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Brief report

Treatment of seasonal allergic rhinoconjunctivitis with a once-daily SQ-standardized grass allergy immunotherapy tablet

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Abstract

Objectives:

Specific immunotherapy with the grass allergy immunotherapy tablet (AIT) has been developed as an effective, well tolerated, and convenient treatment for grass pollen induced seasonal allergic rhinoconjunctivitis (ARC). Six phase II/III randomized, placebo-controlled trials with the duration of a single grass pollen season of treatment using the SQ-standardized grass AIT, Grazax (*Phleum pratense*, 75,000 SQ-T/2,800 BAU, ALK, Denmark), have been published previously. This review compares results from these trials.

Methods:

As outcome measures and methods of assessing them were similar across the trials, we have summarized the main efficacy findings (Total Combined Score [TCS], average daily rhinoconjunctivitis symptom and medication scores, percentage of well days, quality of life scores) during a single season of treatment with grass AIT in adults and children with seasonal ARC.

Results:

The results of the European and North American trials were similar. Compared with the placebo group, who received symptomatic medications only, treatment with grass AIT resulted in fewer rhinoconjunctivitis symptoms, a lower intake of symptomatic medication, better patient self-rated quality of life and a greater percentage of well days during the entire grass pollen season. The data indicate that grass AIT treatment is equally effective in adults and children; the measured effect varies with pollen exposure, but is comparable across regions and continents, with a consistent difference compared with placebo in TCS that was above 20% for all trials. Local adverse events were experienced by the majority of patients. These reactions were generally mild to moderate in severity and transient in duration. Systemic adverse events were rare.

Conclusions:

This review confirms SQ-standardized grass AIT as a suitable therapeutic option for seasonal use in patients aged 5 years or older with grass pollen induced ARC.

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Introduction

The prevalence of grass pollen induced allergic rhinoconjunctivitis (ARC) is high and increasing in many countries. In 2004, it was estimated that up to 26% of the adult population in Western Europe had allergic rhinitis, with

approximately half of the patients suffering from grass pollen induced rhinitis¹. Similarly, a 2006 survey conducted in the United States revealed that approximately 30 million adults have ARC². For many of these persons, grass pollen is a cause of their ARC symptoms. The International Study of Asthma and Allergies in Childhood (ISAAC) showed that the worldwide prevalence of allergic rhinitis in children was similarly high but varied widely between countries³. In a general practice survey in the UK, 27% of adult hay fever sufferers were taking conventional symptomatic medications, such as antihistamines and nasal corticosteroids, but up to 62% of those receiving optimal pharmacotherapy reported their symptoms remain uncontrolled⁴. Allergen-specific immunotherapy (SIT) is the only treatment that may alter the natural course of the allergic disease⁵. Randomized controlled trials (RCTs) have shown that SIT is effective in the first year of therapy, even in patients with severe grass pollen induced ARC that is resistant to conventional treatment^{6,7}.

SIT with grass allergy immunotherapy tablet (AIT) has been developed as a well tolerated, convenient and effective treatment for grass pollen induced seasonal ARC^{8,9}. The SQ-standardized grass AIT, Grazax (*Phleum pratense*, 75,000 SQ-T/2,800 BAU, ALK, Denmark), has been approved by regulatory authorities and available across Europe since 2006. It is indicated for the disease modifying treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific immunoglobulin IgE test to grass pollen¹⁰. Although SIT with drops often involves an up-titration of doses until an optimal maintenance dose is reached¹¹, grass AIT (Grazax) does not require an up dosing. The sublingually administered tablet form dissolves rapidly, is easy to use and patient friendly since AIT is a home-based treatment that requires no injections and fewer visits to the doctor compared with subcutaneous allergen-specific immunotherapy. Furthermore, because there is extensive cross-reactivity between grass pollen allergens, treatment with grass AIT against *P. pratense* is sufficient for treating seasonal ARC induced by temperate grasses^{12,13}.

