

Short communication

Grass allergen tablet immunotherapy relieves individual seasonal eye and nasal symptoms, including nasal blockage

Background: Symptoms of allergic rhinitis have a considerable impact on the quality of life of the sufferer. Sneezing, runny nose, blocked nose and headache are some of the most common symptoms of allergic rhinitis, which affects work, home and social life for many patients. Sublingual immunotherapy has shown to induce a protective immune response and provide sustained symptom prevention for allergic patients.

Aims of the trial: The overall aims were to investigate the efficacy and safety of a sublingual grass allergen tablet (Grazax[®] 75 000 SQ-T; ALK-Abelló A/S, Denmark). Reported here are the effects of Grazax on individual eye and nasal symptoms.

Methods: The trial was a double-blind placebo-controlled trial including 634 participants with significant rhinoconjunctivitis because of grass pollen. Participants were randomized 1 : 1 to Grazax (a fast dissolving, once daily immunotherapy tablet for home administration) or placebo and received treatment for at least 16 weeks prior to and continuing during the grass pollen season of 2005. Four nasal symptoms and two eye symptoms were scored on a scale from 0 (no symptoms) to 3 (severe symptoms) every day during the entire grass pollen season. Nasal symptoms included runny nose, blocked nose, sneezing and itchy nose; eye symptoms included gritty feeling/red/itchy eyes and watery eyes.

Results: Consistent and highly significant reductions in individual eye and nasal symptoms (from 22 to 44%) were observed following treatment with Grazax as compared with placebo ($P < 0.0001$).

Conclusions: Grazax has effects on multiple allergic symptoms, including nasal blockage, and is an effective treatment of rhinoconjunctivitis, thereby reducing the need for topical anti-allergic drugs.

S. R. Durham¹, B. Riis²

¹National Heart and Lung Institute, Imperial College and Royal Brompton Hospital, London, UK; ²Group Clinical Development, ALK-Abelló A/S, Hørsholm, Denmark

Key words: allergy; blocked nose; grass pollen; rhinoconjunctivitis; sublingual immunotherapy; tablet-based.

Stephen R. Durham
National Heart and Lung Institute
Imperial College and Royal Brompton Hospital
Guy Scadding Building
Royal Brompton Campus
Dovehouse Street
London SW3 6LY
UK

Accepted for publication 26 March 2007

An estimated 45 million people in Europe suffer from grass allergy (1). Although trivial for some, symptoms of allergic rhinitis may have a considerable impact on the quality of life of the sufferer. In a survey involving 260 allergic patients, sneezing, runny nose, blocked nose, headache, itchy and watery eyes and itchy nose were the most common symptoms of allergic rhinitis (2). The symptoms were reported to affect work (29% of cases), home (34%) and social life (30%), and symptoms were well-controlled only in 34% of patients with seasonal allergic rhinitis (2). These figures are supported by a practice-based community study in UK (3).

In trials of antihistamines and their effect on seasonal rhinoconjunctivitis symptoms, the total symptom score typically includes four individual scores: sneezing; rhinorrhoea; itchy nose, palate or throat; and itchy, watery or red eyes, while nasal blockage is scored separately (4–6). A common trend is that while total symptom scores were significantly reduced after antihistamine treatment, this

treatment was generally not or only moderately effective in relieving nasal blockage during natural pollen exposure (5, 7, 8). In contrast, intranasal corticosteroids are more effective than antihistamines and may also relieve nasal obstruction (9). In a recent meta-analysis of treatments for allergic rhinitis, the effect sizes for antihistamines (7%), leukotriene receptor antagonists (5%) and intranasal corticosteroids (12%) were modest as compared with placebo (10).

