Quality of Life Research (2007) 16: 191–201
DOI 10.1007/s11136-006-9110-3

Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: A double-blind, randomised study

Sabina Rak[1], William H. Yang[2], Martin R. Pedersen[3] & Stephen R. Durham[4]
[1]*Section of Allergy, Sahlgrenska University Hospital, Göteborg, Sweden (E-mail: sabina.rak@medfak.gu.se);* [2]*Allergy & Asthma Research Centre, Ottawa, Ontario, Canada;* [3]*ALK-Abelló A/S, Hørsholm, Denmark;* [4]*National Heart and Lung Institute, Allergy and Respiratory Medicine, London, UK*

Accepted in revised form 11 August 2006

Abstract

The effect of sublingual immunotherapy on quality of life (QoL) was examined in patients with grass pollen-induced rhinoconjunctivitis. Patients (n = 855) were randomised to once-daily grass allergen tablets (2,500; 25,000; or 75,000 SQ-T *Phleum pratense* extract; GRAZAX®) or placebo. Treatment was initiated 8 weeks before the start of the grass pollen season and continued throughout. If symptoms were present, patients received loratadine or placebo rescue medication. There were three major findings: in patients using loratadine, grass allergen tablets provided QOL benefits over placebo; Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score was 17% ($p = 0.006$) and 20% ($p = 0.020$) greater with 75,000 SQ-T tablet than with placebo at first and second seasonal visit, respectively; in patients not using loratadine, grass allergen tablets improved QoL more than placebo; RQLQ score was 21% greater ($p = 0.021$) with 75,000 SQ-T tablet at second seasonal visit; grass tablets (without loratadine) had a greater effect on QoL than loratadine alone. RQLQ score was 26% ($p = 0.014$) greater with 75,000 SQ-T tablets than loratadine at second seasonal visit. These data show that sublingual immunotherapy with grass allergen tablets improves QOL in allergic rhinoconjunctivitis, reduces symptoms, and that this effect is greater than rescue antihistamine alone.

Key words: Grass pollen allergy, Quality of life, RQLQ, Seasonal allergic Rhinoconjunctivitis, Sublingual immunotherapy

Abbreviations: SF-36 – Medical Outcome Study Short Form Health Survey; IgE – immunoglobulin E; FEV1 – Forced Expiratory Volume; RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire; ANOVA – analysis of variance; CI – confidence interval; ITT – intention to treat; PP – per protocol

Introduction

Allergic respiratory disease is a major health problem affecting a significant proportion of the global population. In a recent study involving individuals aged 16–60 years from 10 European countries, the prevalence of allergic respiratory disorders was estimated to be between 12 and 34% [1], and in a second study of 6 countries in Western Europe the average prevalence of allergic rhinitis was 23% (range 17–29%) [2].

Allergic respiratory disorders include allergic rhinitis, allergic rhinoconjunctivitis, and allergic asthma. Allergic rhinitis encompasses nasal symptoms such as sneezing, and running, congested or itchy nose, while allergic rhinoconjunctivitis incorporates additional ocular symptoms (e.g. itchiness, redness or irritation). Asthma symptoms

include difficulty in breathing, wheezing, and tightness in the chest. Regardless of the exact nature of the symptoms, these allergic disorders result from a pathological immune response to allergens, most commonly grass and tree pollen (seasonal allergens), and dust mites and animal dander (perennial allergens).

While the symptoms of allergic rhinitis and allergic rhinoconjunctivitis are not life-threatening, they can have a substantial impact on patients' quality of life (QoL) and daily functioning, causing daytime sleepiness, sleep disturbances, impaired social functioning, and diminished productivity [3–6]; disturbances in mood and cognition have also been documented [7, 8]. In one study, patients with seasonal allergic rhinitis (n = 33), reported significantly poorer QoL in terms of physical functioning, limitations in physical role, bodily pain, and vitality during the pollen season than outside of the pollen season [9], as assessed by the Medical Outcome Study Short Form Health Survey (SF-36). In a second study using the same survey, individuals with seasonal allergic rhinitis reported increased daytime sleepiness, and limitations in physical role and physical functioning during the pollen season; but no such change was reported in individuals without allergic rhinitis [6]. Deterioration in QoL is also reported in individuals with perennial rhinitis. For example, Bousquet et al. [3] reported that perennial allergic rhinitis was associated with significantly poorer QoL on eight of the nine SF-36 domains when compared with healthy individuals.

Treatment strategies for allergic respiratory disorders include allergen avoidance, symptomatic therapies (e.g. antihistamines, nasal corticosteroids, and decongestants), and specific immunotherapy. Immunotherapy should only be used when sensitivity to a specific allergen can be identified. Once identified, the basic principle of specific immunotherapy is to provide consistent, controlled exposure to the allergen. This overexposure results in hyposensitisation, reducing symptoms in response to exposure to the naturally occurring allergen. The most effective way to prevent allergy symptoms is to treat the allergic condition, and specific immunotherapy is the only treatment capable of modifying the underlying immunological response to allergens.