An extensive clinical trial program has investigated the efficacy and safety of treatment with the grass AIT in patients with seasonal ARC. Six phase II/III randomized, placebo-controlled trials of a single grass pollen season of treatment performed in Europe and North America have been published so far^{7,14–18}. This short communication summarizes key clinical trial data from these published studies on efficacy and safety during a single season of treatment with the grass AIT in adults and children with grass pollen induced ARC in Europe and North America.

Clinical trials design and methods

An overview of the trial design and patient characteristics for each of the six phase II/III clinical trials is given in Table 1. All six trials were multicenter, randomized, double-blind, parallel-group, placebo-controlled trials in subjects with a history of grass pollen induced rhinoconjunctivitis requiring symptomatic treatment^{7,14–18}. Four of the trials^{7,16–18} included adults aged 18 to 65 years, and two trials^{14,15} included children aged from 5 years to 16 or 17 years. Two trials were conducted in North America (one adult trial, one pediatric trial)^{14,18}, three in Europe^{15–17} and one trial (the dose-finding trial) in Europe/North America (Canada)⁷. In all six trials, seasonal treatment commenced before the start of the grass pollen season, dosing continued throughout the grass pollen season (GPS) and stopped after the GPS.

All patients demonstrated a positive skin prick test and specific IgE in serum (sIgE) against *P. pratense*. The majority were polysensitized. Patients who had a history of allergic symptoms caused by other allergens during the grass pollen season were excluded. All trials excluded patients with severe asthma¹⁹, but most trials included patients with mild-to-moderate grass pollen induced asthma.

All six trials used grass AIT at the same single dose (75,000 SQ-T tablet once daily) in both children and adults. The dose-finding trial⁷ investigated three doses of grass AIT (2500, 25,000 and 75,000 SQ-T once daily) and showed the efficacy of grass AIT to be dose dependent, leading to selection of 75,000 SQ-T as the effective dose for the phase III trials.

The outcome measures and methods of assessment were similar across the trials. The primary efficacy endpoints were the average daily rhinoconjunctivitis symptom and medication scores over the entire grass pollen season, and the Total Combined Score (TCS), which was the sum of the average daily symptom and medication scores (maximum of 18 for symptom score added to maximum of 30–38 for medication score, depending on study; see below).

Each day patients rated their rhinoconjunctivitis and asthma symptoms in electronic diaries. Six rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes) were rated using the same scale (0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms and 3 = severe symptoms) across all trials; therefore, the total daily rhinoconjunctivitis symptom score for each subject could range from 0 to 18. In case of symptoms of rhinoconjunctivitis or asthma, patients had access to symptomatic relief medications that could be taken in a stepwise fashion according to the severity of symptoms. Use of symptomatic medications was also entered into the electronic diary, and daily use was scored according to predetermined criteria (Table 2). The scores for symptomatic medication use were added together to give the daily

Table 1. Overview of the six phase II/III trials on the first season of treatment.

