Rhinitis, sinusitis, and upper airway disease

Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen

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Background: Specific allergen immunotherapy is most often delivered subcutaneously, but sublingual immunotherapy may confer greater benefit in terms of tolerability and safety, accessibility, and improved antigen delivery.

Objective: This randomized, double-blind, placebo-controlled trial was conducted to identify a safe and effective maintenance dose range of sublingual standardized glycerinated short ragweed pollen extract in adults with ragweed-induced rhinoconjunctivitis.

Methods: In May 2006, a total of 115 patients with ragweed-induced rhinoconjunctivitis were randomly allocated to placebo (n = 40), medium-dose extract (4.8 μg Amb a 1/d; n = 39), or high-dose extract (48 μg Amb a 1/d; n = 36). In a 1-day (rush) dose-escalation regimen, ragweed pollen extract was administered sublingually in incremental doses until maximum tolerable or scheduled dose was reached and then maintained during the ragweed pollen season. Patient diaries were used to monitor nasal and ocular symptoms and medication. The primary endpoint was symptom score.

Results: Both active treatment groups achieved a 15% reduction in total rhinoconjunctivitis symptom scores compared with placebo during the entire ragweed pollen season, but the difference was not statistically significant ($P > .10$) However, in an analysis of covariance correcting for preseasonal symptoms, both mean daily symptom scores (0.19 ± 1.16 vs 1.00 ± 2.30) and medication scores (0.0003 ± 1.64 vs 0.63 ± 1.06) for the entire pollen season were significantly reduced in the high-dose versus placebo groups, respectively ($P \leq .05$). Ragweed-specific IgG, IgG$_4$, and IgA antibodies were increased after treatment in the medium- and high-dose groups and not the placebo group. Frequency of adverse events was similar between the placebo and treatment groups, but oral-mucosal adverse events occurred more often with treatment.

Conclusion: Standardized glycerinated short ragweed pollen extract administered sublingually at maintenance doses of 4.8 to 48 μg Amb a 1/d was safe and can induce favorable clinical and immunologic changes in ragweed-sensitive subjects. However, additional trials are needed to establish efficacy. (J Allergy Clin Immunol 2010;125:660-6.)

In the United States, specific allergen immunotherapy is currently delivered most often via subcutaneous injection.[1,2] Adverse events (AEs) associated with subcutaneous immunotherapy (SCIT) have prompted the investigation of alternative routes of administration.[3]

In the past 15 years, sublingual immunotherapy (SLIT) has become a widely accepted alternative in European countries,[2,4] but not in the United States.[5] SLIT has been shown to be effective in the management of rhinoconjunctivitis and asthma in both adults and children,[3,4,6-12] with the potential to confer greater benefit than SCIT in terms of tolerability and safety, accessibility, and improved antigen delivery.[2,13]

Previous SLIT studies had major shortcomings, including small patient populations, high withdrawals, short treatment duration, and inadequate randomization data.[14] Questions remain with regard to the mechanisms of action of SLIT, treatment schedules, duration of treatment, optimal dose, cost-effectiveness, and compliance.[3,4,15]

The purpose of this clinical trial was to identify a safe and effective target maintenance dose of sublingual standardized glycerinated short ragweed pollen allergenic extract. The design was based on the results of an earlier trial showing that daily sublingual dosing of up to 60 μg Amb a 1 of extract was generally safe and well tolerated in adults with ragweed-induced rhinoconjunctivitis.[16]

METHODS
Study design

In this randomized, double-blind, placebo-controlled dose-response trial (Fig 1), the safety and efficacy of sublingual standardized glycerinated short ragweed pollen allergenic extract (Greer Laboratories, Inc, Lenoir, NC)

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were investigated in 115 adults with rhinoconjunctivitis caused by ragweed pollen at 4 US study sites (Madison, Wis [n = 34]; Evansville, Ind [n = 10]; Pittsburgh, Pa [n = 40]; and Iowa City, Iowa [n = 31]). A single batch of short ragweed pollen allergenic extract, standardized on the basis of Amb a 1 content, was used throughout the study for skin prick testing, nasal provocation testing, and SLIT. Study objectives were to identify an efficacious dose range of the extract, determine the rate of treatment-related AEs, and evaluate systemic ragweed-specific antibody responses after SLIT. The primary endpoint was symptom score.