Specific immunotherapy involving a series of subcutaneous injections has been available for many years for the treatment of allergic disorders. Its efficacy is well documented and has been shown to persist after treatment has been discontinued [10–13]. A minor disadvantage of this treatment is that the safety profile of injection-based specific immunotherapy restricts its use to specialist centres. More recently, non-injection routes for immunotherapy administration have been developed to increase safety and patient accessibility; sublingual immunotherapy is the most widely used of these non-injection routes. Over 20 studies and a meta-analysis have demonstrated the efficacy of sublingual immunotherapy in reducing symptoms and rescue medication use in patients with allergic rhinitis, with the magnitude of clinical benefit ranging from 20 to 50% (e.g. [14–17]).

Few studies have examined the effect of specific immunotherapy on QoL, however. We have only been able to find five studies that have investigated this issue, and all suggest that specific immunotherapy can improve QoL. Three of these studies involved injection immunotherapy [18–20]; while the remaining two studies involved sublingual immunotherapy in patients with allergic asthma (with or without rhinitis) to house dust mites [21, 22]. Therefore, there appear to be no data available examining the effects of sublingual immunotherapy on QoL in patients with seasonal allergic rhinoconjunctivitis.

The grass allergen tablets (GRAZAX®, ALK-Abelló A/S, Denmark) used in this study have been developed to increase patient accessibility to specific immunotherapy. Their active ingredient is a standardised allergen extract derived from pollen of *Phleum pratense* grass. However, there is substantial cross-reactivity between allergenic elements of grass pollen species [23], so this tablet is expected to be effective in treating grass pollen allergies in general. In this study, we examined the effect of specific sublingual immunotherapy with grass allergen tablets on QoL in patients with allergic rhinoconjunctivitis. The primary efficacy and safety variables from this patient cohort have been reported elsewhere [24].

Methods

Participants and setting

Participants were aged 18–65 years with mild to moderate grass pollen-induced allergic rhinoconjunctivitis (requiring treatment and/or causing significant restrictions in activities) for at least 2 years; both men and women were included. All patients had a positive skin prick test and specific immunoglobulin E (IgE) to *Phleum pratense*. Exclusion criteria included: clinical history of significant asthma outside of the grass pollen season; Forced Expiratory Volume (FEV_1) < 70% of that predicted; significant medication-requiring allergic rhinitis due to allergens other than grass; significant recurrent acute or chronic sinusitis, conjunctivitis, asthma or rhinitis at randomisation or screening visits; history of anaphylaxis or angiodema; immunosuppressive treatment; serious conditions including cystic fibrosis, diabetes, renal insufficiency, cardiovascular disease; hypersensitivity to excipients of trial medications; and previous immunotherapy with grass pollen allergen within the previous 10 years, or any other allergen within the previous 5 years.

Two cohorts with a combined total of 855 participants were enrolled from 55 centres in Austria, Belgium, Canada, Denmark, Germany, Norway, Sweden, and the U.K. Cohort 1 was enrolled in 2002 and provided baseline data (not presented here). Cohort 2 was enrolled in 2003. Participants in cohort 2, and all completed and protocol-compliant participants from cohort 1, were randomised to treatment in the 2003 season.

Trial design

This was a randomised, double-blind, placebo-controlled trial, in which participants were randomised using a computer-generated schedule. The study evaluated the efficacy of immunotherapy with grass allergen tablets 2,500, 25,000, and 75,000 SQ-T (75,000 SQ-T corresponds to 15 μg of the major allergen *Phleum pratense* phl p 5) compared with placebo tablets, as assessed by rhinoconjunctivitis symptom and medication score over the pollen season [24].

QoL was determined at each visit using the disease-specific Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; [25]); the number of well days was also assessed. The RQLQ was used instead of the SF-36 because it was developed specifically for use in patients with rhinoconjunctivitis as opposed to the SF-36, which is a generic QoL measure. The RQLQ contains 28 questions to evaluate 7 QoL domains: activity limitations, sleep problems, non-nose/non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function. Patients rate how troublesome each item has been based on their experience during the preceding week using a 7-point scale (0–6; higher scores indicate more severe symptoms). The investigator was not present during the completion of the RQLQ. Well days were days without the use of rescue medication and with a total rhinoconjunctivitis symptoms score of 2 or less; the rhinoconjunctivitis symptoms score is the sum of ratings of six rhinoconjunctivitis symptoms, each measured on a scale of 0 (no symptoms) to 3 (severe symptoms); the maximum score is therefore 18. Adverse events, withdrawals and laboratory assessments were used to measure safety.

The trial consisted of six visits (visit 1, 10–14 weeks before the pollen season; visit 2, 8 weeks before the season (pre-season visit); visit 3, at the start of the season; visits 4 and 5, during the season (on-season visits); and visit 6, 1 week after the end of the season (post-season visit), and a telephone follow-up. The visits took place in hospitals and private specialist clinics. Treatment was initiated 8 weeks before the anticipated start of the grass pollen season and continued for a maximum of 24 weeks.

