Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents

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Background: Allergy immunotherapy tablet (AIT) treatment might be a safe and convenient form of specific immunotherapy but it has not been investigated in North American children and adolescents.

Objective: We sought to investigate the efficacy and safety of timothy grass AIT treatment in North American children/adolescents with grass pollen–induced allergic rhinoconjunctivitis (ARC) with or without asthma.

Methods: Three hundred forty-five subjects (5-17 years old) were randomized to once-daily grass AIT treatment (2,800 bioequivalent allergen units, 75,000 standardized quality tablet, approximately 15 μg of Phl p 5) or placebo approximately 16 weeks before the 2009 grass pollen season (GPS). Treatment continued through the GPS. Daily symptoms and allergy rescue medication use were recorded. The primary end point was the total combined score (TCS) of the daily symptom score (DSS) and daily medication score (DMS) for the entire GPS. DSS, DMS, Rhinoconjunctivitis Quality of Life Questionnaire score, and Phl p 5–specific IgG4 and IgE-blocking factor levels were secondary end points. Safety was assessed through adverse events.

Results: Eighty-nine percent of subjects were multisensitized. TCS, DSS, DMS, and Rhinoconjunctivitis Quality of Life Questionnaire score versus placebo improved 26% ($P = .001$), 25% ($P = .005$), 81% ($P = .006$), and 18% ($P = .04$). Phl p 5–specific IgG4 and IgE-blocking factor levels were significantly higher at the peak and end of the GPS ($P < .001$). Treatment was well tolerated. Adverse events were generally mild and transient. Although no investigator-assessed systemic allergic reactions were reported, 1 grass AIT–treated subject experienced an event indicating a systemic reaction (lip angioedema, dysphagia, and cough).

Conclusions: Use of once-daily timothy grass AIT treatment effectively treats timothy grass (cross-reactive with Festucoideae grasses) pollen–induced ARC in North American children 5 years and older. Given its convenient administration, lack of dose build-up requirement, safety profile, and efficacy, AIT treatment might become an important addition to the North American ARC treatment armamentarium. (J Allergy Clin Immunol 2011;127:64-71.)

Key words: *Allergy immunotherapy tablet, allergic rhinoconjunctivitis, specific immunotherapy, grass pollen, children, sublingual immunotherapy*

Recent studies suggest approximately 13% to 17% of children in the United States live with allergic rhinoconjunctivitis (ARC),[1,2] and the prevalence might be as high as 42%.[3] Grass pollens, particularly of the subfamily Festucoideae (timothy, rye, meadow fescue, Kentucky bluegrass [also known as June grass], cocksfoot [also known as orchard grass], redtop, and sweet vernal) are extensively cross-reactive (partially cross-reactive with Johnson grass)[4,5] and are a significant trigger for ARC. In some North American regions, sensitivity to these grasses has been found to be as high as 50% to 70% in patients with ARC.[6,7] In children ARC has been found to adversely affect daily life by disturbing sleep, diminishing school performance, and limiting school or outdoor activities.[1] Standard treatment for ARC in North America consists of allergen avoidance procedures and use of over-the-counter (ie, antihistamines), and prescription (ie, nasal corticosteroids) medications. Another treatment option is allergen immunotherapy, which is the only current treatment that modifies the disease process.[8] Studies have shown that patients treated with immunotherapy benefit from long-term symptom relief and improvement in quality of life after treatment discontinuation.[9-11] In children immunotherapy has been shown to reduce the risk of new sensitizations and asthma associated with ARC.[12-16]

In the United States immunotherapy is generally administered subcutaneously. However, concerns about serious (and possibly life-threatening) systemic reactions, as well as fear of injection, are believed to deter some patients from this treatment.[8,17] These factors underscore the need for safer and more convenient modes of immunotherapy administration in North America. Sublingual allergy immunotherapy tablet (AIT) treatment without build-up regimens has been used safely and effectively in Europe since

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Abbreviations used
AE: Adverse event
AIT: Allergy immunotherapy tablet
ARC: Allergic rhinoconjunctivitis
DMS: Daily medication score
DSS: Daily symptom score
GPS: Grass pollen season
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
TCS: Total combined symptom and medication score

2005. Timothy grass AIT treatment has been demonstrated to be efficacious and well tolerated in European adults.[18-20] The effect of medications on children has not always been evaluated in clinical trials. Instead, it is presumed that the results of adult trials are applicable to children, but this is not always the case.[21] A trial of grass AIT treatment was conducted in European children with ARC to confirm the efficacy of this treatment in children and, like in the adult trials, demonstrated significantly improved rhinoconjunctivitis and asthma symptoms and decreased symptomatic medication use, as well as generally good tolerability.[22] It is not known whether grass AIT results from trials in European populations can be extrapolated to North American populations because sensitization patterns and environmental factors might differ. In North America results from only 3 sublingual trials (all with allergy drops) in adults have been reported,[23-25] but none have been reported in children or with tablets. The objective of the current study was to investigate the efficacy and safety of grass AIT treatment in North American children/adolescents 5 years of age and older with grass pollen–induced ARC with or without asthma.

