapy trials depend very much on the amount of airborne pollen, and it is evident that pollen counts were consistently reduced until year

3 and then levelled off in years 4–5, which could potentially influence the results.

Efficacy outcomes were measured by total rhinoconjunctivitis symptoms score, with a 0–3 severity score for a series of nasal and eye symptoms. Medication scores were allocated by the use of modern antihistamines, eye drops or nasal spray. A few patients required treatment with oral steroids. Comparing the active treatment to the placebo group at 2 years after treatment, the adjusted mean symptom scores show a highly significant reduction of 24.8%. In year 1, the median subjective symptoms score for the active group compared with the placebo group showed a significant 32% reduction.

Over the first 3 years, a trend for reduction was seen in the placebo group paralleling the reduction in pollen counts. Clinical benefits in the treatment group were maintained with a 44% reduction in median symptom score in year 2 and a 37% reduction in year 3. The effect, as measured by total symptom score, was sustained at 31% reduction in median symptom score, 2 years after the treatment completion. As a secondary outcome, we generated a combined score normalized for medication use (symptom score/medication score) that adjusts the symptom score appropriately downward for medication use. This outcome showed a highly significant 27% reduction in symptoms 2 years after the treatment completion, indicating a robust outcome by two different measures.

Evaluation of patient relief

To evaluate the effect for the patient, we defined a severe day as one or more of the following: maximum score in at least two of four nose symptoms; maximum in one of two eye symptoms; or overall symptom score >9 of 18. The mean number of severe days was significantly reduced by 55.3% by Grazax[®]. The safety profile over the course of the trial gave no cause for concern. In general, more treatment-related adverse events were reported in the active treatment group in the first year, with fewer in the second and third years of treatment. Almost all adverse events were mild or moderate and transient in nature, with oral and ear pruritus, throat and mouth irritation, and mouth oedema, as the most frequently reported. The severe effects were mostly local, with no impairment of breathing or airway compromise. A total of 10 Grazax[®]-related severe events were reported in five

Table 1 Efficacy of grass AIT 2 years after the treatment completion

Relative difference	medians (%)	adj. means (%)	P-value*
Rhinoconjunctivitis symptom score	31	25	0.004
Blocked nose score	30	16	0.234
Runny nose score	26	23	0.041
Sneezing score	24	24	0.003
Itchy nose score	52	28	0.006
Gritty eye score	33	26	0.006
Watery eye score	42	36	0.012
Rhinoconjunctivitis medication score	21	20	0.114
Combined score	33	27	0.003

*P-value for difference in adjusted means. Bold figures indicate primary or secondary endpoints.

patients (1.6% of those exposed) during first year of treatment, and they essentially disappeared in years 2 and 3, with only a single event each year. No serious adverse events were reported over all 5 years of the trial. Allergen-specific IgG₄ showed a sustained increase throughout the period of study in the active treatment group, and this was maintained, although at slightly lower levels, in the 2 years of follow-up. This was accompanied by increase in a functional assay, the inhibition of specific-IgE binding.

In summary, Grazax[®] reduced grass-induced rhinoconjunctivitis symptoms for 3 years of treatment and 2 years of follow-up with a parallel reduction in the combined symptom and medication scores (Table 1). This was accompanied by sustained effects in blocking antibody activity. Sustained benefits for two years after the treatment completion meet the European regulatory requirements for disease modifying effect of immunotherapy, suggesting the possibility of earlier introduction of Grazax[®] in patients with moderate-to-severe allergic rhinoconjunctivitis.

Conflict of interest

Stephen Durham has received research grants from ALK-Abelló and Novartis and consultancy and lecture fees from ALK-Abelló.

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