Material and methods

In a recent large double-blind placebo-controlled trial of the sublingual grass allergen tablet (Grazax[®] 75 000 SQ-T; ALK-Abelló A/S, Denmark) (11), the effect of sublingual immunotherapy on individual eye and nasal symptoms was analysed. The trial included 634 participants with significant rhinoconjunctivitis due to grass pollen. They were randomized 1 : 1 to Grazax (a fast dissolving, once daily immunotherapy tablet for home administration) or

placebo and received treatment for at least 16 weeks prior to and continuing during the grass pollen season of 2005 [primary results published in (11)]. The average overall rhinoconjunctivitis symptom score was derived from individual symptom scores for four nasal symptoms and two eye symptoms during the entire grass pollen season. Nasal symptoms included runny nose, blocked nose, sneezing and itchy nose; eye symptoms included gritty feeling/red/itchy eyes and watery eyes. Each symptom was scored on a scale from 0 (no symptoms) to 3 (severe symptoms) on a daily basis during the grass pollen season and presented as an average for each participant on each day. Independent rhinoconjunctivitis medication scores were derived based on the use of trial rescue medication (Desloratadine tablets, Budesonide nasal spray, Prednisone tablets) [published in (11)].

Comparison of the two treatment groups was performed by analysis of variance with the efficacy endpoint as response variable, treatment group as a fixed effect, and pollen region as random effect. Each treatment group was adjusted for different error variation. The calculated *P*-values were as a result of the multiplicity issue as compared with a Bonferroni adjusted significance level (0.006) to keep the overall probability of type I error less than 5%.

Results

A total of 634 subjects were randomized and included in the present analysis. Grass pollen counts were obtained from 33 pollen stations in the participating countries. The grass pollen season lasted on average 57.8 days (range: 16–86 days). The average daily rhinoconjunctivitis symptom scores were presented separately as nasal and eye symptoms (Table 1). For both symptoms, the score for the actively treated group was lower than in the placebo group. A further separation of the nasal symptoms into four individual symptoms showed consistently lower symptom score for each symptom in the Grazax group as compared with placebo (Fig. 1A). A separation of the eye symptoms into two individual symptoms also showed consistently lower symptom score for each symptom in the immunotherapy group as compared with placebo (Fig. 1B). The percentage reductions relative to placebo

ranged from 22 to 44% and were in all cases statistically highly significant ($P < 0.0001$) (Table 1).

On top of the reduction in symptom scores, the participants in the Grazax group also used significantly less rescue medication as compared with placebo [reduction of total symptom score 38%, $P < 0.0001$; see (11)]. The total number of participants who use different types of rescue medication is shown in Fig. 1B. The reduced score was mainly because of fewer participants using Desloratadine tablets and Budesonide nasal spray in the immunotherapy group as compared with placebo.

Discussion

Grazax is the first allergy tablet to address the underlying cause of grass pollen allergy. The tablet has been investigated in a large clinical programme involving more than 2400 grass pollen allergic patients (11–16). All trials have shown consistent results in terms of safety and efficacy.

The current analysis of separate eye and nasal symptoms, which included correction for multiple comparisons, gave consistent and highly statistically significant results. The observed effect sizes for Grazax over placebo compare favourably with those observed in recent placebo-controlled trials with the antihistamines Cetirizine (10 mg), Levocetirizine (5.0 mg) and Fexofenadine (120 or 180 mg) which showed effect sizes of 12–26% as compared with placebo (4–6, 8). However, while the symptom scores for antihistamines in most trials did not include nasal blockage, Grazax has proven to reduce this symptom by 32%. Furthermore, antihistamines only reduce symptoms with relapse within days when discontinued. There appears to be a contribution of H1, H2 and H3 receptors to histamine-induced nasal blockage in normal human subjects, which may explain why single antihistamines have a limited effect on relieving nasal blockage (17).