Trials ID (ref)	Country	Design ^a /Objective	Patients (Grass AIT/Placebo)	Year of GPS	Treatment duration prior to start of GPS	Overall treatment duration
<i>Children</i>						
GT-12 (Bufe <i>et al.</i> , 2009) ¹⁵	Europe (26 centers in Germany)	Phase III Efficacy and safety trial	253 (126/127) children with ≥ 1 year history of GP-induced ARC with symptomatic treatment were randomized Male: 66%/65% Mean age: 10.1/10.1 years	2007	Mean 17.1 weeks, minimum 8 weeks (range 7.9–23.4 weeks)	Approx. 26 weeks (treatment duration was 24–36 weeks for 82% of patients, and >36 weeks for 4.4%) Approx. 24 weeks
P05239 (Blaiss <i>et al.</i> , 2011) ¹⁴	North America (41 centers in USA, 8 centers in Canada)	Phase III Efficacy and safety trial	345 children with history of GP-induced ARC with/without asthma were randomized 175/169 received at least one dose of medication Male: 67%/62% Mean age: 12.1/12.6 years	2009	Mean 15 weeks, median 15.6 weeks (range 0.3–22.3 weeks)	
<i>Adults</i>						
GT-02 (Durham <i>et al.</i> , 2006) ⁷	Europe and Canada (40 centers in Europe, 15 centers in Canada)	Phase II/III Dose-finding trial: 3 doses of grass AIT (2500; 25,000; 75,000 SQ-T once daily)	855 adults with a history or troublesome symptoms* of GP-induced ARC ≥ 2 years were randomized Male: 62.3%; Female: 37.7% Mean age: 35.1 years Patients receiving single-blind rescue medication (loratadine): 2500 SQ-T ($n = 136$), 25,000 SQ-T ($n = 139$), 75,000 SQ-T ($n = 141$), placebo ($n = 136$) Patients receiving no rescue medication: 75,000 SQ-T ($n = 153$), placebo ($n = 150$)	2003	Mean 8.9 weeks (range 0–13.6 weeks)	Max 24 weeks; Mean 17 weeks
GT-07 (Dahl <i>et al.</i> , 2006) ¹⁶	Europe (4 centers in Sweden, 11 centers in Denmark)	Phase II Safety and efficacy trial	114 (74/40) adults with a history of GP-induced ARC and mild-to-moderate GP-induced asthma ≥ 2 years were randomized Male: 72%/60% Mean age: 36.5/34.1 years	2004	Mean 12.0 weeks (range 0.1–14.7 weeks)	Mean 20 weeks (± 4.5 weeks)
GT-08 (Dahl <i>et al.</i> , 2006) ¹⁷	Europe (Austria, Denmark, Germany, Italy, the Netherlands, Spain, Sweden, UK; 51 centers in 8 countries)	Phase III Efficacy and safety trial	634 (316/318) adults with history ≥ 2 years of GP-induced ARC were randomized Male: 57%/61% Mean age: 33.8/34.5 years	2005	Mean 26 weeks, minimum 16 weeks (range 16–35 weeks)	Trial extended to cover 3 years of treatment and 2 years of follow-up
P05238 (Nelson <i>et al.</i> , 2011) ¹⁸	North America (44 centers USA, 7 centers Canada)	Phase III Efficacy and safety trial	439 adults with history of GP-induced ARC with/without asthma were randomized 213/225 received at least one dose of medication Male: 49%/50% Mean age: 35.9/35.9 years	2009	Mean 17 weeks, median 17 weeks (range 7.3–23.7 weeks)	Approx. 24 weeks

^aAll six trials were multicenter, randomized, parallel-group, double-blind, placebo-controlled trials.

*‘Troublesome symptoms’ were: significant grass pollen induced allergic rhinoconjunctivitis of 2 years or more, either requiring treatment during the grass allergy season and/or causing significant restrictions of activities. AIT = allergy immunotherapy tablet; ARC = allergic rhinoconjunctivitis; GP = grass pollen; GPS = grass pollen season.

Table 2. Daily scoring of rescue medication.

Step	Medication	Maximum daily score
Rhinoconjunctivitis		
1	Antihistamine	
	Loratadine tablets	6
	Levocabastine/olopatadine eye drops	4, 6 or 8*
2	Nasal corticosteroid	
	Budesonide or mometasone furoate	8
3	Oral steroid	
	Prednisone	16
Total maximal score		30, 34, 36 or 38*
Asthma		
A	Bronchodilator	8
B	Inhaled steroid	8
C	Oral steroid	16
Total maximal score		32

*Maximum score varied depending on the study.

medication score: the total maximal daily rhinoconjunctivitis medication score was 30^{7,17}, 34¹⁵, 36^{14,18} or 38¹⁶ points, dependent upon the scoring system used in each study. Another efficacy endpoint assessed across all trials was the percentage of 'well days' or 'minimal symptom days' during the entire grass pollen season, which were defined as days with no intake of symptomatic medication and a rhinoconjunctivitis symptom score ≤ 2 as reported in the patient diary. Patient quality of life was assessed in four of the trials^{7,14,17,18} using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)^{20,21}, where patients rate 28 items in seven domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose or eye symptoms, practical problems and emotional function) using a scale ranging from 0 (not impaired) to 6 (severely impaired). Safety was assessed through reported adverse events. Blood samples were taken at trial visits before, during and after the pollen season, and serum samples analyzed for levels of IgG4, IgE and IgE-blocking factor specific to *P. pratense*. Because the same method of assessment was used for many outcome parameters, we have descriptively summarized the data across the trials.