Subjects received SLIT approximately 8 to 10 weeks before the predicted ragweed pollen season and discontinued treatment at the completion of the pollen season, which may have varied by location. The average duration of the treatment course was 17 ± 3 weeks.

The study was performed in accordance with protocol requirements, the International Conference on Harmonization guideline E6 (Good Clinical Practice), and the US Code of Federal Regulations applicable to clinical studies. Properly constituted institutional review boards approved the protocol and monitored the conduct of the study.

Study participants

Male and female patients age 18 to 50 years with moderate to severe isolated or uniseasonal allergic rhinoconjunctivitis caused by ragweed pollen for 2 years or more were eligible for the study. Sensitivity to ragweed pollen was documented by a positive skin prick test (defined as a mean wheal diameter 3 mm greater and a mean erythema diameter 6 mm greater than those of the negative control at 15-20 minutes).

Exclusion criteria included rhinoconjunctivitis and/or asthma symptoms in the previous 4 weeks, a history of anaphylaxis or persistent asthma, abnormal spirometry, use of ragweed allergen immunotherapy in the 3 years before study entry, and use of inhaled, oral, or injected corticosteroids, tricyclic antidepressants, monoamine oxidase inhibitors, β-blockers, or medications that could induce adverse gastrointestinal reactions. The use of leukotriene antagonists was not an exclusion criterion.

Screening, randomization, and allocation

At the screening visit, informed consent and a medical history were obtained, and a physical examination, skin prick test, and nasal provocation test (NPT) were performed. Blood samples were collected to determine serum IgE, IgG, IgG$_4$, and IgA antibodies toward ragweed pollen. Subjects were allocated to placebo, medium-dose, or high-dose treatment using a block randomization scheme, with stratification based on asthma diagnosis. The allocation was concealed by using sequentially numbered containers, pharmacy control, and central randomization. The placebo (50% glycerosaline diluent) was masked by using caramel coloring. The sublingual swallow technique was used to administer treatment.

Preliminary dosing

At preliminary dosing (ie, visit 1), subjects received up to 4 incremental doses of extract (medium-dose group: 0, 0.48, 1.7, and 4.8 μg Amb a 1; high-dose group: 0, 4.8, 17, and 48 μg Amb a 1) or placebo at intervals of 15 to 20 minutes while under observation to determine maximum tolerable dose (MTD), defined as definite awareness of signs/symptoms that were bothersome but tolerable (ie, moderate). Subjects recorded all symptoms, and AEs were reviewed by investigators to determine fitness of the subject for study

continuation. Doses were increased until MTD or maximum scheduled dose was reached, and that was termed the assigned dose.

Treatment course

During the treatment course (visits 2-11), the assigned daily dose of extract or placebo was self-administered by using a 20-mL vial equipped with a metered-dose pump capable of delivering 50 or 140 μL and a sublingual actuator (Greer Laboratories, Inc); rescue medications (eg, ophthalmic, oral, and nasal antihistamines) for rhinoconjunctivitis symptoms were allowed, as were β-agonists to control asthma symptoms on an as-needed basis. Systemic steroids were not allowed for rescue medication; leukotriene inhibitors were not specifically disallowed but were not prescribed or used. Determination of dose adjustment occurred at visits 3 through 11 if the subject was not already receiving the maximum scheduled dose. If severe symptoms were reported, a dose reduction was considered; conversely, if no severe symptoms were reported, a dose increase was considered.

Subjects returned for a posttreatment (twelfth) visit after the ragweed pollen season ended, at which time a physical examination and NPT were performed. Subjects were then either discharged or followed until symptom resolution.

Subjects were allowed to discontinue treatment at any time for any reason. Investigators could discontinue treatment for the occurrence of significant side effects or serious/unexpected AEs from study drug, failure to adhere to study protocol, violations of eligibility criteria, serious intercurrent illness, or progression of disease requiring alternative treatment.

Efficacy analysis

Subjects recorded all SLIT doses administered and symptom and medication scores in the AM and PM each day using an online electronic diary system (StudyWorks; PHT Corp, Charlestown, Mass).

