Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis

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Background: Sublingual immunotherapy with liquid extracts provides an appealing alternative to subcutaneous immunotherapy for the treatment of allergic rhinoconjunctivitis (ARC), but a lack of robust evidence has deterred its use in North America.

Objective: To determine the efficacy and tolerability of standardized glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related ARC.

Methods: This phase 3, randomized, placebo-controlled trial was conducted in North America. Subjects (age range, 18-55 years) with or without asthma were selected based on ARC symptom severity and erythema skin prick reaction to short ragweed. Subjects self-administered the maximum tolerated dose of RW-SAIL (n = 218) or placebo (n = 211) daily beginning approximately 8 to 16 weeks before and through the end of the ragweed pollen season. The primary end point was subject-assessed total combined daily rhinoconjunctivitis symptom and medication scores (TCS).

Results: During the entire season, there was a 43% decrease in TCS in subjects treated with RW-SAIL compared with placebo. Similar decreases were observed in TCS between the 2 groups during peak season (42%) and in daily symptom scores during the entire (42%) and peak (41%) seasons. The occurrence of adverse events was similar between the treatment groups; most were mild in severity. Treatment-related oromucosal local application site reactions occurred early and were transient and self-limited. No anaphylaxis occurred.

Conclusions: This is the first successful North American confirmatory phase 3 clinical trial to demonstrate the safety and efficacy of a sublingual standardized ragweed allergen immunotherapy liquid extract for the treatment of ARC. (J Allergy Clin Immunol 2014;133:751-8.)

Key words: *Allergen-specific IgE, allergen-specific IgG$_4$, allergy immunotherapy, combined score, ragweed, specific immunotherapy, sublingual immunotherapy*

Subcutaneous immunotherapy has been the conventional mode of therapy in the United States and Canada for patients with seasonal allergic rhinoconjunctivitis (ARC) and milder asthma that is unresponsive to pharmacotherapy.[1] This effective form of treatment is burdened, however, by a prolonged injection schedule,[2] patient noncompliance due to frequent physician visits necessitated by the regimen,[3] the discomfort associated with injections,[4] and the recognized risk of anaphylaxis.[1] Sublingual immunotherapy (SLIT) represents an alternative mode of treatment that may afford a safe, convenient, and effective treatment modality for the management of allergic respiratory disease.[2,5,6] Sublingual aqueous forms of immunotherapy have been espoused in Europe, and various studies have shown degrees of improvement with pollens and dust mite.[4,7] However, SLIT is not approved by the US Food and Drug Administration (FDA), and it is used off-label with limited safety or dose-defining efficacy studies.[8-13]

Ragweed, the dominant seasonal aeroallergen for much of North America,[14] causes significant morbidity, is associated with disease sequelae, and adversely affects the economic burden. The objective of this study was to demonstrate the efficacy and tolerability of SLIT with a standardized glycerinated short ragweed allergenic extract in adult subjects with ragweed-pollen-related ARC, with or without mild asthma. Here, we report the first successful confirmatory phase 3 clinical trial to demonstrate the tolerability and efficacy of a standardized ragweed sublingual allergen immunotherapy liquid extract (SAIL) (Greer SAIL, Greer Laboratories Inc, Lenoir, NC).

METHODS

Study design and oversight

This phase 3, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT01353079) was conducted at 26 US and Canadian centers from April 2011 (before the natural ragweed pollinating season) until

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Abbreviations used

AE: Adverse event
ANCOVA: Analysis of covariance
ARC: Allergic rhinoconjunctivitis
DSS: Daily symptom score
FDA: US Food and Drug Administration
ITT: Intent to treat
LS: Least squares
MTD: Maximum tolerated dose
RW-SAIL: Ragweed sublingual allergen immunotherapy liquid extract
SLIT: Sublingual immunotherapy
TCS: Total combined symptom score and medication score
TRAE: Treatment-related adverse event

November 2011 (the end of the 2011 ragweed pollen season). Eligible subjects were randomized (1:1) by an interactive voice response system according to a computer-generated block-randomization scheme into ragweed SAIL (RW-SAIL) or to placebo groups. The study drug was administered sublingually, held under the tongue for up to 2 minutes, and then the residual was swallowed. Double blinding was ensured through use of a placebo identical to RW-SAIL in taste and appearance. Blinding was maintained until the database was locked. No fewer than 8 but no more than 16 weeks before the ragweed pollen season, all the subjects received a single subject-blinded placebo dose (Fig 1). The patients who reacted to that dose in the 15-20 minute follow-up were eliminated from the trial; those who could tolerate the initial dose received up to 2 incremental RW-SAIL doses (approximately 18 μg Amb a 1 or approximately 50 μg Amb a 1) or placebo at 15- to 20-minute intervals while being observed by the clinic staff. The dose was increased to the maximum tolerated dose (MTD) unless the subject experienced bothersome but tolerable symptoms. The MTD for each subject served as the subject's starting study dose. The MTD was self-administered once daily in the morning before food until the end of the ragweed pollen season. The subjects were provided with self-injectable epinephrine in case of a severe allergic reaction to treatment and as-needed antiallergy medications (loratadine 10 mg oral tablet once daily; olopatadine 0.1%, 1 drop twice daily) to use in a stepwise manner during the ragweed season for relief of moderate-to-severe ARC symptoms. Use of β-agonists was allowed for the subjects with asthma. The subjects were seen by the investigator every 30 days (±7 days) during the treatment phase of the study. Treatment compliance was assessed by using daily electronic diary entries, and treatment vials were inspected during the monthly visits to confirm adherence to the dosing regimen. The subjects recorded each dose in their diary and were referred for further training if compliance dropped below 80%.