METHODS

Study design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter (41 United States and 8 Canadian sites, listed in Table E1 of this article's Online Repository at www.jacionline.org) phase III study conducted between April 2008 and September 2009 in North America. The study was conducted in compliance with Good Clinical Practice guidelines. The protocol was approved by institutional review boards for each center. All subjects provided written informed consent before any study activity. There were 2 periods to the study: an observational period and a treatment period (Fig 1). The purpose of the observational period (2008 grass pollen season [GPS]) was to ensure recruited subjects had adequate grass pollen–induced symptoms to secure a symptomatic population for the treatment period. No investigational treatment was administered during this period. Additional subjects were enrolled after the observational period to meet the necessary enrollment goals. During the treatment period (2009 GPS), subjects were randomized 1:1 to a once-daily sublingual dose of 2,800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, *Phleum pratense*, 75,000 standardized quality tablet, containing approximately 15 μg of Phl p 5; Schering-Plough Corp, a division of Merck & Co, Kenilworth, NJ) or placebo (identical in composition and physical properties to active treatment but with no grass pollen extract included). The tablet was placed under the tongue and dissolved within seconds. Randomization was conducted by an external randomization group using an interactive voice-response system according to a computer-generated schedule in appropriately sized blocks and was stratified by study site and the subject's asthma status. Subjects and investigators were blinded to treatment by using a matching placebo in identical packaging to the grass AIT treatment. Blinding was maintained until the data were locked. Treatment began approximately 16 weeks before the GPS and continued through the entire GPS for a total treatment period of 23 weeks. The first 3 daily doses of study medication were administered at the study site, and the subjects were monitored for adverse events (AEs) on site for 30 minutes after administration. Subsequent doses were taken at home. Subjects or their legal guardians were contacted by telephone for the first 4 days of at-home treatment to determine whether the subject experienced any study treatment–related reactions. Self-injectable epinephrine (EpiPen; Dey Pharma, Basking Ridge, NJ) was provided for use in the event of a significant systemic allergic reaction.

Study subjects

Subjects included in the study were 5 to 17 years of age with a clinical history of physician-diagnosed grass pollen–induced ARC with or without asthma. Key inclusion criteria for the observation and treatment periods were aimed at recruiting subjects with moderate-to-severe ARC and were as follows: treatment for ARC during the previous GPS; a positive skin prick test response to *P pratense* (standardized timothy grass extract, 100,000 bioequivalent allergen units/mL, 5-mL vial, administered by means of a DuoTip [Lincoln Diagnostics, Decatur, Ill] to the inner forearm), with the average of the horizontal and vertical wheal diameters 5 mm or larger than that elicited by the saline control (positive control was Histatrol Histamine Positive Control 1.0 mg/mL, 5-mL vial [ALK-Abelló, Hørsholm, Denmark]), a positive specific IgE level against *P pratense* of 0.7 kU/L or greater (measured by means of ImmunoCAP; Phadia AB, Portage, Mich), and an FEV_1 of 70% or greater of predicted value at screening. Key exclusion criteria were as follows: clinical history of symptomatic seasonal or perennial ARC, asthma, or both requiring medication because of an allergen other than grass during or potentially overlapping the GPS; immunosuppressive treatment in the 3 months before screening; clinical history of persistent severe asthma, chronic urticaria/angioedema, or chronic rhinosinusitis; or current severe atopic dermatitis. For subjects who participated in the observational period, those who did not experience a rhinoconjunctivitis symptom score increase of 4 points or more for at least 2 days compared with the preseason score or did not use ARC symptomatic medication for at least 2 days during the observational period were also excluded.

Grass pollen season

Each study site obtained daily pollen counts (grass, tree, and ragweed) during the trial. The start of the GPS was defined as the first 3 consecutive days with a pollen count of 10 grains/m^3 or greater, and the end of the GPS was defined as the last day of the last occurrence of 3 consecutive days with a pollen count of 10 grains/m^3 or greater. The peak of the GPS was defined as the period of 15 consecutive recorded days with the highest average among all possible 15 consecutive-day averages across the GPS.

Assessments

The primary end point of the study was the total combined score (TCS), which is the sum of the rhinoconjunctivitis daily symptom score (DSS) and the daily medication score (DMS) averaged over the entire GPS. Key secondary end points were average DSS and average DMS over the entire GPS and the combined average weekly scores from the validated Juniper Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; for ages 6-<11 years [the 5-year-olds did not complete the questionnaire])[26] and the validated Adolescent RQLQ (for ages 12-18 years)[27] during the GPS. Additional end points included the determination of Phl p 5–specific IgG4 antibody levels in milligrams of specific antigen per liter and IgE-blocking factor levels before and throughout the GPS and the average DSSs and DMSs during the peak GPS.

Subjects/parents/guardians scored daily 6 rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty/red/itchy eyes, and watery eyes) and 4 asthma symptoms (cough, wheeze, chest tightness/shortness of breath, and exercise-induced symptoms) in an electronic diary from randomization through the end of the GPS using a 4-point scale: 0, no symptoms; 1, mild symptoms (easily tolerated); 2, moderate symptoms (bothersome but tolerable); or 3, severe symptoms (hard to tolerate and interferes with daily activities). Open-label rhinoconjunctivitis and asthma medication (for asthmatic subjects) were provided approximately 2 weeks before the start of the GPS, and their use was recorded by the subject/parent/

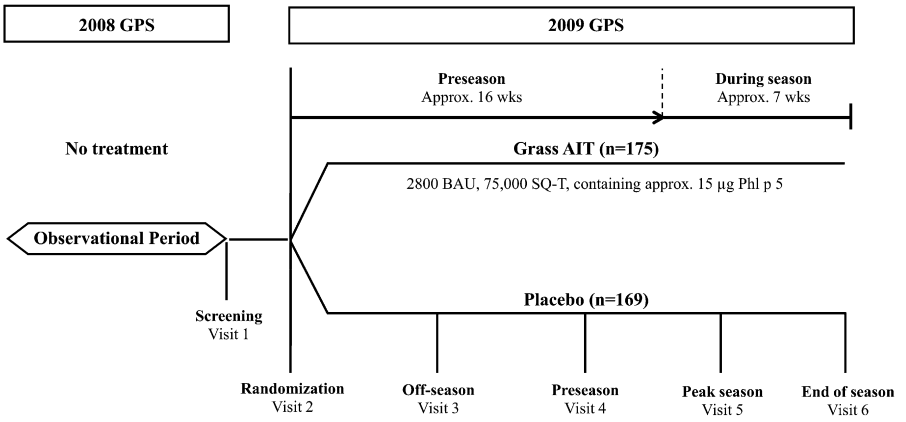

FIG 1. Study design. *BAU*, Bioequivalent allergen units; *SQ-T*, standardized quality tablet.