Table 1. Effect of sublingual immunotherapy with Grazax on seasonal nose and eye symptoms

	Score in subjects receiving Grazax <i>n</i> = 316	Score in subjects receiving placebo <i>n</i> = 318	Difference (%)	95% CI	<i>P</i> -value
Nose symptoms	1.69	2.32	–0.63 (–27%)	–0.86; –0.41	<0.0001
Runny nose	0.42	0.56	–0.15 (–26%)	–0.21; –0.08	<0.0001
Blocked nose	0.36	0.53	–0.17 (–32%)	–0.24; –0.10	<0.0001
Sneezing	0.51	0.66	–0.15 (–22%)	–0.21; –0.08	<0.0001
Itchy nose	0.40	0.57	–0.17 (–30%)	–0.24; –0.11	<0.0001
Eye symptoms	0.65	1.03	–0.37 (–36%)	–0.49; –0.25	<0.0001
Gritty eyes	0.44	0.64	–0.21 (–32%)	–0.28; –0.14	<0.0001
Watery eyes	0.22	0.38	–0.17 (–44%)	–0.22; –0.11	<0.0001

CI, confidence interval; %, per cent difference in the Grazax group as compared with placebo. Average daily symptom scores were calculated from diary data during the entire pollen season. The comparison of the two treatment groups was performed by use of ANOVA with average symptom score as response variable and treatment group as a fixed effect and pollen region as a random effect as well as adjusting for different error variation for each treatment group. As a result of Bonferroni adjustment for multiple comparisons, the significance level was 0.006.

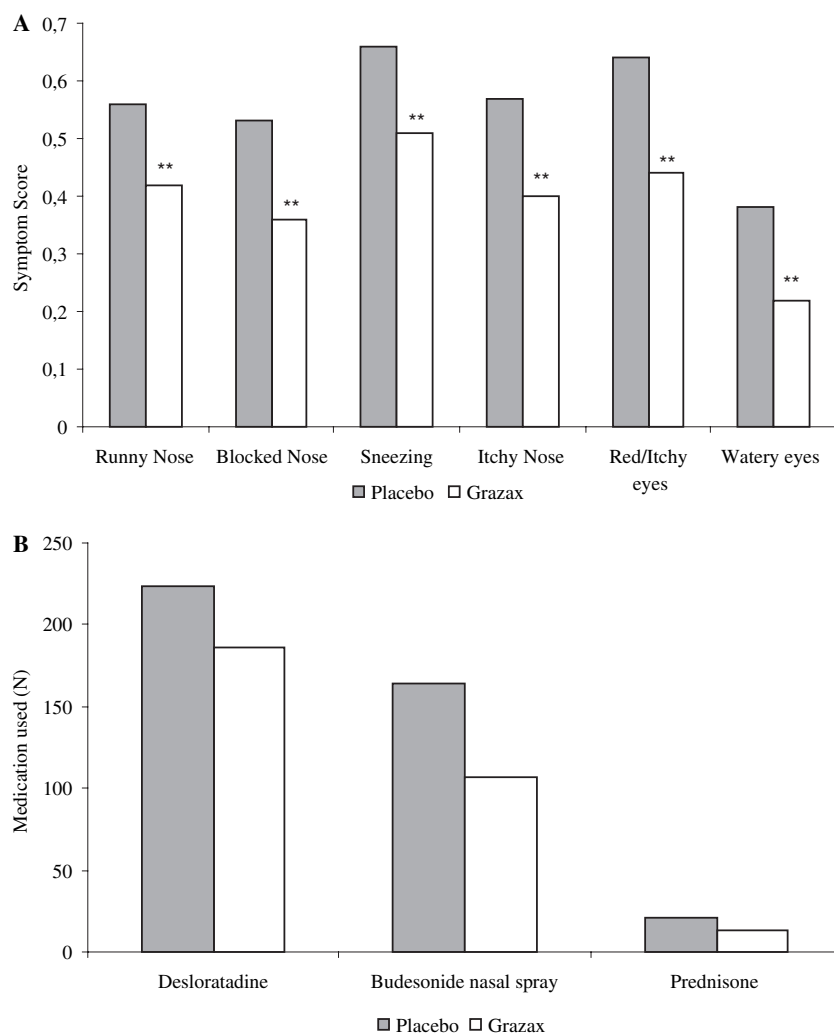


Figure 1. Reductions in rhinoconjunctivitis symptoms and use of medication after treatment with Grazax previous to and during one grass pollen season. (A) Nasal and eye symptom scores; four nasal symptoms and two eye symptoms were scored on a scale from 0 (no symptoms) to 3 (severe symptoms) each day during the entire grass pollen season. The score presented is the sum of individual nasal and eye symptoms calculated as an average for each participant on each day. **: the *P*-value for the difference between Grazax and placebo is <0.0001 . (B) The total number of participants (*n*) with use of rescue medication [also published in (11)].