The study had three broad aims, and a number of different treatment regimens were used to assess these. The first aim was to compare different doses of grass allergen tablet with placebo tablets when patients were also allocated loratadine rescue medication, to be taken as necessary (Groups 1–4). The second aim was to compare grass allergen tablets with placebo tablets without the use of loratadine rescue medication (Group 6 vs. Group 5). The third aim was to compare directly grass allergen tablets (without concomitant loratadine) with loratadine alone (Group 6 vs. Group 1) (Table 1).

Table 1. Treatment regimens

Group	Initial randomisation	Step 1 rescue medication
1	Placebo tablet	Loratadine (active)
2	Grass allergen tablet 2,500 SQ-T	Loratadine (active)
3	Grass allergen tablet 25,000 SQ-T	Loratadine (active)
4	Grass allergen tablet 75,000 SQ-T	Loratadine (active)
5	Placebo tablet	Placebo
6	Grass allergen tablet 75,000 SQ-T	Placebo

Allocation of loratadine or placebo rescue medication was termed Step 1 rescue medication. If this Step 1 rescue medication was ineffective or if asthma was present, patients were assigned further open-label rescue medication with intranasal budesonide, oral prednisone, salbutamol, or fluticasone, as deemed appropriate by the investigator. Investigators were instructed to 'step-down' these additional medications when possible. At each visit, participants were asked to bring any unused medication. Tablet count was used to assess treatment adherence.

During the trial, participants were instructed to place the grass allergen or placebo tablet under the tongue and refrain from swallowing for 1 min. Eating and drinking were not permitted for 5 min. Pollen counts were measured daily in the vicinity of the trial sites (assuming that most patients enrolled in the trial lived or worked in these areas), and expressed as grains per cubic metre of air. The start of the pollen season was defined as the first day of three consecutive days in which the pollen count was 10 or more; the last day was the day prior to 3 days with a pollen count less than 10.

Statistical analysis

The primary objective of this clinical trial was clinical efficacy as assessed by average rhinoconjunctivitis symptom and medication score (results reported elsewhere, [24]). Data from the baseline season (2002) indicated that 125 participants per group would provide sufficient power to detect a 20% ($\alpha = 0.05$; two-sided) decrease in symptom score. Power was not calculated for QoL measurements.

The overall, mean RQLQ score (range 0–6) was calculated for each participant from the mean scores of each domain. This calculation was made for the screening visit, pre-season visit, both on-season visits and the post-season visit. The data were analysed using a repeated-measurement model assuming the RQLQ response to be normally distributed with treatment, pollen region, visit, and treatment $\times$ visit (interaction) as fixed effects. Participants were included as a random effect and screening visit values as a covariate. All available data from the treatment groups were included in each pairwise comparison. It seems reasonable to assume that a 20% change in RQLQ score would be clinically relevant.

The percentage of well days was defined for each participant by summing the well days, dividing this by the duration of the grass pollen season and multiplying by 100. The data were analysed using an analysis of variance (ANOVA) with treatment group and pollen region as fixed effects. In the analysis of RQLQ and well days, the following pairwise comparisons were made: Group 1 vs. Group 2; Group 1 vs. Group 3; Group 1 vs. Group 4; Group 2 vs. Group 3; Group 2 vs. Group 4; Group 3 vs. Group 4; Group 6 vs. Group 5; Group 6 vs. Group 1.

Results

Of the 855 randomised patients, 790 (92%) completed the study (Figure 1). Baseline characteristics of the patients included in each treatment group were similar (Table 2).

The mean total duration of treatment was 124.5 $\pm$ 28 days (range 1–174 days). Mean duration of treatment pre-season was 62.2 $\pm$ 14.3 days, and during the season was 48.7 $\pm$ 21.8 days. Overall adherence to treatment appeared to be high in all groups throughout the trial, with 94–98% of tablets taken.

Average rhinoconjunctivitis scores showed that symptoms were reduced by 16% ($p = 0.071$) and

