

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 2013;■■■:■■■-■■■.)

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

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

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

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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 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.
- **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

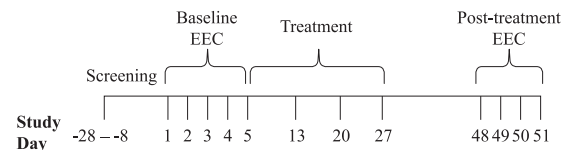


FIG 1. Study design.

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/m³. 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.

Responders were defined (retrospectively) as subjects with an improvement in TSSs of more than 5 points (ie, greater than the mean placebo response in this study). This corresponds to approximately 30% of the mean baseline value in all treatment groups.

Rhinoconjunctivitis Quality of Life Questionnaire for use in the EEC. Subjects were asked to complete the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for use in the EEC (RQLQ-EEC)³³ twice at each EEC session, once before entering the EEC and once at the end of the EEC session. The RQLQ-EEC administered before entering the

TABLE I. Demographics and baseline characteristics of subjects

Variable	ITT set			PP set		
	Ragweed MATA MPL (n = 95)	Ragweed MATA (n = 40)	Placebo (n = 93)	Ragweed MATA MPL (n = 90)	Ragweed MATA (n = 35)	Placebo (n = 87)
Age $\pm$ SD*	39 $\pm$ 10.4	37 $\pm$ 10.2	37 $\pm$ 12.7	39 $\pm$ 10.5	37 $\pm$ 9.9	37 $\pm$ 12.8
Sex, no. (%)						
Male	45 (47.4)	19 (47.5)	39 (41.9)	43 (47.8)	17 (48.6)	36 (41.4)
Female	50 (52.6)	21 (52.5)	54 (58.1)	47 (52.2)	18 (51.4)	51 (58.6)
Race, no. (%)						
Asian	14 (14.7)	6 (15.0)	4 (4.3)	14 (15.6)	5 (14.3)	4 (4.6)
White	44 (46.3)	20 (50.0)	57 (61.3)	43 (47.8)	17 (48.6)	54 (62.1)
Black	30 (31.6)	12 (30.0)	28 (30.1)	26 (28.9)	12 (34.3)	26 (29.9)
Mixed/other	7 (7.4)	2 (5.0)	4 (4.3)	7 (7.8)	1 (2.9)	3 (3.4)
Allergy symptoms,† no. (%)						
Conjunctivitis	93 (97.9)	39 (97.5)	90 (96.8)	88 (97.8)	34 (97.1)	84 (96.9)
Rhinitis	95 (100.0)	40 (100.0)	92 (98.9)	90 (100.0)	35 (100.0)	86 (98.9)

*Age is given in years.

†History of ragweed allergy symptoms.

EEC was divided into 3 domains: nonnose/eye symptoms, practical problems, and emotions. Scores ranged from 0 to 6, with higher scores indicating more symptoms/trouble. The mean score of the 3 domains yielded an overall quality-of-life score. The RQLQ-EEC administered at the end of the EEC session consisted of these 3 domains and an additional global assessment domain.

Immunogenicity. Levels of the immunoglobulins IgG, IgG₁, and IgG₄ were measured by using solid-phase radioimmunoassay for quantitation of human IgG antibody specific for short ragweed (*A. artemisiifolia*) in serum.³⁴ Changes in ragweed-specific immunoglobulin levels (IgG, IgG₁, and IgG₄) were assessed from baseline to approximately 3 weeks after treatment.

Safety and tolerance. Safety and tolerability were assessed by adverse events (AEs) reported by subjects at each postrandomization clinic visit.

Study objective. The primary objective of this study was to assess the clinical efficacy of Ragweed MATA MPL compared with placebo as measured based on TSSs in reducing SAR symptoms caused by ragweed pollen in an EEC model. Secondary objectives included evaluation of the effect of Ragweed MATA MPL on quality of life, immunogenicity (ragweed-specific IgG, IgG₁, and IgG₄), and assessment of safety and tolerability. A Ragweed MATA treatment group was included as a reference group but was not powered for statistical significance.