guardian in the electronic diary. Subjects were instructed to take the rescue medication in a stepwise fashion once the start of the GPS was established and when subjects experienced a threshold of symptomatology confirmed by the treating physician. Rhinoconjunctivitis medication use was scored to obtain the DMS (see Table E2 in this article's Online Repository at www.jacionline.org). During the treatment period, the RQLQ was completed by the subject/parent/guardian at visits 2, 4, 5, and 6. A higher score indicates more severe impairment. Blood samples for immunologic assessment of Phl p 5–specific IgG4 antibody and IgE-blocking factor levels were collected at treatment period visits 1, 5, and 6 and were assessed by means of immunoassay (for more details, see the Methods section in this article's Online Repository at www.jacionline.org).

Safety

Safety was measured based on spontaneously reported AEs. AEs were recorded by the subject/parent/guardian in a paper diary and rated by the investigators as mild, moderate, severe, or life-threatening. Investigators also assessed the relationship of each AE to treatment (unlikely, possibly, or probably related).

Statistics

Power analysis revealed 340 subjects would be sufficient to detect a 5% level of significance (2-sided test) for a treatment difference of 1.63 in TCS, assuming a pooled SD of 4.77. Differences in TCSs, DSSs, DMSs, and RQLQ scores between the placebo and grass AIT groups for the entire GPS were evaluated by using a linear model with asthma status, study site, and treatment group as fixed effects and adjusting for different error variation for each treatment group. Additional nonparametric analysis with the Wilcoxon rank sum test was conducted on the DMS because the data were not normally distributed and were heavily weighted by zero values. Additional statistical information is described in the Methods section of this article's Online Repository. All efficacy analyses were conducted on the intent-to-treat population based on all randomized subjects who had data available (at least 1 posttreatment diary data entry) for analysis. Safety data were assessed in all treated subjects. There was no imputation of missing data. The software used for statistical analysis was SAS version 9.1 (SAS Institute, Inc, Cary, NC) in UNIX.

RESULTS

Demographics and baseline characteristics

Of the 345 children who were randomized, 344 received at least 1 dose of study treatment, and 282 completed the study (Fig 2). The intent-to-treat population consisted of 149 subjects in the grass AIT group and 158 subjects in the placebo group. The majority of subjects were white males, and the mean overall age was 12.3 years (Table I). Although the inclusion criteria were for ages 5 to 17 years, 1 subject was 18 years of age. In each treatment group 26% of subjects had asthma. A large percentage of subjects (89%) overall were sensitized to other allergens than grass (multisensitized, Table I). Preseason TCSs and DSSs were significantly different between the grass AIT and placebo groups (Table I). When 7-day moving averages were evaluated in reverse from the start of the GPS, the difference between the groups was not significant at day −22 and all earlier time points. Therefore it is unlikely that there was any imbalance before the start of treatment (a median of 109 days before the GPS).

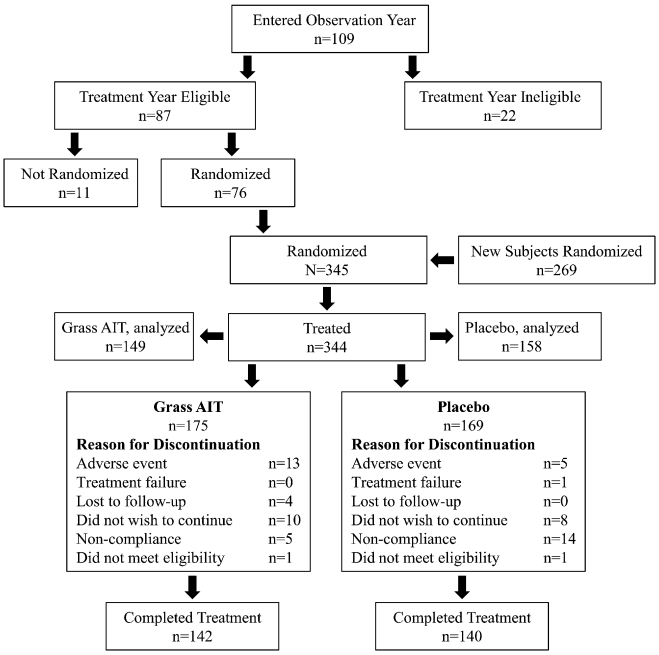

FIG 2. Subject disposition.

GPS

The GPS lasted a median of 56 days in the grass AIT group and 57 days in the placebo group, with a mean grass pollen count

TABLE I. Demographics and baseline characteristics

	Grass AIT group (n = 175)	Placebo group (n = 169)
Sex, no. (%)		
Male	118 (67)	105 (62)
Race, no. (%)		
White	153 (87)	149 (88)
Black	12 (7)	13 (8)
Age (y)		
Mean	12.1	12.6
5-11 (n)	73	61
12-18 (n)	102	108
Range	6-17	5-18
Subjects with asthma (%)	26	26
Mean % predicted FEV_1	95	93
Sensitive to nongrass allergens (%)	87	91
Tree pollens	68	65
Weed pollens	63	66
Cat/dog	51	54
Mite	29	34
Mold	28	27
Grass sensitivity		
Mean histamine wheal diameter (mm)	5.6	5.4
Mean *P pratense* wheal diameter (mm)	10.6	10.7
Specific IgE (kU/L)	31.7	34.8
Preseason scores*		
TCS	3.13‡	4.52
DSS	2.83‡	4.18
DMS†	0.30	0.33

*Maximum TCS = 54; maximum DSS = 18; maximum DMS = 36.
†Rescue medication was not dispensed until 2 weeks before the anticipated start of the GPS, and its use was prohibited during this period unless specifically advised by the investigator.
‡$P < .001$ versus placebo.

