

Short communication

Effect of grass pollen immunotherapy with Alutard SQ[®] on quality of life in seasonal allergic rhinoconjunctivitis

Background: Treatment of allergic rhinitis with subcutaneous allergen immunotherapy is effective in terms of reductions in symptoms and seasonal use of reliever medication. Its effect on quality of life (QoL), reflecting the impact of symptoms on work/school performance and leisure activities is, however, important and often overlooked.

Aims of the study: To assess effect on QoL of specific immunotherapy with two doses of Alutard SQ[®] *Phleum pratense* in patients with moderately to severe seasonal allergic rhinoconjunctivitis inadequately controlled by standard drug therapy.

Methods: Double-blind, randomized, placebo-controlled study of 410 patients with seasonal allergic rhinoconjunctivitis. Participants were randomized (2 : 1 : 1) to receive Alutard SQ[®] *P. pratense* (ALK-Abelló) at maintenance doses of 100 000 SQ-U (203 subjects), 10 000 SQ-U (104 subjects) or placebo (103 subjects) given by subcutaneous injections. The groups were well matched for demographics and baseline symptoms. Quality of life was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire which covers seven domains of health before and in the peak of the pollen season.

Results: While all domain scores were significantly improved when comparing 100 000 SQ-U with placebo, two domain scores were significantly improved when comparing 10 000 SQ-U with placebo. When comparing 100 000 SQ-U with 10 000 SQ-U, four domain scores were significantly improved.

Conclusion: Treatment with Alutard SQ[®] significantly improved the seasonal QoL of patients suffering from allergic rhinoconjunctivitis. The improvement was more pronounced and wider ranging in patients who received the higher 100 000 SQ-U maintenance dose.

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Allergic rhinoconjunctivitis represents a global health problem, and affects up to 34% of people in Western Europe (1). Allergy to grass pollen is one of the commonest inhaled allergens leading to impaired quality of life (QoL) and increased healthcare expenditure (2). Specific immunotherapy (SIT) is currently the only treatment modality able to change the underlying mechanisms of allergic disease and thereby prevent allergic symptoms (3).

Specific immunotherapy involves administering allergens in order to increase immunological tolerance to the allergen. The efficacy of subcutaneous grass pollen SIT has been confirmed in terms of reduced symptoms and medication requirements in several studies in participants with seasonal allergic rhinoconjunctivitis (4–7). Further, SIT has been shown to induce long-term remission, for at least 3 years following its discontinuation (7) and in children with seasonal pollinosis SIT reduced two- to

threefold the risk of progression of rhinitis to asthma (8, 9). Finally, subcutaneous SIT has been shown to improve QoL measured by a validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; 10). Quality of life measurements assessing the impact of symptoms on work, school and leisure activities represent an important and often overlooked outcome measure in SIT studies. The RQLQ score covers seven dimensions of health. However, in most SIT studies, only the overall RQLQ score is presented rather than individual RQLQ domain scores.

This paper reports the effects of SIT on RQLQ domain scores in a large 1-year double-blind, placebo-controlled study of subcutaneous SIT in patients with grass pollen-induced seasonal allergic rhinoconjunctivitis, inadequately controlled by symptomatic drug therapy. Data from the same trial regarding symptoms, use of medication and safety are presented elsewhere (11).

Methods

Double-blind, randomized, placebo-controlled design with standardized depot preparation of grass pollen extract (Alutard SQ® *Phleum pratense*, ALK-Abelló, Denmark) given by subcutaneous injections. The trial was conducted at 26 UK hospital clinics. A total of 410 subjects were randomized in a 1 : 1 : 2 ratio to receive placebo, Alutard SQ® *P. pratense* 10 000 SQ-U or 100 000 SQ-U (ALK-Abelló) and 347 (85%) completed the treatment. Subject demographics and symptom duration are summarized in Table 1.