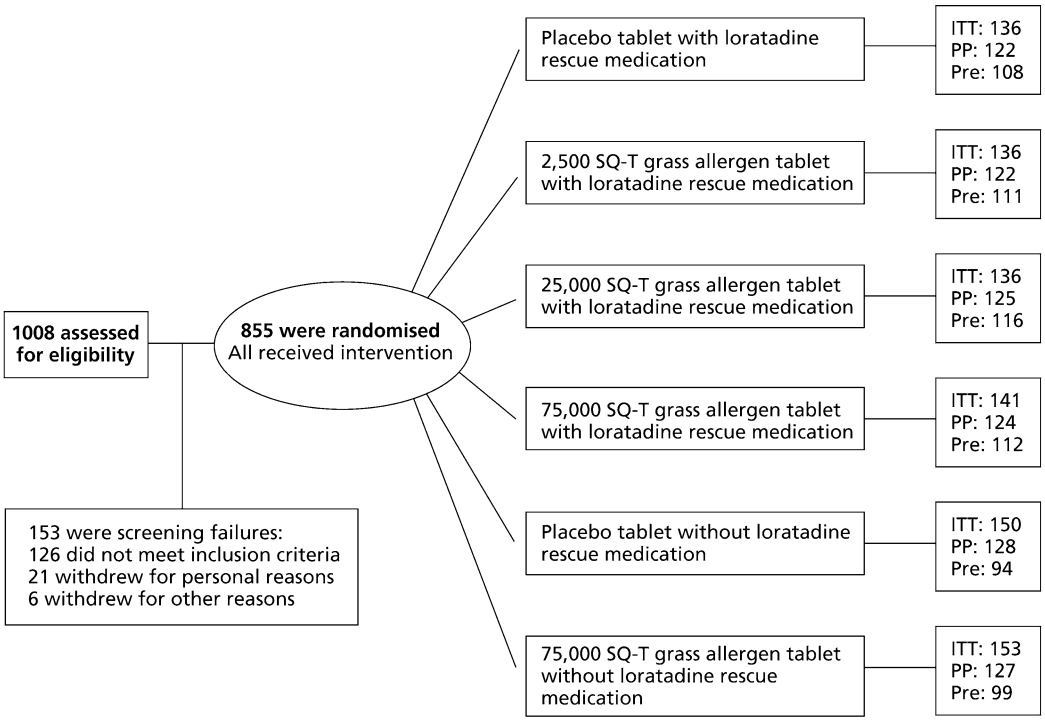

Figure 1. Participant allocation and completion.

medication use by 28% ($p = 0.047$) in patients allocated 75,000 SQ-T grass allergen tablet with loratadine, compared with those allocated placebo tablets with loratadine. There were no significant differences in symptoms or medication use in patients receiving 2,500 SQ-T or 25,000 SQ-T tablets compared with placebo (groups were also allocated loratadine, taken when necessary). In patients not allocated loratadine, symptoms and medication use were reduced by 13% ($p = 0.088$), and by 30% ($p = 0.017$) in patients receiving 75,000 SQ-T compared with those receiving placebo tablets (for more detailed efficacy results see Durham et al. [24]).

Table 2. Baseline demographics

	Group 1 Placebo tablet with loratadine rescue medication (n = 136)	Group 2 2,500 SQ-T tablet with loratadine rescue medication (n = 136)	Group 3 25,000 SQ-T tablet with loratadine rescue medication (n = 139)	Group 4 75,000 SQ-T tablet with loratadine rescue medication (n = 141)	Group 5 Placebo tablet with loratadine rescue medication (n = 150)	Group 6 75,000 SQ-T tablet without loratadine rescue medication (n = 153)
Cohort I	87	85	91	92	–	–
Cohort II	49	51	48	49	150	153
Canada	24	23	24	23	71	70
Male/female	89/47	84/52	92/47	84/57	89/61	95/58
Age	33	34	34	37	36	36
IgE class	3.46	3.53	3.47	3.46	3.11	3.45
Other allergens (%)	17	15	18	18	42	43
Any rescue med. (%)	96	96	96	98	93	90
AH eye drops (%)	49	44	60	53	22	17

RQLQ

The results are reported according to the three study aims outlined in the methods.

Grass allergen tablets vs. placebo tablets in patients also allocated loratadine rescue medication (Groups 1–4)

There was a clear dose–response relationship in the effect of grass allergen tablets on QoL as measured by RQLQ score in the groups also taking loratadine when necessary. Treatment with 75,000 SQ-T grass allergen tablet and 25,000 SQ-T grass allergen tablet significantly improved QoL relative to placebo tablet (Figure 2); mean RQLQ score (95% confidence interval; CI) was 17% (5–29%) and 14% (2–26%) greater in patients receiving 75,000 SQ-T grass allergen tablets and 25,000 SQ-T grass allergen tablets, respectively, compared with placebo tablet, at the first seasonal visit, ($p = 0.006$ and $p = 0.023$, respectively, intention-to-treat (ITT) population). At the second seasonal visit, the difference in mean RQLQ score between patients receiving 75,000 SQ-T grass allergen tablets and those receiving placebo tablets was even more marked (20% (95% CI: 3–37%); $p = 0.020$), although the difference between 25,000 SQ-T grass allergen tablet and placebo tablet did not reach statistical significance (12% (95% CI: − 5–29%); $p = 0.158$).

Between-group differences in different doses of grass allergen tablets were also evident. At the first seasonal visit, patients receiving 75,000 SQ-T grass allergen tablets and those receiving 25,000 SQ-T grass allergen tablets had significantly greater mean RQLQ scores than patients receiving 2,500 SQ-T (by 22% (95% CI: 11–33%) and 19% (95% CI: 8–30%), respectively, $p < 0.001$); this difference was maintained at the second seasonal visit for the 75,000 SQ-T group only (18% (95% CI: 1–35%); $p = 0.039$). None of the other pairwise comparisons was significant. Similar results were obtained for the per protocol data set. Furthermore, the dose-dependent effect of grass allergen tablets on mean RQLQ score was clearly evident across all domains of the scale, with the exception of sleep (no statistical analysis was performed) (Figure 3).