(weighted by number of subjects exposed) of 28 grains/m^3 per day (Fig 3). Although tree pollen was present at the start of the GPS and many subjects (grass AIT group, 68%; placebo group, 65%) were sensitive to tree allergens, symptom and medication scores in the grass AIT treatment group did not seem to be markedly influenced by the high tree pollen counts (Fig 3).

Symptom and medication scores

Separation of TCSs between the 2 treatment groups began approximately 4 weeks before the start of the GPS, coincident with low levels of grass pollen before the protocol-defined start of the GPS. An increase in TCSs paralleled increasing pollen counts throughout the season, and the same relationship was observed as pollen counts waned (Fig 3). The mean TCSs (maximum, 54) for the entire GPS were 4.62 in the grass AIT group and 6.25 in the placebo group, corresponding to a significant improvement in the grass AIT group relative to that seen in the placebo group of 26% ($P = .001$, Table II). The differences in TCSs in favor of grass AIT treatment were observed for both the pediatric (5-11 years; 32%) and adolescent subgroups (12-17 years; 16%), indicating grass AIT treatment was effective in both age groups. Mean DSSs (maximum, 18) were 3.71 in the grass AIT group and 4.91 in the placebo group, corresponding to a significant improvement in the grass AIT group relative to that seen in the placebo group of 25% ($P = .005$, Table II). The improvements in scores for ocular and nasal symptoms were 28% and 23%, respectively, relative to placebo (both $P = .003$). Mean DMSs (maximum, 36) were not normally distributed, and therefore median values were analyzed. Median DMSs were 0.12 in the grass AIT group and 0.64 in the placebo group, corresponding to a significant improvement in the grass AIT group relative to that seen in the placebo group of 81% ($P = .006$, Table II); however, it should be noted that use of allergy rescue medication was low in both treatment groups. Improvements in mean TCS, DSS, and DMS in the peak GPS for grass AIT treatment relative to placebo were 31% ($P < .001$), 28% ($P < .001$), and 41% ($P = .05$), respectively (Table II).

Quality of life

The mean difference in RQLQ score (maximum, 6) for the grass AIT group (score, 1.45) relative to the placebo group (score, 1.77) during the entire GPS was 0.32, corresponding to an 18% improvement over placebo ($P = .042$, Table II). The difference in RQLQ score for the grass AIT group (score, 1.19) relative to the placebo group (score, 1.91) during the peak season was greater than that observed during the entire GPS, resulting in a minimal important difference of 0.72 and 38% improvement ($P = .005$, Table II).

Effects on asthma

Treatment with grass AIT did not significantly reduce asthma symptoms (asthma DSS) relative to treatment with placebo ($P = .174$). Mean asthma DSSs for the grass AIT and placebo groups were 0.86 and 1.08, respectively (maximum, 12), a difference of 21%. The subjects enrolled with asthma had well-controlled disease, and asthma treatment was allowed; therefore the inability to detect a treatment effect was expected.

Immunologic measures

Levels of Phl p 5–specific IgG4 and IgE-blocking factor were similar between the 2 groups at baseline and increased over time in the grass AIT group. By peak season, log-transformed IgG4 levels were significantly greater in the grass AIT group compared with those in the placebo group ($P < .001$, Fig 4; for non–log-transformed values, see Fig E1 in this article's Online Repository at www.jacionline.org). This treatment effect continued through the end of the season ($P < .001$). The values for IgE-blocking factor were similarly increased by grass AIT treatment, with significantly greater levels at the peak and end of the season compared with values after placebo treatment ($P < .001$, Fig 4).

Safety

Grass AIT treatment was generally well tolerated. No life-threatening events, investigator-diagnosed systemic allergic reactions, anaphylactic shock, or respiratory compromise were reported in either treatment group. Overall, 82% of subjects experienced treatment-emergent AEs. Of subjects receiving grass AIT treatment, 70% experienced treatment-related AEs compared with 25% of placebo-treated subjects. Oral pruritus and throat irritation were the most common treatment-emergent and treatment-related AEs (Table III). Mild erythema and mouth irritation (coded as "stomatitis" because of a standardized coding convention) were also common. (In this trial the term did not generally refer to ulcerations or infection in the mouth.) Of 7 (4.0%) reports of urticaria in the grass AIT group, 3 were

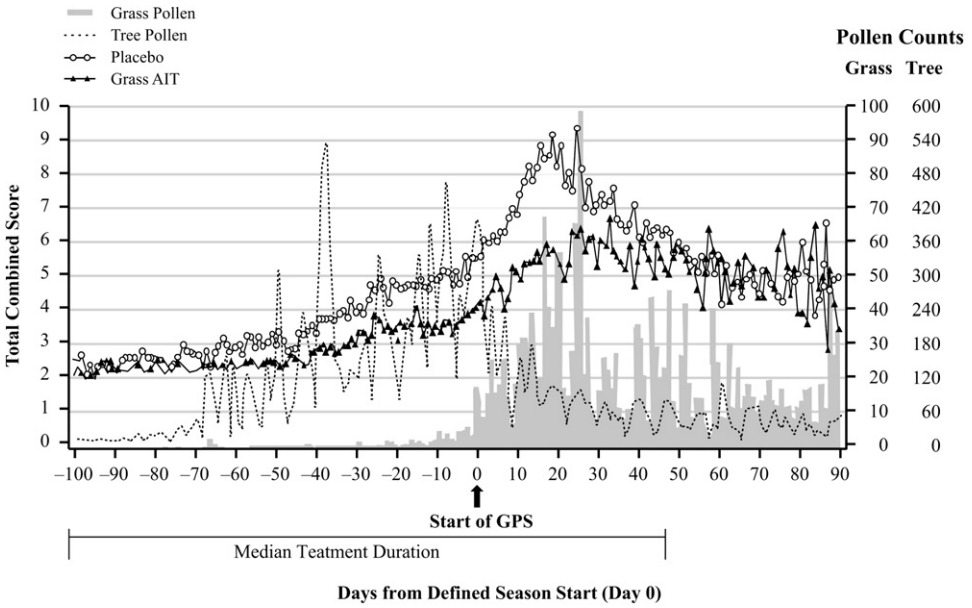

FIG 3. Total combined score and pollen counts over time. Pollen counts (in grains per cubic meter) were weighted by the number of subjects exposed.