Results

Immunologic changes

After initiating treatment, there were allergen-specific changes in sIgG4 and sIgE-blocking factor in the grass AIT group prior to the start of the pollen season, which continued to increase until the end of the grass pollen season as shown in children in Figure 1¹⁵. Data from the other studies are consistent with this (data not shown). There was a significantly higher induction of sIgG4 and sIgE-blocking components in the grass AIT group compared with the placebo group.

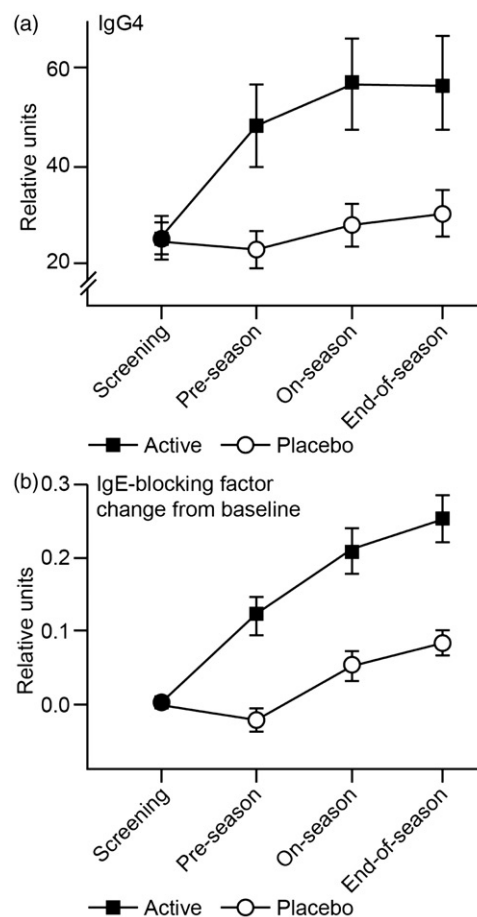


Figure 1. Immunological changes in children. Immunology results reported as change from baseline for each of the two treatment groups at different time points, with 95% CIs. Top (a): Mean levels of *P. pratense* specific IgG4 antibodies. Bottom (b): IgE-blocking factor, *P. pratense* (mean values). Reprinted from *J Allergy Clin Immunol* 2009;123(1), Bufe A et al., Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy¹⁵. Copyright (2009), with permission from Elsevier.

Efficacy

Table 3 summarizes the main efficacy outcomes for the six trials. It shows that seasonal treatment with grass AIT initiated a mean 9–26 weeks before the grass pollen season (Table 1) reduced rhinoconjunctivitis symptoms and resulted in a lower intake of rescue medications, better patient self-rated quality of life and a greater percentage of well days during the entire grass pollen season, compared with the placebo group who received treatment with symptomatic medications only. The reduction in mean average daily rhinoconjunctivitis symptom scores with grass AIT (relative to placebo) ranged from 16% to 31% ($p \leq 0.05$ for all studies except GT-02 where $p = 0.071$).

Mean daily rhinoconjunctivitis medication scores were lower in patients treated with grass AIT, and the reduction

Table 3. Efficacy outcomes for the six phase II/III trials.