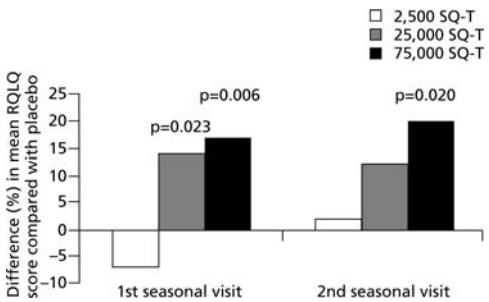

Figure 2. Difference in mean RQLQ score at the first and second seasonal visit following treatment with grass allergen tablets compared with placebo tablets in patients receiving loratadine rescue medication.

Grass allergen tablets vs. placebo tablets in patients not allocated loratadine rescue medication (Group 6 vs. Group 5)

When loratadine rescue medication was not used, differences between grass allergen tablet and placebo tablet were also evident. While there was no significant difference at the first seasonal visit, by the second seasonal visit mean RQLQ score (95% CI) was 21% (3–40%) greater in patients receiving 75,000 SQ-T grass allergen tablets, than in those receiving placebo tablets ($p = 0.021$, Figure 4).

Grass allergen tablet without loratadine vs. placebo tablets with loratadine (Group 6 vs. Group 1)

The direct comparison of the QoL benefits of grass allergen tablets vs. loratadine also favoured the use of specific immunotherapy. Mean RQLQ score (95% CI) was 26% (5–46%) greater at the second seasonal visit in patients receiving 75,000 SQ-T grass allergen tablets without loratadine than in patients receiving placebo tablets with loratadine ($p = 0.014$, Figure 5).

At the post-seasonal visit, 1 week after the end of the pollen season, there were no differences in mean RQLQ score between any of the treatment groups in the ITT or per protocol (PP) populations.

Patients receiving at least 8 weeks' pre-season treatment

Because the onset of the grass pollen season can only be estimated, some patients did not receive the planned 8 weeks of pre-season treatment. An exploratory analysis was therefore performed on RQLQ scores from the subset of ITT patients

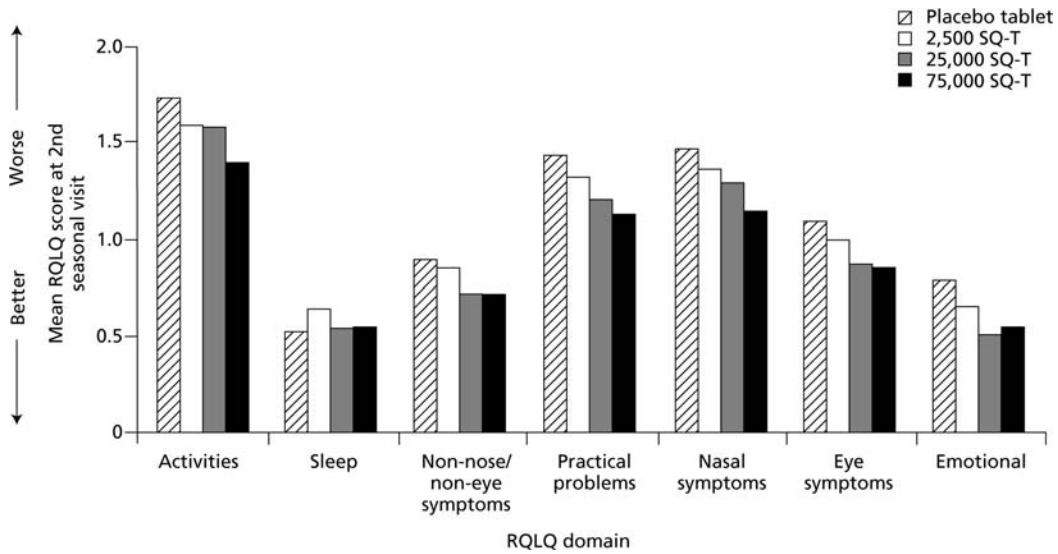

Figure 3. Effect of grass allergen tablets on each domain of the RQLQ at the second seasonal visit in patients receiving loratadine rescue medication.

(n = 640, 75%) who received at least 8 weeks of pre-season treatment. Generally, these results were consistent with those of the complete cohort. Mean RQLQ score was significantly greater with 75,000 SQ-T grass allergen tablet with loratadine than with placebo tablet with loratadine, by 21% (95% CI: 7–34%; $p = 0.002$) and 20% (2–38%, $p = 0.028$) for seasonal visit 1 and 2, respectively. Additionally, the dose–response of tablet immunotherapy was evident. Compared with patients receiving 2,500 SQ-T grass allergen tablets with loratadine, mean RQLQ was 23% (95% CI: 10–36%) greater in patients receiving 75,000 SQ-T grass allergen tablets with loratadine ($p < 0.001$) and 15% (95% CI: 3–27%) greater in patients receiving 25,000 SQ-T grass allergen tablets with loratadine ($p = 0.017$) at the first seasonal visit.

In patients not allocated loratadine, mean RQLQ score was 21% (95% CI: 1–42%) greater at the second seasonal visit with 75,000 SQ-T grass allergen tablets than with placebo tablets ($p = 0.044$). There were no other differences between groups in this exploratory analysis.

