Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen

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Background: Specific immunotherapy acts to modify the underlying cause of allergic rhinoconjunctivitis. Addition of adjuvants, such as monophosphoryl lipid A (MPL), might allow for efficacious and safe treatment with only 4 injections administered preseasonally, which is in contrast to most available schedules requiring long injection courses.

Objective: The primary objective was to assess the clinical efficacy of Ragweed MATA MPL (short ragweed pollen allergoid adsorbed to L-Tyrosine + MPL) versus placebo in reducing allergic rhinoconjunctivitis symptoms caused by ragweed pollen in an environmental exposure chamber (EEC) 3 weeks after treatment.

Methods: This was a randomized, double-blind, placebo-controlled phase IIb study to evaluate the clinical efficacy and safety of Ragweed MATA MPL compared with placebo by using controlled ragweed pollen exposure in an EEC. Two hundred twenty-eight patients with a history of ragweed allergy and positive skin prick test responses to ragweed were randomized and received 4 weekly injections of active treatment or placebo. Total nasal and nonnasal symptom scores were obtained in the EEC before and after treatment.

Results: Mean improvement in total symptom scores in the Ragweed MATA MPL group was statistically significantly greater than in the placebo group (relative mean improvement of active vs placebo, 48%; $P < .05$; median improvement, 82%). The majority of adverse events (AEs) experienced by subjects were mild injection-site reactions. No severe systemic AEs or serious AEs occurred during the study.

Conclusion: This study demonstrated that an ultrashort course of Ragweed MATA MPL is efficacious in reducing allergy symptoms in patients with seasonal allergic rhinitis and that it is well tolerated. (J Allergy Clin Immunol 2014;133:121-9.)

Key words: *Allergic rhinoconjunctivitis, specific immunotherapy, ragweed, ultrashort course, environmental exposure chamber*

Allergic rhinoconjunctivitis (AR) is a common type I allergic disease caused by exposure of the mucosa to aeroallergens, such as pollen, animal dander, or dust mite residues. It is estimated to affect up to 30% of the populations in industrially developed countries,[1-3] and this has been increasing over the last few decades.[4-7] AR is a chronic inflammatory disease, and although it is rarely life-threatening, common allergy symptoms, such as nasal congestion, sneezing, rhinorrhea, and ocular symptoms, often have a significant effect on quality of life. Moreover, AR is considered a risk factor for asthma, and current understanding suggests an underlying relationship between the 2 diseases.[8,9]

Specific immunotherapy (SIT) with allergen extracts is the only available treatment strategy directly addressing the underlying mechanism of allergic conditions.[10-12] SIT significantly reduces allergy symptoms and the use of symptomatic medication in appropriately selected patients with AR[8,13,14] and has been associated with long-term benefits after repeated courses of therapy.[15-18] If administered in accordance with current recommendations, SIT generally is safe and well tolerated, and the risk for serious systemic reactions is low.[13,19] However, the use of SIT is limited by the high number of injections required in conventional therapies, which might lead to decreased patient compliance and a greater chance of adverse effects.

Ragweed MATA MPL is a preparation containing modified short ragweed *(Ambrosia artemisiifolia)* pollen allergoid adsorbed onto tyrosine and with the adjuvant monophosphoryl lipid A (MPL). It is a novel ultrashort-course SIT for the treatment of seasonal allergic rhinitis (SAR) caused by ragweed pollen allergen that is administered in only 4 weekly preseasonal injections.

Modification with glutaraldehyde improves the tolerability of the product by reducing reactivity with IgE antibody while maintaining other important immunologic properties, such as IgG and T-cell activities.[20] The adsorption of the allergoid onto tyrosine results in controlled release, further improving product safety.[21] A novel characteristic of Ragweed MATA MPL is the addition of MPL adjuvant (derived from the LPS of the bacterium *Salmonella minnesota*), which assists in redressing a healthy balance between T_H1- and T_H2-type activity and enhances production of allergen-specific IgG.[22-26] The combination of these 3 features, allergen modification, tyrosine adsorption, and addition of MPL, allows for effective and safe annual treatment with only 4 doses.[23,27-29]

The environmental exposure chamber (EEC) is an ideal setting in which to test aeroallergen exposure in human subjects under

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Abbreviations used
AE: Adverse event
AR: Allergic rhinoconjunctivitis
EEC: Environmental exposure chamber
ITT: Intention to treat
MPL: Monophosphoryl lipid A
PP: Per protocol
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
SAR: Seasonal allergic rhinitis
SIT: Specific immunotherapy
SU: Standardized units
TSS: Total symptom score

controlled and reproducible conditions.[30] Furthermore, clinical studies assessing allergic rhinitis in an EEC are encouraged by the US Food and Drug Administration.[31] The EEC offers a more controlled environment compared with natural pollen exposure, during which variables such as unpredictable pollen levels, varying weather conditions, and varying levels of pollen exposure are eliminated. The symptomatic response of patients with rhinitis in the EEC is similar to the response outdoors during a peak pollen day.[30]

This randomized, double-blind, placebo-controlled study evaluated Ragweed MATA MPL for efficacy, tolerability, and safety compared with placebo in adults with moderate-to-severe SAR caused by ragweed pollen exposure in an EEC 3 weeks after completing SIT treatment. The study also included a reference group treated with Ragweed MATA (without MPL).