The primary efficacy endpoint, the daily symptom score (ie, the average of nonmissing AM and PM symptom scores), was graded as follows: 0, no sign or symptom; 1, mild symptoms (minimal awareness of sign/symptom that is clearly present but easily tolerated); 2, moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable); and 3, severe symptoms (sign/symptom is difficult to tolerate and causes interference with activities of daily living and/or sleeping). The medication score (ie, sum of individual daily scores for oral, ophthalmic, and nasal antihistamines) was graded as follows: 0, no medication taken; 1, two antihistamine eye drops; 1, two puffs of antihistamine nasal spray; 1, one puff of β-agonist; and 3, one antihistamine tablet. A symptom-medication score was also calculated by summing the daily symptom and medication scores.

Safety analysis

All AEs were described according to severity, duration, and cause. Safety was assessed by comparing the frequency of AEs in the treatment and placebo groups through review of patient diaries, self-reports, and physical examinations.

Mechanistic studies

Nasal provocation test with ragweed pollen extract was performed before and after completion of the treatment course as previously described.[17] Blood samples were obtained from subjects before and after treatment to determine serum IgE, IgG, IgG$_4$, and IgA antibodies toward ragweed pollen by using ImmunoCAP specific reagents, the ImmunoCAP 1000 system, and ImmunoCAP Data Manager software (Phadia AB, Portage, Mich), according to the manufacturer's instructions.

Statistical methodology

The average daily rhinoconjunctivitis symptom score, the primary efficacy outcome measure, was estimated to have an SD of 2.33 based on the initial phase 1 safety and dosing trial.[16] The sample size estimated to detect a
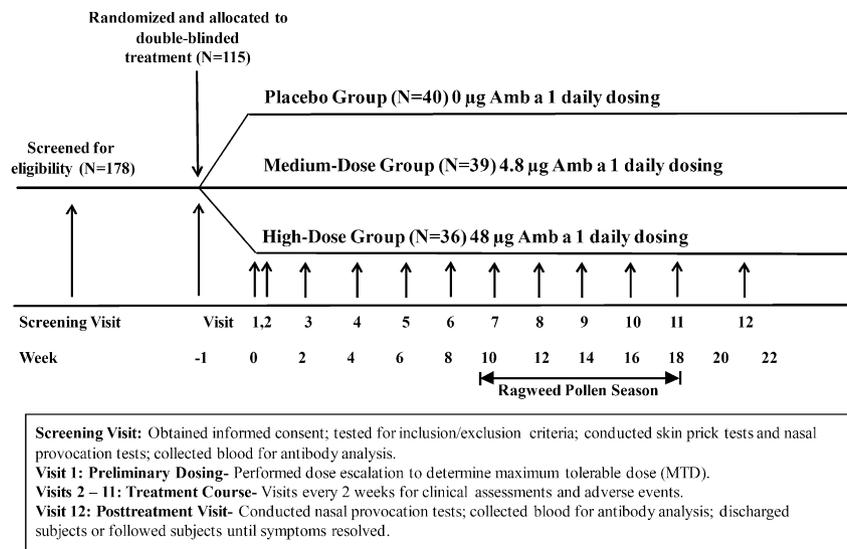
FIG 1. Study design. Timeline of screening, preliminary dosing, treatment course, posttreatment visit, and dosing adjustment/escalation. Assessments performed at each visit are shown at the *bottom* of the timeline.

minimum accepted difference of 1.50 (with a 2-sided significance level of 5% and 90% power) was 90 subjects (ie, 30 subjects in each study arm). Planned enrollment was 44 subjects in each study arm based on unbalanced allocations and a dropout rate of up to 25%.

All subjects reporting rhinoconjunctivitis symptom and medication scores during the ragweed pollen season were included in the efficacy analysis, and such scores (along with combined scores) were provided for both the entire ragweed pollen season and the peak ragweed pollen season. No data imputation was used for missing data, which were simply excluded from the analysis. Between-group analysis of symptom and medication scores, change in ragweed-specific antibody concentration, and change in NPT was performed by using an ANOVA, and the Tukey HSD (honestly significant difference) test was used to detect differences between groups. Nonparametric analysis (Kruskal-Wallis test) was used when the normality assumption was questionable. Analysis of covariance (ANCOVA) was undertaken to correct for allergens other than ragweed pollen that may have affected symptom and medication scores.

RESULTS

Baseline characteristics were similar between study arms, but men were underrepresented in the 2 active treatment arms. Skin testing showed that a majority of study participants had sensitivities to 3 other fall allergens. An asthma diagnosis was reported in <10% of subjects (Table I).