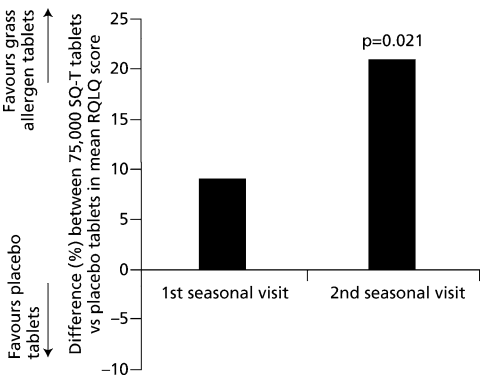

Figure 4. Difference (%) in mean RQLQ score in patients receiving 75,000 SQ-T grass allergen tablets and those receiving placebo tablets (both groups without loratadine) at the first and the second seasonal visit. Significant *p*-value indicates a significant between-group difference.

Well days

Grass allergen tablets vs. placebo tablets in patients allocated loratadine rescue medication (Groups 1–4)

For patients randomised to loratadine, those receiving 75,000 SQ-T grass allergen tablets had an 18% increase in the percentage of well days during the pollen season compared with those receiving placebo tablets (95% CI: 1–35%; $p = 0.041$, ITT population). Again, there was evidence of a dose-dependent effect of tablet immunotherapy; a higher percentage of well days was reported in the 75,000 SQ-T grass allergen tablet with loratadine group compared with the 25,000 SQ-T grass allergen tablets with loratadine

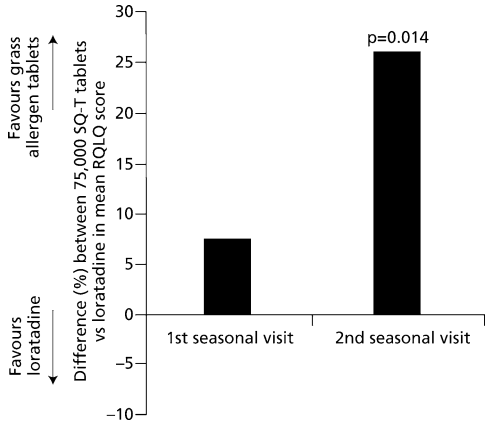

Figure 5. Difference (%) in mean RQLQ score in patients receiving 75,000 SQ-T grass allergen tablets (without loratadine) and those receiving loratadine (with placebo grass allergen tablets) at the first and the second seasonal visit. Significant *p*-value indicates a significant between-group difference.

group (16% increase, 95% CI: 0–33%) and the 2,500 SQ-T grass allergen tablets with loratadine group (13% increase, 95% CI: − 3–30%) but these differences did not reach significance ($p = 0.055$ and 0.105, respectively). Similar results were reported in the PP analyses.

Grass allergen tablets vs. placebo tablets in patients not allocated loratadine rescue medication (Group 6 vs. Group 5)

There was a non-significant increase of 12% in the percentage of well days in patients receiving 75,000 SQ-T grass tablets compared with placebo tablets in the groups not allocated loratadine.

Grass allergen tablets without loratadine vs. placebo tablets with loratadine (Group 6 vs. Group 1)

There was a non-significant increase of 5% in the percentage of well days in patients receiving 75,000 SQ-T grass tablets compared with those allocated loratadine alone.

Patients receiving at least 8 weeks' pre-season treatment

The percentage of well days was also compared in the subset of ITT patients who received at least 8 weeks of pre-season treatment (n = 640, 75%). Patients receiving 75,000 SQ-T grass allergen tablets with loratadine reported a greater mean percentage of well days (95% CI) by 19% (1–38%), 13% (− 5–31%) and 23% (4–43%) compared with placebo tablets ($p = 0.043$), 2,500 SQ-T grass allergen tablets ($p = 0.146$) and 25,000 SQ-T grass allergen tablets ($p = 0.017$), respectively. Additionally, in patients not allocated loratadine, those receiving 75,000 SQ-T grass allergen tablets had a 19% (95% CI: − 3–41%) increase in mean well days relative to those receiving placebo tablets, although this did not achieve significance ($p = 0.089$). No other differences approached significance.

Safety and tolerability

The grass allergen tablets were generally well tolerated. The most commonly reported treatment-related adverse events were oral itching and throat irritation. Of patients treated with 75,000 SQ-T grass allergen tablets, 52% reported oral itching, but the daily duration was limited to minutes/hours and, in 50, 75 and 90% of the affected patients, itching did not recur after 8, 53, and 108 days, respectively. This means that 74% of patients treated with the grass allergen tablet did not experience oral itching after 8 days of treatment. Few patients withdrew because of adverse events. No life-threatening systemic reaction was reported.