Statistical methods

With 80% power to detect a clinical difference of 25% between the active treatment and placebo groups with an SD of 5.6 and a type I error of 5%, a sample size of 80 per group was estimated to be sufficient. Approximately 100 patients were planned to be randomized to Ragweed MATA MPL, and approximately 100 patients were planned to be randomized to placebo.

The PP analysis set was used for the primary and secondary analyses, and the primary analysis was repeated for the ITT analysis set also, as defined *a priori* in the statistical analysis plan. The ITT set was used for safety analysis.

The primary outcome was the change from baseline in TSSs in the Ragweed MATA MPL group compared with the placebo group. While in the EEC at each visit, patients completed a total of 6 symptom diary cards recording their SAR symptoms. The average of the maximum of 6 assessments of a visit was used as the TSS for that visit. Change from baseline is defined as the TSS over the pretreatment EEC (visits 2-5) minus the TSS over the posttreatment EEC (visits 10-13). Baseline TSSs were compared between groups. Because the baseline comparison was found to be nonsignificant, efficacy was assessed by using ANOVA, where the treatment was the independent variable and the change from baseline TSS was the response. Immunoglobulin levels were analyzed analogously.

Baseline RQLQ-EEC scores were compared between treatments by using 1-way ANOVA. The mean changes in RQLQ-EEC were compared between

treatments by using analysis of covariance in which baseline and treatment were covariates.

All statistical analyses were performed with SAS System 8.2 software (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

The ITT set consisted of 228 subjects (95 in the Ragweed MATA MPL group, 93 in the placebo group, and 40 in the Ragweed MATA group). Subject age ranged from 18 to 64 years, with a mean of 37.7 years. Subjects in all treatment groups were comparable with regard to their demographics and other baseline characteristics, with no significant differences (Table I). Ninety (94.7%) subjects in the Ragweed MATA MPL group and 38 (95%) subjects in the Ragweed MATA group completed their treatment course, and 87.1% and 88.9%, respectively, received only 4 injections as scheduled. Fig 2 provides an overview on subject disposition. Of 228 randomized subjects, 216 completed the study. Sixteen subjects were excluded from the PP set because they did not complete the study, because they did not receive the top dose of study medication, or both, and therefore the PP set comprised 212 (93.0%) subjects, 90 in the Ragweed MATA MPL group, 87 in the placebo group, and 35 in the Ragweed MATA group.

Efficacy

The TSSs for all treatment groups were not statistically significantly different at baseline. The mean change from baseline (ie, improvement in symptoms) for PP subjects in the Ragweed MATA MPL group was significantly greater than that for subjects in the placebo group (−6.61 vs −4.47, $P = .007$, Fig 3). The improvement in TSSs from baseline in the Ragweed MATA MPL group was 42%, and the relative improvement compared with the placebo group

$$\left(\frac{\text{Ragweed MATA MPL mean change from baseline [MCFB]} - \text{Placebo MCFB}}{\text{Placebo MCFB}} \right) * 100$$

was 48%. Median improvement in TSS was −6.46 in the Ragweed MATA MPL group compared with −3.54 in the placebo