Ninety-seven of 115 enrolled subjects (84%) completed the treatment course; see this article's Fig E1 in the Online Repository at www.jacionline.org for the disposition of study participants. Reasons for withdrawal included pregnancy (n = 2), personal (n = 4), noncompliance (n = 6), and AEs (n = 6). Five of the 6 AEs occurred in subjects receiving high-dose treatment, and 1 AE occurred in the placebo group. The 5 subjects in the high-dose treatment group who withdrew because of AEs reported diverticulitis, a swollen uvula, upset stomach and eye swelling, skin rash, and nausea and cramps; the 1 subject in the placebo group who withdrew because of an AE reported lethargy and fatigue. Percent compliance was 93.3 ± 8.0 in the placebo group, 93.1 ± 7.8 in the medium-dose group, and 91.6 ± 9.7 in the high-dose group.

TABLE I. Baseline patient characteristics

	Placebo (n = 40)	Medium dose (n = 39)	High dose (n = 36)
Sex (male/female)	19/21	10/29	12/24
Mean age (y)	34.9	34.4	33.6
Age range (y)	20-50	19-49	20-49
Asthma diagnosis, no. (%)	3 (7.5)	3 (7.7)	2 (5.9)
Ethnic origin, no. (%)			
Caucasian	39 (98)	35 (90)	32 (89)
African	0	1 (2)	3 (8)
Hispanic	1 (2)	0	1 (3)
Asian	0	3 (8)	0
Skin test			
Mean ragweed wheal (mm)	7.87 ± 3.32	8.45 ± 4.35	7.61 ± 3.05
Sensitivity to other fall allergens,* no. (%)	31 (78)	27 (69)	21 (62)
Nasal provocation			
Preseasonal threshold (μg Amb a 1/mL)	1.08 ± 1.95	1.61 ± 2.46	1.48 ± 2.39

*Fall allergens include *Alternaria*, lamb's quarter, and mugwort pollen.

Thirty-two of 40 subjects (80%) in the placebo group, 27 of 39 (69%) in the middle-dose group, and 23 of 36 (64%) in the high-dose group tolerated the maximum scheduled dose. The average cumulative dose administered through the entire treatment course was 498 ± 185 μg Amb a 1/mL in the medium-dose group and 4941 ± 1487 μg Amb a 1/mL in the high-dose group. No significant difference in cumulative dose of Amb a 1 or subject tolerability was observed among the different clinical centers. Of particular note, moderate symptoms reported by subjects who received placebo were similar in rate and type to those reported by subjects in the medium-dose and high-dose groups. Mean MTD was estimated to be 3.21 (±1.64) and 30.54 (±16.14) μg Amb a 1 in the medium-dose and high-dose groups, respectively.

On average, both active treatment groups achieved a 15% reduction in total rhinoconjunctivitis symptom scores compared

TABLE II. Adjusted average daily symptom and medication scores during the ragweed pollen season

Entire pollen season	Placebo (n = 36)	Medium dose (n = 34)	High dose (n = 33)
Symptom score	1.00 ± 2.30	0.46 ± 1.40	0.19 ± 1.16*
Medication score	0.63 ± 1.06	0.16 ± 0.92	0.0003 ± 1.64*
Combined score	1.63 ± 2.99	0.63 ± 2.02	0.19 ± 2.32*

Peak pollen season	Placebo (n = 34)	Medium dose (n = 34)	High dose (n = 32)
Symptom score	1.24 ± 2.88	0.74 ± 1.95	0.53 ± 1.35
Medication score	1.01 ± 2.07	0.40 ± 1.35	0.28 ± 0.70*
Combined score	2.25 ± 4.25	1.14 ± 3.03	0.81 ± 1.74

Average scores are presented as means after adjustment (subtraction) using respective baseline preseasonal scores as the covariate.

*$P \leq .05$. The P value is with respect to placebo; no significant differences were noted between treatment groups.

with placebo during the entire ragweed pollen season, but the difference was not statistically significant ($P > .10$). Using ANOVA, the mean average daily symptom scores during the entire pollen season were 3.27 (±2.60), 2.78 (±1.93), and 2.77 (±2.07) in the placebo, medium-dose, and high-dose groups, respectively; average daily medication scores were 1.34 (±1.77), 0.84 (±1.63), and 0.66 (±1.16), respectively. Nonparametric Kruskal-Wallis tests were significant for rescue medication scores during the peak ragweed pollen season ($P = .048$).