Discussion

This study showed that treatment with grass allergen tablets improves QoL in patients with seasonal allergic rhinoconjunctivitis induced by grass pollen. A clear dose–response relationship for grass allergen tablets was evident in terms of overall RQLQ score, with the most marked improvements in QoL occurring following treatment with 75,000 SQ-T grass allergen tablets. In particular, when patients could use loratadine as needed, this 75,000 SQ-T dose led to significantly greater mean RQLQ score relative to placebo grass allergen tablets at both the first and second seasonal visit, and the percentage of well days throughout the trial was also significantly increased. In the 25,000 SQ-T grass allergen tablet group, mean RQLQ score was significantly greater than placebo at the first seasonal visit only, and

this dose had no effect on the percentage of well days; no significant benefit of the 2,500 SQ-T dose on mean RQLQ score, or on well days was reported. Thus, when used in combination with loratadine rescue medication, 75,000 SQ-T grass allergen tablets, and to a lesser extent 25,000 SQ-T grass allergen tablets, offered significant QoL benefits over placebo tablets. Furthermore, the benefit of 75,000 SQ-T on QoL is clearly evident across all RQLQ domains, with the exception of sleep.

The 75,000 SQ-T grass allergen tablet also led to significantly better QoL than placebo tablets when patients were not using loratadine rescue medication. Furthermore, in a direct comparison of grass allergen tablet (75,000 SQ-T; without loratadine) vs. loratadine (without grass allergen tablet), immunotherapy-treated patients reported significantly better RQLQ scores than loratadine-treated patients. Thus, specific immunotherapy alone also has advantages over rescue medication alone.

Importantly, 1 week after the end of the pollen season, there were no between-group differences in QoL measures. A similar pattern of QoL results was reported in the subset of patients who received at least 8 weeks of pre-season exposure, although there was some indication of greater QoL benefits (at least at the first seasonal visit) in patients receiving the 75,000 SQ-T dose.

Juniper et al. [25] previously suggested an improvement in RQLQ score of 0.5 to be indicative of clinically meaningful improvement. This was calculated from a within-subject design, however, rather than a between-subject design as used in the present study. We suggest that an improvement in RQLQ score of 20% could be indicative of clinically relevant improvement in QoL. Using this criterion, the improvement in RQLQ with 75,000 SQ-T tablets (with or without loratadine) compared to placebo tablets (with loratadine) could be deemed clinically relevant at the second seasonal visit. Similarly, the improvement in RQLQ score with 75,000 SQ-T vs. placebo tablets, when neither group received rescue loratadine, at the second seasonal visit could also be considered clinically relevant. The confidence intervals for the results presented in this study suggest that the difference in RQLQ score between 75,000 SQ-T tablets and placebo tablets could be as great as 46%.

The differences in QoL documented here are consistent with the other efficacy findings from this cohort. As reported by Durham et al. [24], the greatest improvements in symptoms and largest reduction in medication use were in individuals receiving 75,000 SQ-T grass allergen tablets.

To our knowledge, this study is the first to report that, in patients with seasonal allergic rhinoconjunctivitis, specific sublingual immunotherapy can:

1. improve disease-specific QoL compared with placebo in patients taking rescue medication such as loratadine;
2. improve disease-specific QoL compared with placebo in patients not taking loratadine;
3. when used without loratadine, improve disease-specific QoL to a greater extent than loratadine alone.

Improved QoL in patients with allergic rhinitis has also been found following injectable immunotherapy. For example, Fell et al. [18] reported that 63% of patients with seasonal or perennial allergic rhinitis had improvements in social functioning following initiation of specific subcutaneous immunotherapy, and 55% reported an increased energy level. In a second study, QoL during the pollen season improved to a significantly greater extent with immunotherapy than with placebo overall, and in five of the seven RQLQ domains (non-hay fever symptoms, nasal symptoms, eye symptoms, activities, and emotions) in patients with seasonal rhinitis and asthma [20]. Finally, Moncayo Coello et al. [19] reported improved QoL in 54 children (aged 7–17 years) with allergic rhinitis receiving specific immunotherapy compared with those receiving placebo as assessed by the paediatric rhinoconjunctivitis QoL questionnaire; measures of distress caused by nasal pruritus, nasal obstruction, and eye rubbing were particularly improved.

The results of this study are also consistent with the available data on the effects of sublingual immunotherapy on QoL in patients with allergic asthma (with or without rhinitis) induced by house dust mites. For example, Bousquet et al. [22] showed that 25 months of sublingual immunotherapy improved QoL (as assessed by the short Form Health Status Survey 20) relative to placebo

in patients with allergic asthma, with scores on 'general perception of health' and 'physical pain' showing the greatest differences (35 and 26% greater than placebo, respectively). In a second study of 32 children with allergic rhinitis and asthma, 6 months of sublingual immunotherapy resulted in a 16% improvement in QoL relative to baseline as assessed by the paediatric asthma QoL questionnaire ($p < 0.01$, [21]).