	Adults				Children	
	Europe (Dahl <i>et al.</i> , 2006) ¹⁷	North America (Nelson <i>et al.</i> , 2011) ¹⁸	Dose finding ^a (Durham <i>et al.</i> , 2006) ⁷	Europe (Dahl <i>et al.</i> , 2006) ¹⁶	Europe (Bufe <i>et al.</i> , 2009) ¹⁵	North America (Blaiss <i>et al.</i> , 2011) ¹⁴
Trial ID	GT-08	P05238	GT-02	GT-07	GT-12	P05239
Number of patients ^b , grass AIT/placebo	282/286	208/225	141/136	68/39 ^c	117/121	173/167
Total combined score (TCS, sum of symptom and medication scores) ^d						
<i>N</i>	568	391	260	107	238	307
TCS difference relative to placebo, % (95% CI [confidence interval])	34 (26, 42)	20 (6, 33)	21 (7, 37)	29 (−2.0, 51.8)	24 (5, 41)	26 (10, 38)
<i>P</i> value	<0.001	0.005	0.021	0.081	0.022	0.001
Rhinoconjunctivitis symptom score ^e						
Grass AIT, adjusted mean	2.85	3.83	2.47	2.27	2.18	3.71
Placebo, adjusted mean	4.14	4.69	2.94	3.04	2.80	4.91
Difference relative to placebo, %	31	18	16	25	22	25
<i>P</i> value	<0.001	0.015 ^f	0.071	0.050	0.022	0.005 ^f
Rhinoconjunctivitis medication score						
Grass AIT, adjusted mean	1.65	1.25	1.46	2.60	2.13; 0.78 (median)	0.91
Placebo, adjusted mean	2.68	1.70	2.05	3.81	2.53; 1.19 (median)	1.33
Difference relative to placebo, %	39	26	28	32	34	32
<i>P</i> value	<0.001	0.084 ^f	0.047	0.136	0.016 (Wilcoxon rank sum)	0.066 ^f
Quality of life score						
Grass AIT, adjusted mean	1.03	1.30	0.84	N/A	N/A	1.45
Placebo, adjusted mean	1.40	1.57	1.05	N/A	N/A	1.77
Difference relative to placebo, %	26	17	20	N/A	N/A	18
<i>P</i> value	<0.001	0.022 ^f	0.020	N/A	N/A	0.042 ^f
Percentage of well days/minimal symptom days						
Grass AIT, adjusted mean	45.02	40.21	52.27	58.9	51.57	47.37
Placebo, adjusted mean	32.61	33.78	44.43	38.2	42.33	35.33
Difference relative to placebo, %	38	19	18	54	22	34
<i>P</i> value	<0.001	0.064	0.041	0.002	0.023	0.001

^aData presented for Grazax 75,000 SQ-T daily dose and placebo in the groups with loratadine rescue medication.^bIntent-to-treat population.^cNumber of patients with seasonal diary data.^dTCS: estimated by a linear mixed effects model (LME), with total combined score as dependent variable, treatment as fixed effect and site within trial as random effect; 95% CIs were calculated by bootstrapping.^eMean daily score over entire pollen season.^f*P* value adjusted with the Benjamini and Hochberg method.*P* value is presented for comparison of the two treatment groups tested using ANOVA unless indicated otherwise.

Rhinoconjunctivitis symptoms assessed: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. Each symptom was scored daily on a scale from 0 to 3 (0 = no, 1 = mild, 2 = moderate, 3 = severe). Rhinoconjunctivitis symptom score calculated as mean of the total daily score for each subject during the grass pollen season; score range 0–18.

Rhinoconjunctivitis medication score: symptomatic relief medication was provided in a stepwise fashion depending on persistence and severity of symptoms. Use of relief medication was scored according to predetermined criteria. Final score calculated as mean of the total daily score for whole grass pollen season. Medications that could be used within a pre-specified limit were loratadine (max daily score 6 points), olopatadine or levocabastine eye drops (max daily score 4, 6 or 8 points), budesonide or mometasone nasal spray (max daily score 8 points) and prednisone tablets (max daily score 16 points). Total maximal daily score was 30^{6,16}, 34¹⁴, 36^{13,17} or 38¹⁵.

Quality of life: assessed using the RQLQ which included 28 items in seven domains of activity limitation, sleep problems, nose symptoms, non-nose/eye symptoms, practical problems and emotional function; score range 0–6. Overall RQLQ score is the mean of all 28 responses and the average score during the pollen season.

Well days or minimal symptom days were both defined as days with no intake of relief medication and with a rhinoconjunctivitis symptom score ≤2.

AIT = Allergy immunotherapy tablet; N/A = not available.

relative to placebo ranged from 26% to 39% across the six trials (p -values ranged from <0.001 to 0.136; statistically significant in three studies).