The decrease in rhinoconjunctivitis symptom scores for Grazax-treated patients that occurred in parallel with a marked reduction in their requirement for rescue medication provides additional evidence for the efficacy of sublingual immunotherapy over and above usual pharmacotherapy for rhinitis.

The quality of life of the patients is an important component of the efficacy of hay fever medication. When asked the participants in this trial how they felt overall in the treatment season as compared with previous seasons, 49% more than in the immunotherapy group relative to the placebo group responded that they felt better or much better (11), which implies that their quality of life in the treatment season was better than previously.

Whether sublingual immunotherapy, like subcutaneous immunotherapy (18), has the potential to produce long-

term remission is currently being investigated in a prolonged and double-blinded, placebo-controlled extension of the current trial over a 5-year period.

In conclusion, Grazax has effects on multiple allergic symptoms, including nasal blockage, and is effective in the treatment of rhinoconjunctivitis, thereby reducing the need for topical anti-allergic drugs.

Acknowledgments

The trial was sponsored by ALK-Abelló A/S, Denmark. We thank the GT-08 study group and participating investigators (W. Aberer, M. Andersson, J. Arned, M. Augustin, V. Backer, C. Baumgarten, A. Bentley, C. Bindslev-Jensen, G. Cadario, M. Calderon, R. Cantone, L. -O. Cardell, T. Chivato, G. Colombo, R. Dahl,

S. R. Durham, W. Emminger, P. Ewan, A. Fay, M. Fernández Rivas, W. J. Fokkens, A. Frew, L. Frølund, G. Gazzola, M. Grove, J. Hald, H. Harving, B. Hauswald, W. Heppt, A. Huissoon, A. P. H. Jansen, A. Kapp, J. Kleine-Tebbe, P. Lange, B. Lassen

Brandelev, G. Marcer, C. Martinez Cócera, J. G. R. de Monchy, C. M. G. Nieuwhof, N. Novak, R. J. Powell, R. K. Rajakulasingam, S. Rak, G. Rasp, H. Riechelmann, N. Reider, G. Scadding, G. Senna, F. W. J. M. Smeenk, A. Stewart, M. Worm and O. Zetterström).

References

1. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;**24**:758–764.
2. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. *Clin Otolaryngol Allied Sci* 2000;**25**:551–557.
3. White P, Smith H, Baker N, Davis W, Frew A. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clin Exp Allergy* 1998;**28**:266–270.
4. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;**104**:927–933.
5. Leynadier F, Mees K, Arendt C, Pinelli M-E. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg* 2001;**55**:305–312.
6. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;**79**:443–448.
7. Wilson AM, Haggart K, Sims EJ, Lipworth BJ. Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. *Clin Exp Allergy* 2002;**32**:1504–1509.
8. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;**114**:838–844.
9. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids vs oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *Br Med J* 1998;**317**:1624–1629.
10. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;**116**:338–344.
11. Dahl R, Kapp A, Colombo G, de Monchy J, Rak S, Emminger W et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**118**:434–440.
12. Malling H-J, Lund L, Ipsen H, Poulsen LK. Safety and immunological changes during specific sublingual immunotherapy with SQ standardized grass allergen tablets. *J Investig Allergol Clin Immunol* 2006;**16**:162–168.
13. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;**61**:185–190.
14. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**117**:802–809.
15. Calderon M, Essendrop M. Specific immunotherapy with high dose SQ standardised grass allergen tablets was safe and well tolerated. *J Investig Allergol Clin Immunol* 2006;**16**:338–344.
16. Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006;**61**:181–184.
17. Taylor-Clark T, Sodha R, Warner B, Foreman J. Histamine receptors that influence blockage of the normal human nasal airway. *Br J Pharmacol* 2005;**144**:867–874.
18. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–475.