considered treatment related; none of the 6 (3.6%) reports of urticaria in the placebo group were considered treatment related. Only 1 (0.6%) subject in the grass AIT group reported a treatment-related asthma event. The majority of treatment-related AEs were local application-site reactions, and all but 3 treatment-related AEs (in 2 subjects) were rated as mild to moderate in severity. Generally, the local application-site AEs began on the first day of treatment and were reported for 1 to 2 days (Table IV). The number of discontinuations because of AEs was small (grass AIT group, n = 13; placebo group, n = 5). No events of tablet aspiration were reported; the tablet is dissolved within seconds.

Serious AEs were reported by 5 subjects (placebo group, n = 4; 1 nonrandomized subject); none were considered treatment related. Two subjects in the grass AIT group and 1 subject in the placebo group received epinephrine. Only 1 epinephrine administration was due to a reaction to the tablet. This subject experienced lip angioedema, slight dysphagia, and intermittent cough immediately after the first dose of grass AIT on day 1 of the study. The event was not accompanied by wheezing, respiratory distress, urticaria, vomiting/diarrhea, or hypotension and was not considered a systemic reaction by the investigator. The symptoms resolved after investigator-administered epinephrine, and the investigator graded the severity of the event as moderate. This subject was discontinued. An inappropriate epinephrine administration occurred in an actively treated subject who was given a diagnosis of viral pharyngitis. The subject visited the emergency department on day 23 of the study for a persistent sore throat. Large tonsils were observed, although there was no breathing difficulty or stridor. Epinephrine was administered in the emergency department but did not alter the results of throat examination. The subject was discharged from the emergency department with a diagnosis of viral pharyngitis. A placebo-treated subject was administered epinephrine at the investigational site approximately 12 hours after tablet intake on day 137 of the study in response to inspiratory and expiratory wheezing, which was likely triggered by exposure to a grassy field. During this trial, there were no administrations of epinephrine outside of a health care setting.

DISCUSSION

This is the first study to demonstrate the efficacy and safety of timothy grass AIT treatment in a predominantly multisensitized North American pediatric population. The results from this trial confirm that grass AIT treatment can effectively improve ARC symptoms, decrease the need for allergy rescue medications, and improve rhinoconjunctivitis quality of life in children/adolescents 5 years of age and older with ARC to timothy grass and other related grasses. The 22% improvement in the median DSS in the current study was comparable with the 24% difference reported in a study of grass AIT treatment in European children.[22] The median DMS difference was higher in the current study compared with that in the European study (81% vs 34%, respectively). However, the DMS data must be interpreted with caution because the absolute score value was low, inflating the percentage change. The DSS results were comparable in spite of the shorter duration of the GPS in the current study (approximately one third less than that of the GPS for the European study). RQLQ scores were not assessed in the European study but in this study were significantly improved by grass AIT treatment, reaching the minimal important difference (defined as a difference of ≥0.5[28]) during the peak GPS.

Rescue medication use was lower than that reported in European grass AIT trials.[19,22] Symptom severity (and subsequent rescue medication use) is associated with pollen exposure,[29] and in this study the average and peak pollen counts were relatively low compared with those in the European grass AIT trials,[19,22] which likely influenced the DMS. Given the low grass pollen counts during the GPS, it is not unexpected that rescue medication levels did not reach higher magnitudes. In a pivotal trial of grass AIT treatment (n = 634) conducted in Europe,[19] a strong treatment effect was observed during a more robust (higher peak counts and longer season) GPS; therefore it is expected that if the GPS was

TABLE II. TCSs, DSSs, DMSs, and RQLQ scores* during the entire GPS and peak GPS

	Grass AIT group (n = 173)‡	Placebo group (n = 167)‡	Difference	*P* value	Percentage improvement (difference relative to placebo)	95% CI of the difference
Entire season						
TCS						
Mean (SE)†	4.62 (0.5)	6.25 (0.5)	−1.63	.001	26	−2.60 to −0.66
Median	3.82	5.81			34	
DSS						
Mean (SE)†	3.71 (0.4)	4.91 (0.4)	−1.20	.005‖	25	−1.95 to −0.45
Median	3.39	4.34			22	
DMS						
Mean (SE)†	0.91 (0.3)	1.33 (0.2)	−0.42	.07‖	32	−0.88 to 0.03
Median	0.12	0.64		.006	81	1.22 to 2.30#
RQLQ§						
Mean (SE)†	1.45 (0.1)	1.77 (0.1)	−0.32	.04‖	18	−0.60 to −0.03
Median	1.36	1.69			20	
Peak season						
TCS¶						
Mean (SE)†	4.73 (0.6)	6.85 (0.6)	−2.12	<.001	31	−3.30 to −0.95
Median	4.00	6.53			39	
DSS¶						
Mean (SE)†	3.81 (0.4)	5.30 (0.4)	−1.49	<.001	28	−2.30 to −0.67
Median	3.50	4.73			26	
DMS¶						
Mean (SE)†	0.92 (0.3)	1.55 (0.3)	−0.63	.05	41	−1.26 to 0.00
Median	0.00	0.44			100	
RQLQ**						
Mean (SE)†	1.19 (0.2)	1.91(0.2)	−0.72	.005	38	−1.22 to −0.22
Median	0.95	1.65			42	