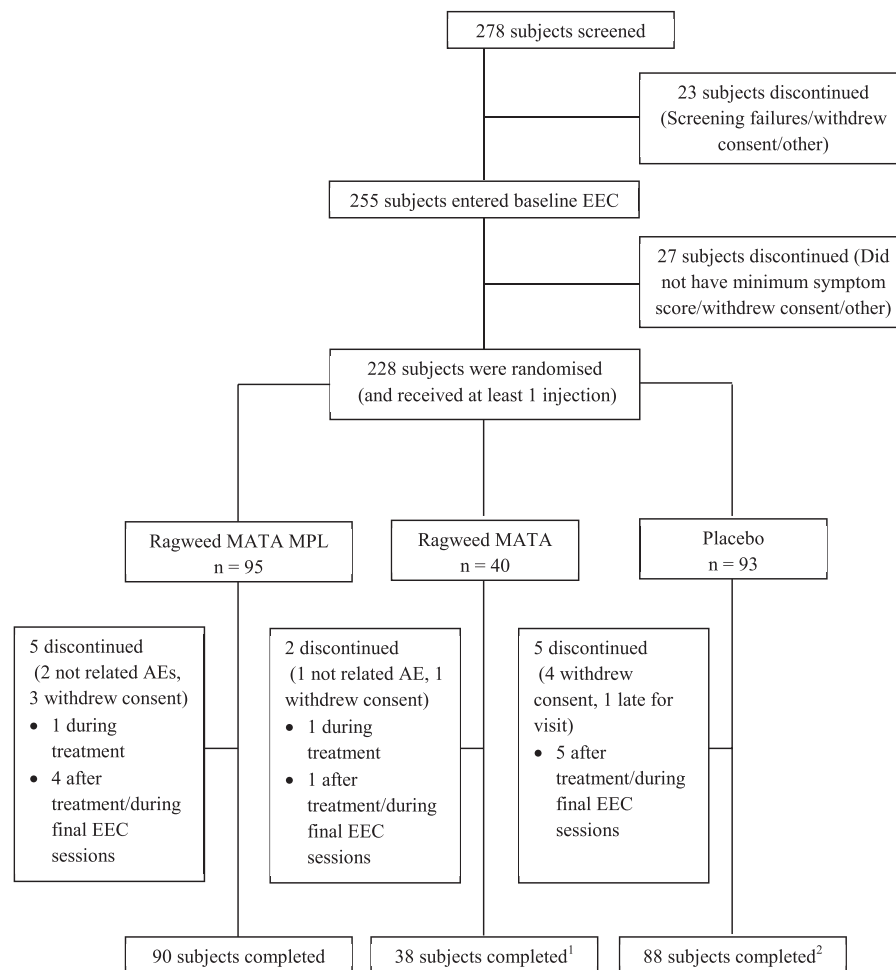
¹ 35 subjects were included in the PP analyses² 87 subjects were included in the PP analyses

FIG 2. Disposition of subjects.

group, resulting in a relative improvement of 82%. The difference in mean and median values shows that the data were somewhat skewed, and therefore the true improvement might be more closely reflected by the median. The average TSS in the Ragweed MATA MPL group improved from a mean of 15.7 (median, 16.2; 16 corresponds to an average score of 2 [ie, moderate] for all 8 symptoms) to a mean of 9.1 (median, 8.8; 8 corresponds to an average score of 1 [ie, mild] for all 8 symptom scores; Table II).

Analysis of the ITT set confirmed these results, with a statistically significant ($P = .021$) relative mean improvement of 40% and a median improvement of 75% compared with placebo.

Ragweed MATA MPL also led to a greater mean (-6.61 vs -4.86) and median (-6.46 vs -4.38) improvement of symptoms in the PP set compared with Ragweed MATA; this comparison approached statistical significance ($P = .067$). Results for the ITT set were similar.

An analysis of responders to treatment showed that the responder rate in the PP set was 63.3% in the Ragweed MATA MPL group compared with 37.9% in the placebo group

($P < .001$) and 40.0% in the Ragweed MATA group ($P = .018$, Table III).

Quality of life

Subjects were also comparable in terms of RQLQ-EEC scores at baseline. After treatment, statistically significant improvements from baseline for Ragweed MATA MPL versus placebo in the PP set were shown for the practical problems domain, as well as for the overall global assessment ($P = .0004$ and $.0280$; relative mean improvement of 151% and 63%, respectively). In addition, the improvement in the overall mean score (mean of all 3 domains, with the exception of global assessment) approached significance ($P = .0538$, relative improvement of 37%, Fig 4). Ragweed MATA MPL also was statistically significantly superior to Ragweed MATA in improving quality of life in the practical problems domain and the overall mean score ($P = .0120$ and $.0448$, respectively).