Analysis of covariance was used to correct for baseline differences in symptom scores (Table II). The covariate was defined as the baseline mean daily rhinoconjunctivitis symptom score recorded before the start of the ragweed pollen season. Using ANCOVA, adjusted average daily symptom scores during the entire pollen season in the placebo, medium-dose, and high-dose groups were 1.00 (±2.30), 0.46 (±1.40), and 0.19 (±1.16; medium-dose vs placebo, $P = .19$; high-dose vs placebo, $P = .05$; and medium-dose vs high-dose, $P = .51$). Adjusted average daily medication scores were 0.63 (±1.06), 0.16 (±0.92), and 0.0003 (±1.64) in the placebo, medium-dose, and high-dose groups, respectively (medium-dose vs placebo, $P = .12$; high-dose vs placebo, $P = .04$; and medium-dose vs high-dose, $P = .59$). The average combined symptom-medication scores in the placebo, medium-dose, and high-dose groups were 1.63 (± 2.99), 0.63 (± 2.02), and 0.19 (± 2.32), respectively (medium-dose vs placebo, $P = .10$; high-dose vs placebo, $P = .02$; and medium-dose vs high-dose, $P = .47$). Combined symptom-medication scores are provided in Fig 2.

Mechanistic studies

A matched-pair analysis of pretreatment and posttreatment ragweed-specific IgE antibody showed statistical significance across subjects ($P = .0004$), but not across groups ($P = .084$). A statistically significant difference was found between high-dose treatment and placebo for ragweed-specific IgG antibody response ($P = .006$). Ragweed-specific IgE, IgG, IgG_4, and IgA responses are shown in this article's Table E1 in the Online Repository at www.jacionline.org.

Increased tolerance to NPT was observed in subjects from all groups after the treatment course ($P < .01$); however, testing across groups did not demonstrate statistical significance (see this
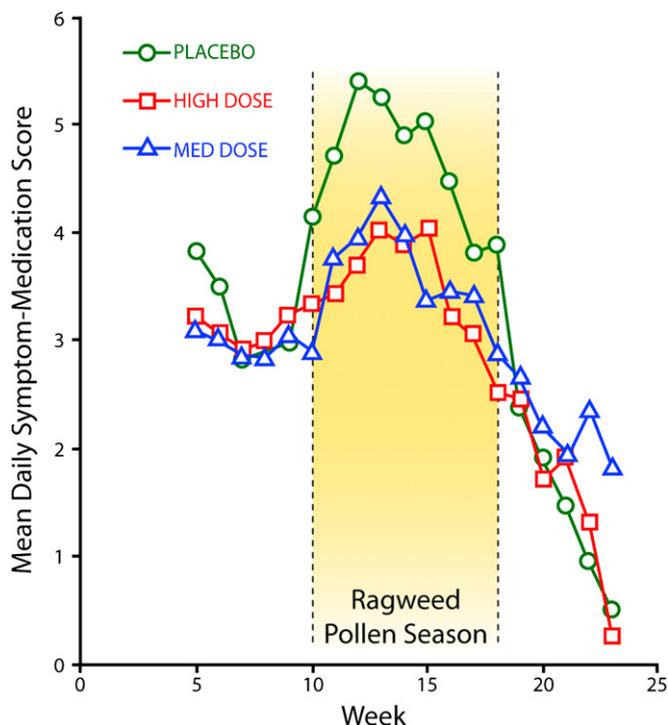

FIG 2. Combined symptom-medication scores. Line graphs of mean daily combined symptom-medication scores by treatment group.

article's Table E2 in the Online Repository at www.jacionline.org). The mean increase in NPT threshold concentration after treatment (calculated from paired data sets) was 0.89 μg/mL in subjects receiving placebo, 0.91 μg/mL in those receiving medium-dose extract, and 1.38 μg/mL in those receiving high-dose extract.

Safety analysis

This article's Table E3 in the Online Repository at www.jacionline.org summarizes the frequency of AEs reported during the treatment phase. A total of 202 AEs (placebo, n = 67; medium-dose, n = 65; high-dose, n = 70) were reported, with frequency ranging from 56% in the high-dose group to 73% in the placebo group; however, the difference was not statistically significant ($P > .10$). AEs attributed to SLIT were based solely on the judgment of the clinical investigator relative to the association of the administration of SLIT to the occurrence of the event.