*Maximum TCS = 54; maximum DSS = 18; maximum DMS = 36; maximum RQLQ score = 6.
†Scores were adjusted by using the ANOVA model, with asthma status, treatment group, and site as factors in the analysis.
‡Number of subjects included in analysis: grass AIT group, n = 149; placebo group, n = 158.
§Number of subjects included in analysis: grass AIT group, n = 109; placebo group, n = 111.
‖*P* values adjusted with the Benjamini and Hochberg method.
¶Number of subjects included in analysis: grass AIT group, n = 147; placebo group, n = 153.
#Interquartile range for the grass AIT and placebo groups, respectively.
**Number of subjects included in analysis: grass AIT group, n = 40; placebo group, n = 46.

stronger, the treatment effect would also be more pronounced. Further studies might be warranted to determine the relationship between symptom control and the severity of the GPS.

Subcutaneous immunotherapy is often perceived to be more efficacious than sublingual immunotherapy. In reality, major differences in trial designs, as well as a lack of well-controlled trials, preclude direct comparison between the outcomes of these 2 modalities. In the only well-controlled, randomized, double-blind, placebo-controlled trial of subcutaneous grass allergen immunotherapy, the difference in DSSs versus those after placebo treatment for high-dose allergen was 29%, and the difference was 22% for low-dose allergen.[30] Because that trial measured lung symptoms in addition to ocular and nasal symptoms when calculating the DSS, direct comparison with the current trial is not possible.

Not all sublingual immunotherapies have been demonstrated to alter specific allergen antibody levels.[31,32] The increases in specific IgG4 and IgE-blocking factor levels observed during this study are consistent with increases observed in other studies of grass AIT treatment in both adults and children[22,33] and are indicators that grass AIT treatment had a stimulating effect on the immune system, as observed with subcutaneous immunotherapy.[34]

Differences in TCSs were observed between the 2 treatment groups before the start of the GPS, but the reasons are unclear. One possibility is that there was a true treatment effect on subjects affected by low-level chronic exposure to grass pollen. Another possible reason is that grass AIT treatment might have had a protective effect on subjects with tree pollen–induced ARC. However, symptom scores do not appear to coincide with levels of tree pollen (ie, no symptom spikes during pollen spikes), and the grass pollen symptom and medication scores do not seem to be markedly influenced by tree pollen. Additional study is needed to examine the cause of preseason differences. Even though differences occur preseasonally, the greater improvements at peak season relative to the entire season indicate that the effect of grass AIT is greatest when relief is needed most.

Consistent with results of the European pediatric study,[22] grass AIT treatment was well tolerated, with oral pruritus and throat irritation being the most common AEs in both studies. Such local application-site AEs are typical of sublingual administration and do not usually result in medication discontinuation. The local application-site reactions generally began on the first day of treatment, were generally experienced for the first 1 to 2 days of treatment, and resolved without intervention. Although data on the duration of each event were not collected in this study, previous safety findings from the pooled results of 2 small studies of grass AIT treatment in children indicated a mean duration of 16 minutes each for oral pruritus and throat irritation.[35]

Safety is one of the most serious concerns for allergen immunotherapy treatment in children, particularly considering the documented history of serious and even fatal reactions after

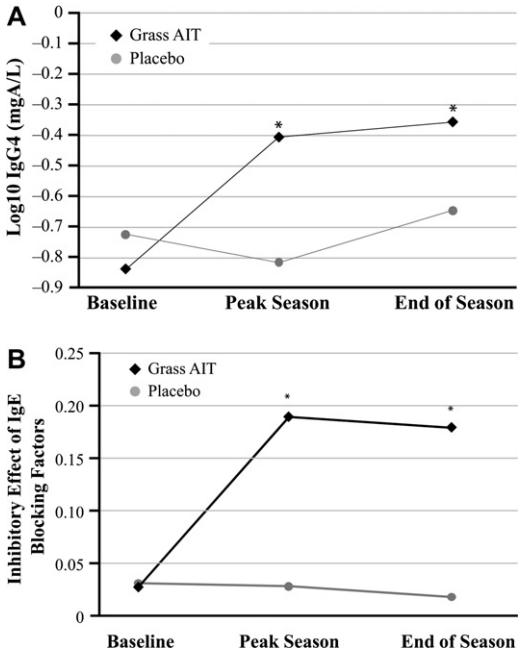

FIG 4. Change from baseline in adjusted mean antibody levels for Phl p 5–specific IgG4 **(A)** and IgE-blocking factor **(B)**. *mgA,* Milligrams of antigen-specific antibody. *$P < .001$ versus placebo.