Ragweed-specific immunoglobulins

There were no statistically significant differences in ragweed-specific IgG levels at baseline. After treatment, ragweed-specific

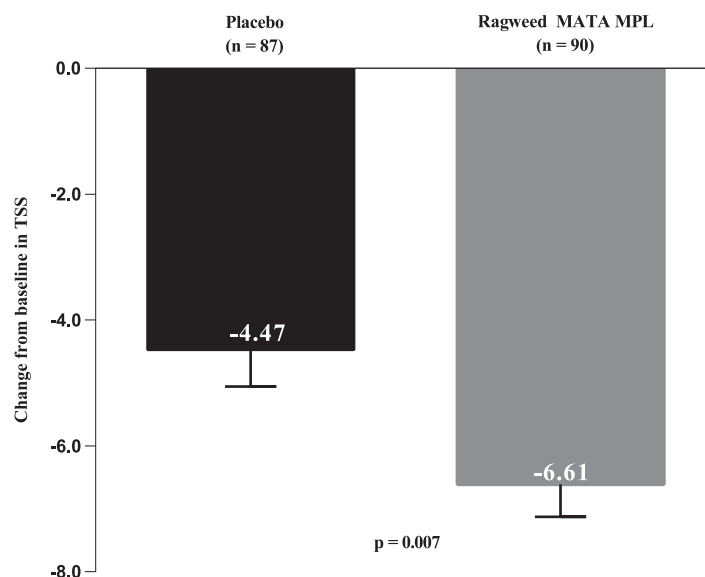


FIG 3. Mean change from baseline in TSS: PP data set. Change from baseline is defined as the average TSS of the 4 posttreatment EEC visits minus the average TSS of the 4 pretreatment EEC visits. The *P* value for treatment comparison was calculated by using ANOVA, in which treatment is the independent variable and change from baseline TSS is the response. Data represent means $\pm$ SEs.

TABLE II. Primary efficacy analysis: ragweed MATA MPL compared with placebo in reducing TSSs for PP patients

Category	Value	Ragweed MATA MPL (n = 90)	Ragweed MATA (n = 35)	Placebo (n = 87)	P value	
					MATA MPL vs MATA	MATA MPL vs placebo
Baseline TSS	Mean $\pm$ SD	15.7 $\pm$ 3.92	15.5 $\pm$ 4.56	16.6 $\pm$ 3.93	.741	.158
	Median	16.2	16.5	17.2		
Posttreatment TSS	Mean $\pm$ SD	9.14 $\pm$ 5.153	10.6 $\pm$ 5.72	12.1 $\pm$ 5.09		
	Median	8.81	11.1	12.0		
Change from baseline TSS	Mean $\pm$ SD	-6.61 $\pm$ 4.874	-4.86 $\pm$ 4.434	-4.47 $\pm$ 5.458	.067	.007
	Median	-6.46	-4.38	-3.54		

TABLE III. Treatment effects comparison in TSS responder rates for PP patients

Decrease of baseline value	Ragweed MATA MPL (n = 90)	Ragweed MATA (n = 35)	Placebo (n = 87)	P value	
				MATA MPL vs MATA	MATA MPL vs placebo
Nonresponders	33 (36.7%)	21 (60.0%)	54 (62.1%)	.018	<.001
Responders	57 (63.3%)	14 (40.0%)	33 (37.9%)		

IgG levels increased considerably in the Ragweed MATA MPL group, whereas they remained relatively unchanged in the placebo group. Median IgG levels increased from 368.5 to 2186.1 ng/mL in the Ragweed MATA MPL group compared with 534.4 to 560.1 ng/mL in the placebo group. The increase from baseline to after treatment was highly statistically significant for the Ragweed MATA MPL group versus the placebo group ($P < .001$). Even more dramatic and significant increases in median levels ($P < .001$) were seen in the Ragweed MATA MPL group for ragweed-specific IgG₁ and IgG₄ levels (from 400 AU/mL at baseline to 3192.5 AU/mL after treatment and 400 AU/mL at baseline to 8320.5 AU/mL after treatment, respectively; Fig 5).