As use of symptomatic medications can impact on symptom severity, it is recommended to assess a combination of the two^{8,22}. Therefore, a TCS (sum of symptom and medication scores) has been calculated for all the trials. For ease of comparison, the calculation has been performed in the same way for all trials. Grass AIT treatment reduced the TCS (relative to placebo) by 20% to 34% ($p \leq 0.05$ for all studies except GT-07 where $p = 0.081$).

Moreover, across the trials, the percentage of well days was increased by 18 to 54% in the grass AIT group compared with placebo (statistically significant in five studies). These improvements with grass AIT treatment were reflected in significant improvements in quality of life scores in all trials where it was measured (see Table 3).

The data in Table 3 show similar efficacy in North America and Europe^{23,24}. Moreover, the two large pediatric trials (one in Europe and one in North America) using the same dose of grass AIT as in the adult trials, showed that grass AIT treatment was effective in children (aged 5 to 16/17 years) with grass pollen induced ARC^{14,15}.

Safety

Treatment with grass AIT was well tolerated by adults and children across the six clinical trials. The majority of subjects exposed to grass AIT reported adverse events; however, the withdrawal rate due to adverse events was low (range across trials was 3–7% of patients receiving grass AIT). The majority of events were local adverse reactions that were transient and mild to moderate in severity (Table 4). Local symptoms mostly appeared soon after administration (usually on the first day) and were generally of short duration, did not require medical treatment, and usually disappeared during the course of treatment. Table 4 shows that the overall adverse-event profile in children was similar to that seen in adults. Across the six phase II/III trials of grass AIT, there were no systemic reactions with significant vascular symptoms.

Discussion

This review compares results from six randomized, single season, placebo controlled studies of SQ-standardized grass AIT in both adults and children, across Europe and North America.

Immunologic changes reported in these studies all indicate alteration of specific allergen antibody levels. Unfortunately, data are reported differently between studies and it is not possible to make a direct comparison. Not all sublingual immunotherapies have been shown to alter antibody levels in this way^{25,26}. However, increases in

Table 4. Adverse events in the six phase II/III studies.

	Adults			Children		
	Europe ¹⁷	North America ¹⁸	Dose finding ⁷	Europe ¹⁵	North America ¹⁴	
Number of patients, grass AIT/placebo	316/318	213/225	141/136 (with rescue med)	126/127	175/169	
All adverse events, grass AIT/placebo, % patients	84/64	83/72	92/74	87/83	86/78	
Treatment-related adverse events, grass AIT/placebo, % patients	75/21	73/28	78/26	63/30	70/25	
Most common treatment-related adverse events (occurring in $>5\%$ of patients), grass AIT/placebo, % patients	46/3	35/3	54/10	32/2	39/4	
Oral pruritus	9/1	29/5	23/0	10/2	37/3	
Throat irritation	12/1	20/1	8/0	—	11/1	
Ear pruritus	18/1	8/1	16/0	—	10/1	
Mouth edema	—	—	—	—	—	
Others	—	Stomatitis: 8/1 Oral paresthesia: 14/2 Pharyngeal edema: 7/0	—	Swelling face: 7/0	Stomatitis: 15/1 Oropharyngeal pain: 8/2 Pharyngeal erythema: 7/2 Lip swelling: 7/0 Eye pruritus: 6/2	

sIgG4 and sIgE-blocking factor seen here positively indicate the stimulating effect of grass AIT on the immune system and are consistent with reports from other studies of immunological changes with grass AIT^{27–29}.

Overall, the data show a statistically significant reduction in mean average daily rhinoconjunctivitis symptom scores. This supports other evidence in the literature including further reports from the pivotal European trial (GT-08), which have shown that grass AIT reduces individual seasonal eye and nasal symptoms, including nasal blockage³⁰ and reduces the number of days with severe symptoms³¹. AIT was also associated with a significantly lower intake of rescue medication for symptomatic relief and a greater percentage of well days with seasonal seasonal treatment regimen.

A key finding in all of the studies summarized was the significant and consistent difference in TCS relative to placebo, ranging from 20% to 34%. Guidance on the minimum difference in TCS that is noteworthy is yet to be defined. However a minimal magnitude of efficacy of 20% has been proposed to be clinically relevant³². The reduced use of symptomatic medication in patients receiving grass AIT was a substantial driver of TCS difference. From the data reported for individual studies, it is not possible to elucidate details of specific symptoms or medication use that had a bearing on TCS, and it would be interesting in future studies, to investigate this further.