Thirteen of the 202 AEs (6%) were classified as severe, 4 AEs (2%) were deemed serious, and 1 additional AE was considered life-threatening. Three of the 13 severe AEs were reported by 2 subjects in the placebo group, and 10 of the severe AEs were reported by 6 subjects in the active treatment groups. The 4 serious AEs occurred in 1 subject in the placebo group (gall bladder surgery), 1 subject in the medium-dose treatment group (life-threatening blood clot in the leg), and 2 subjects in the high-dose treatment group (spontaneous abortion, n = 1; sigmoid diverticulitis, n = 1).

Adverse events occurred most commonly in respiratory, gastrointestinal, dermatologic, and musculoskeletal systems, and frequency of AEs in these body systems was similar between study arms. No asthma-related AEs occurred. Oral-mucosal AEs

occurred more often with medium-dose (13%) and high-dose (11%) treatment than placebo (0%; $P = .01$).

Contingency analysis of severe AE data showed no statistically significant difference between placebo and medium-dose treatment ($P = .74$) or between placebo and high-dose treatment ($P = .33$).

DISCUSSION

In this clinical trial, 2 daily maintenance doses (4.8 and 48 μg Amb a 1) of sublingual standardized glycerinated short ragweed pollen allergenic extract were compared with placebo in adults with rhinoconjunctivitis caused by ragweed pollen. The medium-dose and high-dose strategies corresponded to approximately 10 and 100 times, respectively, the monthly cumulative SCIT maintenance dose. On average, subjects receiving active treatment achieved a 15% reduction in total rhinoconjunctivitis symptom scores, the primary endpoint, during the entire ragweed pollen season compared with those receiving placebo, but the difference was not statistically significant. In addition, medication scores were reduced by 37% in the medium-dose group and 51% in the high-dose group; the reduction approached statistical significance in the latter group during the entire pollen season and was statistically significant during the peak pollen season. An increase in efficacy was observed in the high-dose group, as reflected in a reduction in the use of antiallergy medication; however, this added benefit could have been offset by increased withdrawals as a result of treatment-related complaints. The case can be made that statistical significance was not reached for reduction in symptom scores because of the higher use of rescue medication in the placebo group. For ethical reasons, subjects were provided with registered rescue medication to alleviate symptoms and thus reduce symptom scores. This effect may have biased the mean difference in symptom scores between effective treatment and placebo toward 0.[18]

Sublingual immunotherapy induced ragweed-specific IgE, IgG, IgG$_4$, and IgA in the serum of actively treated subjects, whereas only ragweed-specific IgE antibody levels were increased in the serum of placebo-treated subjects. These findings are consistent with previous reports of successful SLIT using high doses of standardized allergenic extracts[6,7,19,20] and support the hypothesis that immunologic changes induced by SLIT are similar to those associated with SCIT.[21] Thus, at sufficiently high doses, systemic immunologic response can be induced by SLIT. Both the medium and high doses, representing a 10-fold difference in allergen dose, induced comparable ragweed-specific antibody responses in this study. Although the role of so-called "blocking antibodies" in allergen immunotherapy has been debated, their increase during the course of allergen immunotherapy has been correlated with improved clinical outcome.[19,22-24]

The NPT can be useful in monitoring the efficacy of ragweed-specific immunotherapy in patients with allergic rhinitis.[25-27] Increases in threshold concentrations required to induce a positive NPT have been correlated with effective treatment. In this study, all groups, including the placebo group, showed a significant increase ($P < .05$) in posttreatment NPT threshold concentrations. Thus, the increases in allergen dose required to induce a positive NPT among the actively treated subjects were not statistically significant relative to placebo-treated subjects ($P = .74$).

The NPT results in the placebo group differed from those of Connell and Sherman,[28] who reported a priming effect, whereby individuals who received repetitive exposure to pollen required lesser amounts of that pollen to induce the same symptom level. Although others have been unable to reproduce these results,[29] possible explanations for the apparent discrepancy include the variability in procedure and difficulties in standardizing provocation tests performed at different study sites. In the current study, such variability was reduced by using the same sprayers, extract lot, diluent, scoring system, and protocol across study sites. Alternatively, this finding may simply represent a placebo effect.