TABLE III. Adverse Events Experienced by ≥5% of Subjects

	Treatment Emergent			Treatment Related		
Adverse events, n (%)	Grass AIT n=175	Placebo n=169	Total n=344	Grass AIT n=175	Placebo n=169	Total n=344
Oral pruritus	68 (38.9)	6 (3.6)	74 (21.5)	68 (38.9)	6 (3.6)	74 (21.5)
Throat irritation	65 (37.1)	5 (3.0)	70 (20.3)	65 (37.1)	5 (3.0)	70 (20.3)
Stomatitis*	26 (14.9)	2 (1.2)	28 (8.1)	26 (14.9)	2 (1.2)	28 (8.1)
Oropharyngeal pain	23 (13.1)	19 (11.2)	42 (12.2)	14 (8.0)	4 (2.4)	18 (5.2)
Ear pruritus	21 (12.0)	1 (0.6)	22 (6.4)	20 (11.4)	1 (0.6)	21 (6.1)
Mouth edema	19 (10.9)	1 (0.6)	20 (5.8)	18 (10.3)	1 (0.6)	19 (5.5)
Headache	19 (10.9)	20 (11.8)	39 (11.2)	7 (4.0)	4 (2.4)	11 (3.2)
Cough	16 (9.1)	19 (11.2)	35 (10.2)	6 (3.4)	0	6 (1.7)
Eye pruritus	15 (8.6)	4 (2.4)	19 (5.5)	11 (6.3)	3 (1.8)	14 (4.1)
Lip swelling	13 (7.4)	0	13 (3.8)	13 (7.4)	0	13 (3.8)
Pharyngeal erythema	13 (7.4)	3 (1.8)	16 (4.7)	13 (7.4)	3 (1.8)	16 (4.7)
Nasal congestion	11 (6.3)	8 (4.7)	19 (5.5)	7 (4.0)	1 (0.6)	8 (2.3)
Sneezing	9 (5.1)	2 (1.2)	11 (3.2)	6 (3.4)	1 (0.6)	7 (2.0)
Nasopharyngitis	26 (14.9)	32 (18.9)	58 (16.9)	0	0	0
URTI	21 (12.0)	22 (13.0)	43 (12.5)	0	0	0
Viral URTI	11 (6.3)	12 (7.1)	23 (6.7)	0	0	0
Pyrexia	9 (5.1)	12 (7.1)	21 (6.1)	0	0	0

AIT, allergy immunotherapy tablet; URTI, upper respiratory tract infection.
*Mild erythema, not ulcerations or infection.

TABLE IV. Time to onset and number of days reported for local application-site AEs

	Time to onset (d)						No. of days reported			
	Grass AIT group (n = 175)			Placebo group (n = 169)			Grass AIT group (n = 175)		Placebo group (n = 169)	
AE	No.	Median	Range	No.	Median	Range	Median	Range	Median	Range
Oral pruritus	67	1	1-75	6	1	1-2	5	1-192	1.5	1-5
Mouth edema	19	8	1-163	1	2	2	15	1-116	1	1
Throat irritation	65	1	1-38	5	1	1-13	4	1-172	2	1-4
Pharyngeal edema*	7	1	1-26	0	—	—	2	1-13	—	—
Stomatitis†	26	1	1-154	2	53	1-105	2	1-159	1	1
Ear pruritus	21	1	1-36	1	1	1	5	1-185	1	1
Oral paresthesia	7	1	1-3	2	4.5	2-7	1	1-6	1	1

*Mild to moderate edema not causing obstruction/stridor.
†Mild erythema, not ulcerations or infection.

subcutaneous administration.[36,37] Although no subject experienced an investigator-assessed systemic allergic reaction, 1 subject was administered epinephrine in response to a moderate grass AIT treatment–related event of lip angioedema, slight dysphagia, and intermittent cough after the first dose. These symptoms might be interpreted as a systemic allergic reaction. The rate of urticaria (a potential indicator of systemic reaction) was low; events of urticaria were not associated with other signs or symptoms of systemic allergic reactions. The safety results in this trial are consistent with those observed in a total of 5 major European grass AIT trials involving over 1100 subjects with ARC, in which there were no reports of anaphylactic shock and only 1 serious treatment-related AE (uvula edema that did not require treatment or study discontinuation).[18-20,22,38]

Comorbid asthma is a risk factor for experiencing a serious systemic reaction to allergen immunotherapy.[37] Approximately one quarter of subjects in this study had ARC with comorbid asthma. Importantly, there was no indication of asthma worsening in response to treatment. There were also no active treatment-related serious asthma events, although 1 subject in the grass AIT group experienced a mild treatment-related asthma AE that did not require treatment. These data provide evidence that grass AIT is safe for use in children and adolescents with well-controlled asthma. Additional studies are needed to fully investigate the effect of grass AIT treatment on asthma.

Grass AIT treatment might have the potential to modify disease in children. At present, there are no long-term controlled studies in children with ARC to specifically demonstrate disease modification by grass AIT treatment. However, a study in adults has demonstrated that 3 years of treatment with grass AIT resulted in clinical improvements for at least 1 year after treatment discontinuation.[10] Further studies are needed to demonstrate a disease-modifying effect of grass AIT treatment in children.

In conclusion, this was the first study to demonstrate that once-daily timothy grass AIT treatment administered preseasonally and during the GPS was clinically effective and well tolerated in primarily multisensitized North American children/adolescents 5 years of age and older. The results from this trial replicate the

results seen in European children/adolescents. Grass AIT treatment might offer a generally safe, convenient, and potentially disease-modifying treatment option for children/adolescents 5 years of age and older allergic to timothy grass pollen and other related grasses that are extensively cross-reactive, including rye, meadow fescue, Kentucky bluegrass, cocksfoot, redtop, and sweet vernal, and those that are partially cross-reactive, such as Johnson grass. We believe that given its convenient administration, lack of requirement for a dose build-up phase, safety profile, and demonstrated efficacy after 1 season of administration, AIT treatment has the potential to become an important new addition to the North American ARC treatment armamentarium.

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Clinical implications: Self-administration of grass AIT treatment can be used to safely and effectively treat North American children (aged ≥5 years) with timothy grass– and related grass-induced ARC with or without asthma.

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METHODS

IgG4 and IgE-blocking factor measurement

IgG4 (in milligrams of antigen-specific antibody per liter) and IgE-blocking factor in serum samples were assessed by means of immunoassay (ADVIA Centaur Specific IgE 2-step assay with ADVIA Centaur Specific IgE [Simultan], Siemens Healthcare Diagnostics, Deerfield, Ill; ImmunoCAP IgG4 assay, Phadia AB, Portage, Mich). Samples for IgG4 analysis were diluted 1:50, tested in duplicate, and compared with a standard curve. All IgG4 values were log-transformed to obtain approximately normally distributed residuals, and the statistical analyses were conducted on these log-transformed values.