Symptom relief through use of rescue medication, and in particular nasal steroids, is well established and effective for patients with ARC. However, relief is transient, and long term steroid treatment may be associated with side effects, particularly in children and patients with asthma who are prescribed inhaled steroids³³. The reduced symptomatic medication use associated with grass AIT therapy is therefore particularly relevant in these patients.

The significantly better patient self-rated quality of life in patients randomized to grass AIT indicates that the treatment has health-related quality-of-life benefits over use of symptomatic medications alone. These data all support the use of grass AIT as a simple and effective therapy that should provide symptomatic relief, and address the underlying mechanisms of ARC for a broad spectrum of pediatric and adult patients whose quality of life is impaired by ARC.

A general safety concern with subcutaneous immunotherapy is the risk of severe systemic allergic reactions. However, sublingual immunotherapy is generally considered to be better tolerated³² and in all the studies included here AIT treatment was well tolerated with no serious systemic reactions.

The burden of grass pollen allergy is related to many factors, including the length of the pollen season, height of the pollen peak and total pollen counts. In the six clinical trials reported here, treatment was started at least 2 months before the start of the pollen season, which was defined as

the first of three consecutive days with a pollen count of at least 10 grains/m³. This is the lowest atmospheric concentration of grass pollen that can cause rhinoconjunctivitis symptoms³⁴. The trials were conducted in different years (from 2003 to 2009) and in different countries, and the duration and severity of the pollen seasons varied between trials (data not shown). It is well established that the severity, timing of the peak and duration of a grass pollen season varies both geographically and from one season to another^{35,36} and that there is an increase in symptoms in patients when pollen counts are higher. The results of these six trials demonstrate that grass AIT provides consistent treatment effects across continents and populations.

Although the studies reported here are relatively short in duration, longer-term studies have demonstrated evidence that the benefit of treatment persists after the completion of treatment, indicating disease modification in patients receiving grass AIT^{37,38}. In keeping with these findings are results from studies of other sublingual therapies, including both seasonal and continuous treatment schedules, although some limitations in these trials diminish valid interpretation^{39–41}; nevertheless the strongest evidence for disease modification is associated with continuous dosing schedules. Continuous therapy with grass AIT is a cost effective treatment option, due to demonstrated disease-modifying effect and the potential asthma prevention⁴². A pharmacoeconomic analysis indicates a cost per quality-adjusted life-year gained of 4319 pounds sterling, which is considered highly cost effective⁴³.

In conducting a review of phase II and III studies of grass AIT it has been beneficial to be able to make direct comparisons between studies. However, this summary has covered only a small part of the literature pertaining to grass AIT, and a systematic review would provide an additional therapy-specific perspective. Moreover, it would be interesting to carry out a follow-up study comparing the results reported here with other forms of allergen immunotherapy.

Conclusions

Overall, the six phase II/III trials have confirmed that SQ-standardized grass AIT is effective and well tolerated when used in a seasonal treatment regimen in adults and children with grass pollen induced rhinoconjunctivitis in both Europe and North America. The body of clinical evidence is consistent in demonstrating an effect of grass AIT treatment on both symptoms and medication use, and the data of the European efficacy trials have been confirmed in a North American population. No difference between adults and children was observed. Adverse events occurred mostly at treatment start, were transient in duration and mild to moderate in severity. Systemic adverse reactions were rare. Thus, grass AIT is a suitable therapeutic option

for seasonal use in children and adults with grass pollen induced ARC.

Transparency

Declaration of funding

ALK-Abello has sponsored the European studies included in this manuscript. Sherring-Plough / Merck has sponsored the North American trials.

Declaration of financial/other relationships

H.N. was a principle investigator on an ALK-Abello grant to National Jewish to assess the potency of a dog dander extract and is a consultant to Merck on their studies of AIT in the USA. L.L. is an employee of ALK. M.S.B. is a speaker and consultant for Merck.

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