The current study has some important limitations. One limitation is that 90% of study participants were sensitized to multiple perennial and/or seasonal allergens, suggesting that symptoms contributing to the magnitude and variability of rhinoconjunctivitis symptom scores may have been caused by allergens other than ragweed pollen. Ideally, the current study would have assessed efficacy in subjects allergic to ragweed without any overlapping cosensitizations, determined the most safe and effective dose of SLIT, and then tested SLIT efficacy in a trial with polysensitized patients. Polysensitization is often a factor in monotherapy studies; however, such studies do not represent the general approach to immunotherapy in the United States.[4,5] In the current study, ANCOVA used to adjust for this possibility showed that medium-dose and high-dose treatment led to reductions in symptom scores of 40% to 50% and 60% to 80%, respectively, compared with placebo. Well controlled, multiallergen immunotherapy trials in polysensitized individuals are needed to assess more accurately the efficacy of SLIT in this subgroup.

Another potential study limitation is the lack of a run-in pollen season. Some investigators have suggested that the absence of a baseline assessment over a run-in pollen season could potentially compromise the randomization process, thereby leading to a possible imbalance among treatment arms in terms of symptom severity and other outcome measures.[30] Notably, the position of the World Allergy Organization taskforce is that the inclusion of a baseline period of observation (ie, 1 pollen season before randomization) is correct in principle, but unadvisable (or at least not mandatory).[31] The rationale for the World Allergy Organization recommendation is that a run-in period is expensive and time-consuming because of fluctuations in the level of indoor allergens and the unpredictability and variability in allergenic exposure to pollen allergens.[31] Other limitations and factors related to most (if not all) allergen immunotherapy trials include the use of subjective endpoint measures based on symptom scores, variability in the magnitude of natural pollen exposure between and within geographical locations, and variability in patient sensitivity.

Not all subjects achieved the MTD in their respective groups, including those in the placebo group. Many reasons can be cited as to why this dose was not achieved in some subjects: (1) the study drug may not have been taken during vacations or time spent outside of the study area; (2) some subjects may have experienced sinusitis or headaches; (3) tolerance to the study drug differed by subject; (4) determining the necessity of dose adjustment was difficult at the beginning of the pollen season, because some subjects experienced symptoms as a result of natural exposure to pollens; and (5) AEs in the placebo group occurred more often at the third or fourth step of dose escalation, a pattern that may have emerged because the caramel color in the placebo became darker with each dose (ie, a psychological effect).

The frequency and type of AEs were similar among treatment groups; however, as the dose increased, AEs tended to be attributed to SLIT. Severe AEs that could not be definitively

attributed to SLIT included spontaneous abortion, headache, nausea, abdominal pain, acute cholecystitis, and sigmoid diverticulitis; no AEs required the use of epinephrine. Importantly, safety and efficacy results supported the self-administration of SLIT at home under the supervision of an allergy specialist. Although most AEs in SLIT studies have been mild, and no life-threatening AEs or deaths have been reported in the literature,[2,4] safety precautions implemented in the current study (eg, distribution and training in the use of epinephrine) should continue to be practiced until the safety profiles of SLIT products have been established in other patient populations.

Data from numerous studies have demonstrated that both SCIT and SLIT are more effective than placebo in patients with allergic rhinitis/rhinoconjunctivitis.[2,7,15,32-34] In a meta-analysis of 15 trials (n = 1063), symptom scores were significantly reduced in patients with seasonal allergic rhinitis receiving SCIT compared with those receiving placebo (significant mean difference [SMD], –0.73; 95% CI, –0.97 to –0.50; $P < .00001$); similarly, in a meta-analysis of 13 trials (n = 963), medication scores were significantly reduced with SCIT compared with placebo (SMD, –0.57; 95% CI, –0.82 to –0.33; $P < .00001$).[33] A systematic review and meta-analysis of 22 clinical trials (n = 979) found a significant reduction in symptoms (SMD, –0.42; 95% CI, –0.69 to –0.15; $P = .002$) and medication scores (SMD, –0.43; 95% CI, –0.63 to –0.23; $P < .00003$) in patients with allergic rhinitis receiving SLIT compared with those receiving placebo.[35] The effectiveness of SLIT has been demonstrated with mites, grass and tree pollens, and ragweed, with the level of symptom and medication reduction ranging from 20% to 60%.[2]

In summary, the findings of the current study indicate that standardized glycerinated short ragweed pollen allergenic extract administered by sublingual swallow at daily maintenance doses of 4.8 to 48 μg Amb a 1 is safe and shows potential as an effective therapy in adults with rhinoconjunctivitis caused by ragweed pollen.