IgE-blocking factor is evaluated by assessing the proportion of IgE prevented from binding to allergen in the presence of other serum components. The ADVIA Centaur Specific 2-step IgE assay was used to determine Phl p 5–specific IgE levels (in kilounits per liter), and the ADVIA Centaur Specific IgE assay (Simultan) was used to determine Phl p 5–specific IgE levels (in kilounits per liter) in the presence of other serum components. Samples were analyzed in duplicate. IgE-blocking factor is derived as the ratio between allergen-binding IgE activity in serum in the presence of other serum components and allergen-binding IgE activity in serum measured in the absence of other serum components (IgX). That value is then subtracted from 1. If no IgE-blocking antibodies are induced, the 1 − IgX value is close to 0.

Statistics

Assuming a 25% dropout from the 450 subjects in the observational phase, 340 subjects in the treatment phase would be sufficient to detect a 1.63-point difference from placebo (23% difference based on a placebo mean of 7.07 points) in TCS with an 88% power at a 5% level of significance (2-sided test).

The type 1 error rate for the key secondary end points of DSS and DMS during the GPS was controlled by using the Benjamini and Hochberg procedure.[E1] An adjusted *P* value is presented for the key secondary end points, and therefore a *P* value of less than .05 for any of the primary or key secondary end points indicates statistical significance.

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E1. Benjamini Y, Hochberg Y. Controlling the false discovery rate in multiple testing with independent statistics. J R Stat Soc B 1995;57:289-300.

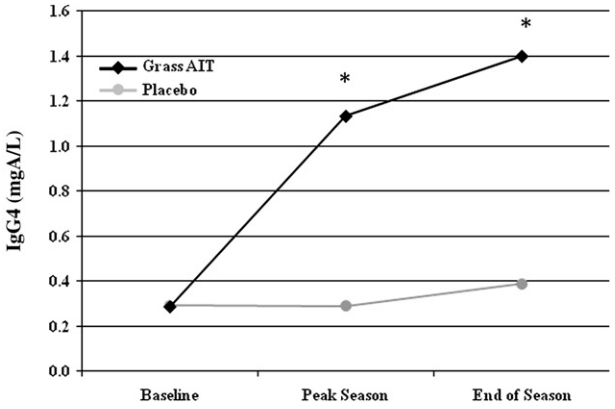

FIGURE E1. Levels of Phl p 5-specific IgG4. *$P < .001$ vs placebo. *P* value calculation was based on log-transformed values. *AIT,* Allergy immunotherapy tablet; mg_A, milligrams of specific antigen.

TABLE E1. List of study sites by region

Region	No. of sites	No. of subjects	
		Grass AIT group	Placebo group
Canada	8	23	23
United States			
Mid-Atlantic	4	8	9
North central	15	28	28
South	7	31	30
West	15	86	79

TABLE E2. Scoring of rescue medication use

Step	Rescue medication	Score/dose unit	Maximum daily score
Rhinoconjunctivitis			
1	Loratadine syrup: 1 mg/mL, 5 mL QD (for age 5 y)	6 (per 5 mL)	6
1	Loratadine tablet: 10 mg, 1 tablet QD; Claritin syrup: 1 mg/mL, 10 mL QD (for ages 6-17 y)	6 (per tablet or 10 mL)	6
1b	Olopatadine hydrochloride 0.1% ophthalmic solution, 1 drop in the affected eye BID	1.5 (per drop)	6
2	Mometasone furoate monohydrate nasal spray: 50 μg, 1 spray in each nostril QD (for ages 5-11 y)	4 (per spray)	8
2	Mometasone furoate monohydrate nasal spray: 50 μg, 2 sprays in each nostril QD (for ages 12-17 y)	2 (per spray)	8
3	Prednisone tablet: 5 mg (day 1, 1 mg/kg/d, maximum of 50 mg/d)	1.6 (per tablet)	16*
3	Prednisone tablet: 5 mg (day 2+, 0.5 mg/kg/d, maximum of 25 mg/d)	1.6 × 2 (per tablet	16*
Maximum daily rhinoconjunctivitis medication score			36
Asthma			
A	Albuterol sulfate HFA inhalation aerosol: 108 μg/inhalation, 2 inhalations every 4-6 h as needed†	2 (per inhalation)	8
B	Fluticasone propionate HFA inhalation aerosol: 44 μg/inhalation, 2 inhalations BID (for ages 5-11 y)‡	2 (per inhalation)	8
B	Fluticasone propionate HFA inhalation aerosol: 44 μg/inhalation, 2 inhalations BID (for ages 12-17 y, maximum of 10 inhalations BID)	1 (per inhalation)	8
C	Prednisone tablet: 5 mg (day 1, 1 mg/kg/d, maximum of 50 mg/d)	1.6 (per tablet)	16*
C	Prednisone tablet: 5 mg (day 2+, 0.5 mg/kg/d, maximum of 25 mg/d)	1.6 × 2 (per tablet	16*
Maximum daily asthma medication score			32
Maximum combined medication score			48*

BID, Twice daily; *HFA*, hydrofluoroalkane; *QD*, once daily.

*Prednisone use was counted in the rhinoconjunctivitis score, asthma score, or both depending on the symptoms and was counted only once in the combined score.

†Labeled strength of 108 μg per inhalation (equivalent to 90 μg of albuterol base) in the United States and salbutamol sulfate (100 μg) in Canada.

‡Labeled strength of 44 μg per inhalation in the United States and 50 μg per inhalation in Canada.