Safety

A total of 190 (83.3%) of the 228 randomized subjects reported 1 or more treatment-emergent AEs: 94.7% of subjects in the

Ragweed MATA MPL group, 92.5% in the Ragweed MATA group, and 67.7% in the placebo group. The difference between the active and placebo groups was significant and is mainly due to the typical injection-site reactions of swelling, pruritus, pain, and warmth that are known to be frequent with SIT, the majority of which are considered related to treatment. Apart from injection-site reactions, the most frequent AEs were headache, nasal congestion, rhinorrhea, and sneezing. For these AEs, the frequency in the placebo group was comparable with that in the active groups. AEs that were experienced by at least 5% of subjects in any one treatment group are summarized in Table IV. The only nonlocal AEs that were considered related to study drug and experienced by more than 2% of subjects in the active groups were headache, rhinorrhea, and urticaria (Table E1).

Most of the AEs were mild in intensity (60.0%, 52.5%, and 53.8% in the Ragweed MATA MPL, Ragweed MATA, and

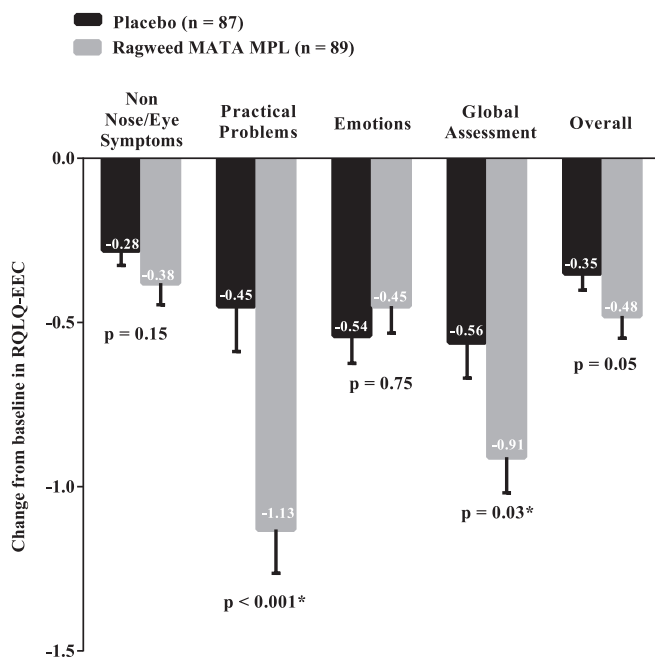


FIG 4. Mean change from baseline in quality of life: PP data set. Quality of Life was measured with the RQLQ-EEC. Change from baseline is defined as the posttreatment minus pretreatment RQLQ changes. *P* values were calculated by using analysis of covariance with baseline and treatment as covariates. Statistically significant *P* values are marked with an asterisk. Data represent means $\pm$ SEs.

placebo groups, respectively) (see Table E2 in this article's Online Repository at www.jacionline.org). Seven subjects experienced severe AEs, and all of them were local (injection-site pruritus experienced by 5 subjects in the Ragweed MATA MPL group and 1 subject in the Ragweed MATA group and injection-site erythema and injection-site pain experienced by 1 subject each in the Ragweed MATA MPL group).

The only possibly related moderate systemic AE was headache, which was experienced by 1 subject in the Ragweed MATA MPL group after the injection of 700 SU/0.5 mL and 2 subjects in the placebo group after the second and fourth injections, respectively.

Three randomized subjects were discontinued from the study because of an AE, 2 in the Ragweed MATA MPL and 1 in the Ragweed MATA group, but none of them were assessed to be related to study medication by the investigator. No severe systemic AEs, serious AEs, or deaths occurred.