Ragweed pollen season was defined as starting on the first day in which ragweed pollen counts were >10 grains/m^3 and ending on the first of 3 consecutive days in which ragweed pollen counts were <5 grains/m^3. The peak season was defined as the maximal 3 noncontiguous peak weeks of pollen counts over the course of the season for each study site, as determined by calculating a moving average of the available pollen counts for each week.

This study was conducted in accordance with the Declaration of Helsinki and the guidelines of the FDA and the International Conference on Harmonisation (Good Clinical Practices). The protocol was approved for each center by institutional review boards; written informed consent was obtained from all the subjects. The study sponsor and we were responsible for study design and/or data collection, data analysis, and manuscript preparation. We attest to the completeness and accuracy of the presented data.

Study population

Subjects, ages 18 to 55 years, with ragweed-related ARC, with or without mild intermittent asthma were included in the study. The subjects had a ≥2-year history of moderate-to-severe ragweed-related ARC symptoms that required antiallergy medications. An orthogonal sum of erythema skin prick test reaction ($\sum$E) ≥60 mm to short ragweed allergenic extract 15 to 20 minutes after application was required. Skin prick tests (Greer Pick; Greer Laboratories) were performed with allergenic extracts, saline solution, and histamine controls. Subjects with a history of anaphylaxis or a history of persistent or unstable asthma were excluded. Other exclusion criteria included ARC symptoms attributable to perennial allergens that overlapped the ragweed season, a history of symptomatic perennial ARC to an allergen to which the subject was regularly exposed, or inability to achieve dose 2 (approximately 18 μg Amb a 1) or higher during preliminary dosing. Subjects who were polysensitized based on skin prick tests in the absence of symptoms were allowed in the trial.

Clinical and safety assessments

The primary efficacy measure was the net average daily rhinoconjunctivitis total combined symptom score and medication score (TCS) during the entire ragweed pollen season. The subjects recorded daily morning and evening symptoms and antiallergy medication use in an electronic diary. Ocular (itchiness, swelling and/or redness, and watery eyes and/or tears), nasal (sneezing, itching, runny nose, and stuffy nose), and aural (itching) symptoms were assessed and rated on an ordinal scale from 0 (no symptoms) through 3 (severe symptoms). Relief medication use was scored as 1 point for each daily use of oral or ocular antihistamine or albuterol treatment (excluding albuterol use before exercise). The TCS score was derived from the ocular (3 components) plus nasal (4 components) plus aural (1 component) (scored, 0-3; maximum symptom score, 24) plus the medication score (1 point for each medication use; maximum medication score, 3). The potential maximum TCS was 27.

Secondary efficacy variables were the TCS during the peak season, net average rhinoconjunctivitis daily symptom score (DSS) reported during the entire season, and the DSS during the 3 peak weeks of the season. Short ragweed specific IgG_4 and IgE antibody levels were exploratory end points evaluated from serum samples (ImmunoCap; Phadia AB, Uppsala, Sweden) collected at screening and the final study visit.

Safety was evaluated by adverse events (AE) self-reported by the subjects, concomitant medication use, vital signs, clinical laboratory evaluations, and changes in physical examinations. AEs were characterized for date and time of onset, duration, severity, and causal relationship with the study drug or other factors.

Statistical analysis

The intent-to-treat (ITT) population included all randomized subjects who received at least 1 dose of double-blinded study medication and who had at least 1 postdose efficacy assessment. The per-protocol population included subjects who met all inclusion and exclusion criteria, had no major protocol violations, and had at least 4 days of valid baseline data and at least 2 valid weeks of data during the entire pollen season. The safety population included all randomized subjects who received at least 1 dose of study medication. A sample size of 188 subjects in each group had 90% power to detect a difference of −1.44 in TCS means between the treatment groups by using a 2-group Satterthwaite *t* test with an SD of 2.9 and a 0.05 2-sided significance level. The sample size was increased by 10% to account for dropouts, which resulted in an estimated 209 subjects per treatment group. A clinically meaningful difference was defined as a 20% decrease in TCS in RW-SAIL versus placebo. Sensitivity testing for missing data for the primary end point included the use of the last-observation-carried-forward method by using the last data available before dropout on posttreatment assessments only, the use of the last-observation-carried-forward method on morning and evening symptom scores separately, examination of the rate of missing data in primary end-point scores between treatment groups, and the use of matched pairs.

Descriptive statistics were used for baseline, posttreatment, and change from baseline by treatment. Baseline symptom scores were determined during the week immediately before the ragweed season; at least 4 days of usable data were required. Efficacy end points were assessed in the ITT population. Analysis of covariance (ANCOVA) was performed to compare the active and