Therapy composed of an up-dosing phase over 8 weeks and a maintenance phase of approximately 12 months. The up-dosing phase composed of 15 injections administered over 8 weeks (patients were injected twice at each weekly visit). At each visit, oral acrivastine 8 mg was given 15 min before the first injection; the second injection was given 30 min later. Maintenance injections were given every 6 ± 2 weeks. 100 000 SQ-U corresponds to 20 µg major allergen (Phl p5) and 10 000 SQ-U to 2 µg. Where clinically appropriate, doses were adjusted following established clinical guidelines (12).

Study medication was provided as a suspension in vials. Placebo and active medication were indistinguishable and identical except for the inclusion of the grass pollen extract in the active preparation. Acrivastine, fluticasone propionate nasal spray and sodium cromoglicate eye drops were freely available as rescue medication throughout the study. Where necessary, further rescue medication was given according to written protocols. Pollen counts were obtained from the National Pollen and Aerobiology Research Unit, Worcester University.

The study was conducted in accordance with good clinical practice guidelines, with full ethical approval and informed written consent from each subject.

The main inclusion criteria were: 18–60 years of age, clinical history of grass pollen-induced seasonal allergic rhinoconjunctivitis, inadequately controlled in previous years despite using antihistamines, topical steroids and/or cromoglicate eye drops; positive skin prick test (wheal diameter ≥ 3 mm using Soluprick® SQ 10 HEP *P. pratense*, ALK-Abelló), and specific immunoglobulin E (IgE) against *P. pratense* (grass pollen-specific IgE $\geq$ class 2; Pharmacia CAP, Uppsala, Sweden). Main exclusion criteria were significant rhinoconjunctivitis, sinusitis and/or asthma outside the grass pollen season, daily contact with animals causing symptoms, or SIT within the past 5 years.

Rhinoconjunctivitis Quality of Life Questionnaire (13) measurements were completed before and at the peak of the pollen season. The RQLQ covers seven dimensions of health: sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms,

specific activities limited by symptoms in the previous week and emotional function. The subjects rated each item on a 7-point scale (0 = not troubled and 6 = extremely troubled). The mean value for all subjects for each health dimension was calculated and the overall RQLQ was expressed as the mean of the seven dimension scores. Further, mean overall RQLQ scores and domain scores were calculated for each subject.

All randomized subjects were included in the analysis [the intention-to-treat (ITT) analysis set]. This included subjects who only received one maintenance dose. Change in RQLQ scores (overall score and domain scores) from baseline to peak season was analysed by ANOVA with treatment group and pollen region as factors. As differences in pollen counts were identified between the pollen regions, RQLQ scores were adjusted for pollen regions. $P < 0.05$ was considered significant. The analyses are explorative and no adjustment for multiplicity has been performed. Results were analysed using SAS® version 8 V.

Results

At the baseline preseasonal visit, there were no differences in overall RQLQ and domain scores between the three treatment groups. In all groups, a higher RQLQ score was observed at the peak of the grass pollen season compared to the preseasonal baseline, indicating a worsening QoL during the season. The differences for the actively treated groups vs placebo in RQLQ domain scores at the peak pollen season ranged from 0.55 to 1.21 in the 100 000 SQ-U group and 0.18 to 0.97 in the 10 000 SQ-U group. While all domain scores were significantly improved when comparing 100 000 SQ-U with placebo ($P < 0.002$), only 2/7 domain scores [eye symptoms ($P < 0.0001$) and emotional function ($P = 0.02$)] improved significantly when comparing 10 000 SQ-U with placebo. When comparing 100 000 SQ-U with 10 000 SQ-U, 4/7 domain scores (activities, non-nose/eye symptoms, practical problems and nasal symptoms) were significantly improved ($P < 0.04$). Changes in RQLQ overall and domain scores from baseline to peak season adjusted for pollen regions are summarized in Fig. 1.

The changes in domain scores were confirmed and furthermore improved in a subset analysis including subjects with at least two maintenance doses before the grass pollen season. The differences in the subset analysis for the actively treated groups vs placebo in RQLQ domain scores at the peak pollen season ranged from 0.61 to 1.36 ($P < 0.0006$) in the 100 000 SQ-U group.