DISCUSSION

The purpose of this study was to assess the clinical efficacy, as measured based on the TSS, of Ragweed MATA MPL versus placebo in reducing allergic rhinitis symptoms caused by ragweed pollen in an EEC. In the primary efficacy analysis Ragweed MATA MPL was shown to be statistically significantly superior to placebo in improving total symptoms of allergic rhinitis in both the PP and ITT sets.

EECs have been in use for the study of airborne allergy since the 1980s, and a review by Day et al³⁰ listed more than 40 publications on trials conducted in allergen challenge chambers in patients with allergic rhinitis. Salapatek et al³⁵ found that for the major drug classes of nasal spray antihistamines and corticosteroids, similar treatment effects were seen for each treatment class

when 1-day treatment effects in the EEC and field trials were compared. The literature on the use of the EEC in immunotherapy is limited and was reviewed similarly by Devillier et al.³⁶ In the EEC model patients with AR are exposed to actual pollen in the circulating air and record their symptoms. In these respects the EEC is the same as a natural field study, with the key differences being that the exposure is specific to 1 pollen and controlled, hence eliminating the variability in interindividual allergen exposure; instantaneous symptom report is supervised, and hence there is reliable and timely completion of symptom assessments, greatly reducing retrospective or missing data and the need for imputation. The lack of reliability of field studies for SIT has been recognized by the US Food and Drug Administration, and the Center for Biologics Evaluation and Research has recently acknowledged EEC studies suitable as supportive phase III pivotal trials in the United States. Another advantage of the use of an EEC is a reliable, prospective, pretreatment baseline assessment, which is of value because it enables the assessment of responders and provides insight into the extent of the placebo response.

The relatively large placebo effect in patients with SAR is recognized but often overlooked. The clinical experience of allergists and patients might lead to the expectation of a 40% to 50% treatment effect. However, the data from recent, randomized, double-blind, placebo-controlled studies of SIT has generally indicated a 20% to 30% treatment effect when compared with placebo.³⁷⁻⁴³ The discrepancy between clinical expectations and data is explained by the placebo effect, which has been estimated to be approximately 22%.⁴⁴

In this study subjects in the Ragweed MATA MPL group experienced a relative improvement in TSS of 48% compared with the placebo group. This equates to a mean improvement of 42% in TSSs in the active group compared with baseline scores (analogous to clinical expectation of allergists and patients) and a posttreatment difference in TSSs between the active and placebo groups of 25% (similar to that from other SIT studies).

In addition, mean pretreatment scores for the Ragweed MATA MPL group (TSS of 8 symptoms, 15.7 points; average, approximately 2 points) were "moderate," which is defined as annoying symptoms, whereas posttreatment, subjects in the Ragweed MATA MPL group on average had "mild" symptoms (TSS, 9.1 points; close to 1 point per symptom), which were defined as minimal awareness of symptoms that are easily tolerated.

The primary efficacy outcome is strongly supported by the outcome of the RQLQ-EEC. Treatment with Ragweed MATA MPL shows statistically significantly improved global assessment compared with placebo (relative mean improvement of 63%). Moreover, the subjects in the Ragweed MATA MPL group also experienced highly significant improvements in the practical problems domain compared with the placebo group (relative mean improvement of 151%). This is notable because the RQLQ-EEC was developed specifically for use in the EEC and practical problems, such as concentration in reading or watching a movie, are more relevant in the EEC-type environment.