Clinical implications: Standardized glycerinated short ragweed pollen extract administered sublingually may be a viable treatment option in patients with ragweed-induced rhinoconjunctivitis.

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┌─────────────────────┐
│    178 Subjects     │
│ Screened for        │
│ Eligibility         │
└──────────┬──────────┘
           │
           ▼
┌─────────────────────┐
│    115 Subjects     │
│ Randomly Allocated  │
│ to Treatment Groups │
└──────────┬──────────┘
           │
```

40 Subjects Allocated to Placebo Group	39 Subjects Allocated to Medium-Dose Group	36 Subjects Allcoated to High-Dose Group
Withdrawals: 6 Reasons: Adverse event: 1 Noncompliance: 2 Personal reason: 3	Withdrawals: 5 Reasons: Adverse event: 0 Noncompliance: 3 Personal reason: 1 Pregnancy: 1	Withdrawals: 7 Reasons: Adverse event: 5 Noncompliance: 1 Personal reason: 0 Pregnancy: 1

FIG E1. Disposition of participants.

TABLE E1. Ragweed-specific antibody responses

	Placebo	Medium dose	High dose
IgE (kU/L)	n = 35	n = 31	n = 31
Mean change	2.55 ± 4.14	25.93 ± 52.83	19.75 ± 56.77
95% CI	0.63 to 1.06	6.55 to 45.31	−1.07 to 45.31
IgG (mg/L)	n = 35	n = 31	n = 28
Mean change	−0.08 ± 1.81	1.69 ± 3.98	2.29 ± 3.97*
95% CI	−0.70 to 0.54	0.23 to 3.15	0.75 to 3.83
IgG4 (mg/L)	n = 32	n = 30	n = 26
Mean change	−0.09 ± 0.77	0.64 ± 1.65*	0.52 ± 0.94
95% CI	−0.37 to 0.20	0.02 to 1.26	0.14 to 0.90
IgA (mg/L)	n = 35	n = 31	n = 28
Mean change	−0.005 ± 0.076	0.041 ± 0.169	0.068 ± 0.152
95% CI	−0.031 to 0.021	−0.021 to 0.103	0.009 to 0.127

*$P \leq .05$. The P value is with respect to placebo; no significant differences were noted between treatment groups.

TABLE E2. Nasal provocation responses

	Placebo (n = 31)	Medium dose (n = 34)	High dose (n = 28)
Before treatment	1.05 ± 1.84	1.64 ± 2.51	1.69 ± 2.45
After treatment	1.94 ± 2.69	2.56 ± 2.98	3.07 ± 3.20
Mean change	0.89 ± 2.41	0.91 ± 2.61	1.38 ± 3.23
95% CI	0.022-1.762	0.002-1.823	0.155-2.609

Responses in terms of threshold μg/mL concentrations of Amb a 1 delivered in 100 μL.

TABLE E3. Summary of adverse events*

	Placebo		Medium dose		High dose	
	No. (%)	AEs	No. (%)	AEs	No. (%)	AEs
No. of subjects	40		39		36	
All AEs	29 (73)	67	25 (64)	65	20 (56)	70
Causality*						
Definitely related	0 (0)	0	1 (2)	1	1 (3)	1
Probably related	3 (8)	5	3 (8)	6	1 (3)	1
Possibly related	4 (10)	7	3 (8)	5	9 (25)	16
Probably not related	12 (30)	20	12 (31)	19	11 (31)	31
Definitely not related	17 (43)	35	21 (54)	34	7 (19)	21

*Adverse events attributed to SLIT were based solely on the judgment of the clinical investigator relative to the association of the administration of SLIT to the occurrence of the event. *Definitely related,* event can be fully explained by administration of the study drug, ie, both AEs were sublingual-oral swelling; *probably related,* event is most likely to be explained by administration of the study drug rather than the subject's clinical state or other agents/therapies, ie, nausea, diarrhea, rhinoconjunctivitis, headache, sinus congestion, and oral-mucosal itching; *possibly related,* event may be explained by administration of the study drug or by the subject's clinical state or other agents/therapies, ie, nausea, diarrhea, abdominal pain, rhinoconjunctivitis, headache, oral-mucosal itching, fatigue, sigmoid diverticulitis; *probably not related,* event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the study drug; *definitely not related,* event can be fully explained by the subject's clinical state or other agents/therapies.