METHODS

This was a randomized, double-blind, placebo-controlled phase IIb study (ClinicalTrials.gov registration no. NCT00110786) that was conducted at a single site in Canada (Allied Research International, Mississauga, Ontario, Canada). This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and with Good Clinical Practice guidelines. Written informed consent was obtained from all subjects. The protocol was approved by IRB Services Canada (Aurora, Ontario, Canada).

Subject population

Healthy male and female subjects 18 to 65 years of age with a minimum 2-year clinical history of SAR who were allergic to ragweed pollen, as defined by a positive case history, positive skin prick test response (wheal diameter >3 mm), positive RAST or equivalent test result (class ≥2), and minimum qualifying score in the 2 final pretreatment EEC sessions (total symptom score [TSS] on ≥1 symptom diary card of ≥10 of a maximum 24 and total nasal symptom score of ≥6 of a maximum 12). Subjects were not monosensitized to ragweed but were excluded if they were symptomatic for interfering allergies other than ragweed pollen at screening (after the washout of antiallergy medication) or if they had contraindications for SIT, a disturbed tyrosine metabolism, a clinical history of immunodeficiency, or any other conditions that might have affected the subject's safety or the interpretation of study results. All randomized subjects constituted the intention-to-treat (ITT) analysis set. The per-protocol (PP) set included subjects without major protocol violations.

Study materials

- *Ragweed MATA MPL*: short ragweed *(A artemisiifolia)* pollen allergoid (300, 700, 2000, and 6000 standardized units [SU]/0.5 mL) adsorbed onto L-tyrosine 2% wt/vol plus 50 μg/0.5 mL of MPL.

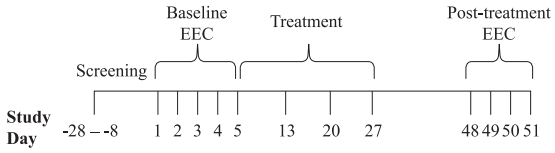

FIG 1. Study design.

- *Ragweed MATA (without MPL)*: short ragweed pollen allergoid (300, 700, 2000, or 6000 SU/0.5 mL) adsorbed onto L-tyrosine 4% wt/vol.
- *Placebo vehicle*: L-tyrosine 2% wt/vol.

All formulations were manufactured by Allergy Therapeutics (West Sussex, United Kingdom).

Study design

Subjects were randomized (1:1:0.4) to receive either Ragweed MATA MPL, matching placebo, or Ragweed MATA injections (a product with a dose regimen and formulation similar to those of Ragweed MATA MPL but without MPL). Eligible patients were randomized sequentially as they qualified. The numeric series of patient randomization numbers contained a built-in randomization, such that patients were randomly assigned to treatment groups in accordance with the planned assignment ratio. This was a double-blind study; no participants (including the patients, investigators, site staff, site pharmacist, or other staff) were aware of the treatment assignments before database lock and unblinding. The study evaluated the clinical efficacy and safety of Ragweed MATA MPL compared with placebo and a Ragweed MATA reference group by using an EEC to expose patients with ragweed allergy to ragweed pollen in a controlled environment. Each subject received 4 weekly subcutaneous 0.5-mL injections of increasing dose strength, as indicated above. Subjects who experienced large local or mild systemic reactions could receive additional unscheduled injections of repeated doses to help with adjustment to higher doses. The study consisted of 4 periods: screening, baseline EEC, treatment, and posttreatment EEC. All visits were conducted outside the natural ragweed pollen season (Fig 1). Antiallergy medications were prohibited during the study.

EEC

The EEC is a clinical research facility specifically designed to allow controlled and consistent exposure to airborne pollen particles. The EEC was validated to provide an average airborne ragweed pollen concentration of 3500 ± 500 grains/m^3. While the chamber was in operation, pollen levels were assessed and documented every 30 minutes (±5 minutes). Greer Laboratories (Lenoir, NC) supplied the short ragweed pollen *(A artemisiifolia)* dispersed in the EEC.

Subjects were exposed to ragweed pollen in the EEC for 2 series of sessions, one taking place before treatment (baseline EEC visits) and the second approximately 3 weeks after the end of treatment (posttreatment EEC visits). The baseline EEC visits, as well as the posttreatment EEC visits, consisted of 4 consecutive daily sessions of 3 hours each, with an interval of approximately 24 hours between sessions. Each series consisted of 4 EEC visits to more closely simulate inflammatory changes and symptoms seen in the natural course of disease caused by repeated daily pollen exposures (or priming).[30,32]

Assessments

TSSs. The TSS was defined as the sum of individual scores for nasal symptoms (rhinorrhea, congestion, sneezing, and itchiness) and nonnasal symptoms (itchy/gritty eyes, tearing/watery eyes, red/burning eyes, and ear/palate itching). A 4-point scale was used for evaluation of the above symptoms: 0, none; 1, mild; 2, moderate; and 3, severe. Subjects recorded their AR symptoms at 30-minute intervals during ragweed pollen exposure. Symptom diary cards for each visit were averaged. For analysis, the average scores of the 4 baseline EEC visits were compared with the average scores of the 4 posttreatment EEC visits.