Discussion

In this study, treatment of patients with severe seasonal allergic rhinoconjunctivitis with Alutard SQ® *P. pratense*, 100 000 SQ-U resulted in highly significant improvements in all RQLQ domains when compared to placebo. These results indicate that SIT ameliorates QoL as well as reducing symptoms and the need for reliever medication in treatment-resistant hay fever (11).

Table 1. Demographics and symptom duration for the three treatment groups

Treatment group	100 000 SQ	10 000 SQ	Placebo
Age (years)			
Mean (SD)	38.3 (9.1)	37.0 (9.0)	37.9 (9.1)
Range	18.4–59.7	19.7–58.2	18.9–59.2
Gender			
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> (diameter in mm), 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

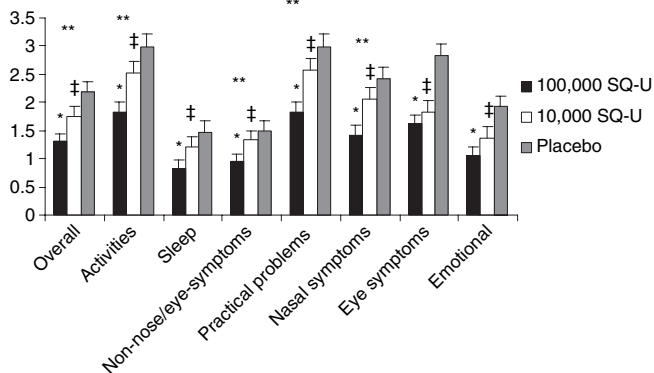


Figure 1. Changes in Rhinoconjunctivitis Quality of Life Questionnaire domain scores [mean (SE)] and overall score from baseline to the peak of the grass pollen season adjusted for pollen region. *refers to significant difference between 100 000 SQ-U group and placebo; ‡refers to significant difference between the 10 000 SQ-U group and placebo and **refers to significant difference between the 100 000 and 10 000 SQ-U groups.

All groups showed higher RQLQ scores in the pollen season compared to baseline (a higher score reflecting a worsening of QoL), indicating a negative impact of the pollen season on QoL. However, the higher changes for RQLQ domain scores in the placebo group compared to the actively treated groups from preseasonal visit to the peak grass pollen season, demonstrated an advantage in favour of the actively treated groups. The benefit of SIT was superior in the 100 000 SQ-U group compared to the 10 000 SQ-U group. The magnitude of differences between the 100 000 SQ-U and placebo groups (0.55–1.21) was comparable to that reported in a previous grass pollen SIT study (10) and superior and impressive to that reported in studies investigating the effect of antihistamines on RQLQ overall and domain scores (actively treated vs placebo treated; 14–16).

Allergic rhinitis may have a major effect on QoL in several ways. The burden of allergic rhinitis may result

in work absenteeism and reduced work/school performance (17). Patients frequently complain of fatigue, headache, malaise and poor concentration (2). Allergic rhinitis may also affect children's ability to learn. Failure to control nasal symptoms such as itching, sneezing, rhinorrhoea and congestion during the day may cause learning problems directly during school hours, while nocturnal sleep loss may lead to daytime fatigue and indirectly affect learning (18). All of these factors underline the importance of SIT in mitigating the impact of allergic rhinitis on QoL (12). A recent smaller SIT study reported improved QoL in 5/7 RQLQ domains (10), but this is the first to demonstrate a dose-response relationship of the effect. Specific immunotherapy has also been demonstrated to improve health-related QoL including physical, social and emotional well-being and productivity within 4–6 months of its initiation (19). The demonstration in the present study of improvements in overall RQLQ score, along with improvements in all seven RQLQ domain scores, confirms that SIT significantly improves allergy patients' QoL. In contrast, 62% of allergic patients receiving symptomatic treatment experienced troublesome residual symptoms and described symptom control as partial or poor (20). The confirmation and improvement in the subset analysis in the present study including subjects with at least two maintenance doses before the grass pollen season underlines the fact that immunotherapy improves QoL.

In conclusion, treatment with Alutard SQ[®] significantly improved the seasonal QoL of patients suffering from allergic rhinoconjunctivitis. The improvement was more pronounced and wider ranging in patients who received the higher 100 000 SQ-U maintenance dose.

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