QoL improvements have also been reported following non-immunotherapy treatment for seasonal allergic rhinitis. For example, Meltzer et al. [26] found that once-daily fexofenadine hydrochloride (an antihistamine) in patients with seasonal allergic rhinitis led to significantly greater reductions in overall work impairment and in daily activity impairment compared with placebo (as measured by the Work Productivity and Activity Impairment instrument); overall RQLQ score was also significantly reduced ($p < 0.01$). In a separate study the use of two intranasal corticosteroid sprays (triamcinolone acetonide and fluticasone propionate) was compared [27]. The preparations were equally effective in improving health-related QoL; scores on the RQLQ were 2.3–4.4 at baseline compared with 1.1–2.2 at endpoint ($p < 0.001$ vs. baseline). It is interesting to note, however, that in this present study treatment with 75,000 SQ-T grass allergen tablets without loratadine led to significantly better QoL (in terms of RQLQ score, but not well days) relative to placebo tablets with loratadine. Thus, grass allergen tablets may have a greater impact on QoL than standard treatments for grass pollen-induced rhinoconjunctivitis. While seasonal allergic rhinoconjunctivitis is rarely a life-threatening condition, it can have a significant negative impact on QoL. It is therefore important that QoL is considered alongside standard efficacy analyses when assessing the effect of treatment. Improvements in QoL can enhance a patient's life in a number of ways, allowing them to engage in outdoor activities, improving productivity, and increasing general feelings of well-being. This study has shown that 75,000 SQ-T grass allergen tablets represent an easy to use immunotherapy, which significantly improves QoL in patients with seasonal allergic rhinoconjunctivitis induced by grass pollen.

References

1. Dahl R, Andersen PS, Chivato T, Valovirta E, Monchy Jde. National prevalence of respiratory allergic disorders. Respir Med 2004; 98: 398–403.
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004; 24: 758–764.
3. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994; 94: 182–188.
4. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma: A population-based study of young adults. Am J Respir Crit Care Med 2000; 162: 1391–1396.
5. Storms WW. Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis. J Allergy Clin Immunol 2004; 114(Suppl) S146–S153.
6. Stuck BA, Czajkowski J, Hagner AE, et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: A controlled clinical trial. J Allergy Clin Immunol 2004; 113: 663–668.
7. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. Ann Allergy 1993; 71: 251–258.
8. Simons FE. Learning impairment and allergic rhinitis. Allergy Asthma Proc 1996; 17: 185–189.
9. Majani G, Baiardini I, Giardini A, et al. Health-related quality of life assessment in young adults with seasonal allergic rhinitis. Allergy 2001; 56: 313–317.
10. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341: 468–475.
11. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol 1995; 96: 879–885.
12. Jacobsen L, Nuchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts IV Results from long-term (6-year) follow-up. Allergy 1997; 52: 914–920.
13. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 1988; 43: 523–529.
14. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. J Allergy Clin Immunol 2003; 111: 437–448.
15. Passalacqua G, Lombardi C, Canonica GW. Sublingual immunotherapy: An update. Curr Opin Allergy Clin Immunol 2004; 4: 31–36.
16. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open label study of specific immunotherapy for respiratory allergy in real life: Clinical efficacy and more. Allergy 2004; 59: 1205–1210.
17. Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2003; (2): CD002893.
18. Fell WR, Mabry RL, Mabry CS. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. Ear Nose Throat J 1997; 76: 528–532, 534–536.

19. Moncayo Coello CV, Rosas Vargas MA, Rio Navarro BE del, Lerma Ortiz L, Velazquez Armenta Y, Sienra Monge JJ. [Quality of life in children with allergic rhinitis before and after being treated with specific immunotherapy (cases and controls)]. Rev Alerg Mex 2003; 50: 170–175 [Article in Spanish].
20. Walker SM, Pajno GB, Torres Lima M, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: A randomised, controlled trial. J Allergy Clin Immunol 2001; 107: 87–93.
21. Arikan C, Bahceciler NN, Deniz G, et al. Bacillus Calmette-Guérin-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. Clin Exp Allergy 2004; 34: 398–405.
22. Bousquet J, Scheinmann P, Guinnepain MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: A double-blind, placebo-controlled study. Allergy 1999; 54: 249–260.
23. Laffer S, Valenta R, Vrtala S, et al. Complementary DNA cloning of the major allergen Phl p I from timothy grass (*Phleum pratense*); recombinant Phl p I inhibits IgE binding to group I allergens from eight different grass species. J Allergy Clin Immunol 1994; 94: 689–698.
24. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass-allergen tablets: A randomised controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006; 117: 802–9.
25. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials involving rhinoconjunctivitis. Clin Exp Allergy 1991; 21: 77–83.
26. Meltzer EO, Casale TB, Nathan RA, Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1999; 83: 311–317.
27. Berger WE, Kaiser H, Gawchik SM, et al. Triamcinolone acetonide aqueous nasal spray and fluticasone propionate are equally effective for relief of nasal symptoms in patients with seasonal allergic rhinitis. Otolaryngol Head Neck Surg 2003; 129: 16–23.

Address for correspondence: Sabina Rak, Section of Allergy Sahlgrenska University Hospital, S-413 45, Göteborg, Sweden
Phone: +46-31-342-1886; Fax: +46-70-729-9063;
E-mail: sabina.rak@medfak.gu.se