The posttreatment allergen challenge was performed approximately 3 weeks after the last injection. This was chosen to allow for a reasonable time to discern treatment effect but not to prolong the study duration. The results show a clear clinical benefit at that time point but do not show onset of action or time to maximal effect. However, on this latter point, the clinical and quality-of-life benefits are underpinned by clear immunologic changes. Median ragweed-specific IgG levels in the Ragweed MATA MPL

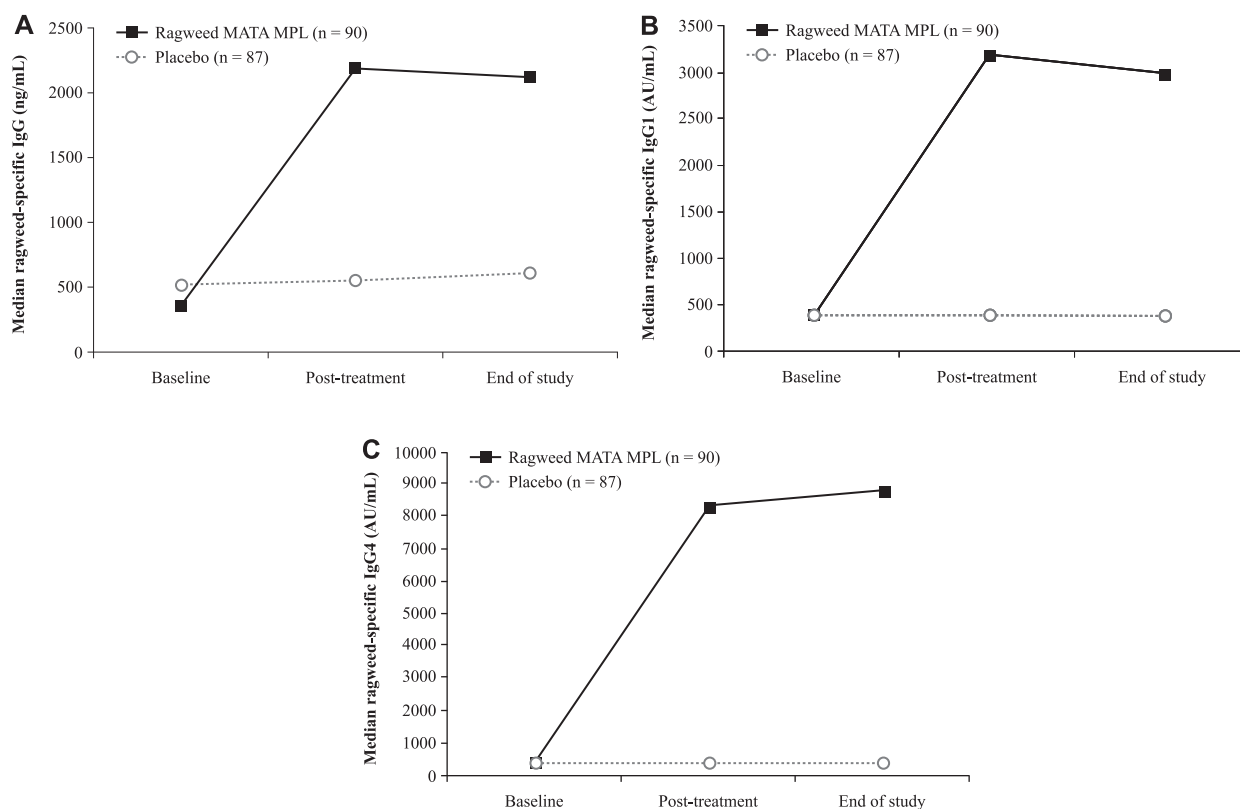


FIG 5. Ragweed-specific immunoglobulins: PP data set. A, IgG; B, IgG₁; and C, IgG₄.

TABLE IV. AEs experienced by 5% or more of subjects in any one treatment group: ITT set

	Ragweed MATA MPL (n = 95)	Ragweed MATA (n = 40)	Placebo (n = 93)
Event, no. (%)			
Injection-site conditions			
Pruritus	76 (80.0)	30 (75.0)	5 (5.4)
Swelling	73 (76.8)	32 (80.0)	15 (16.1)
Pain	57 (60.0)	18 (45.0)	31 (33.3)
Warmth	26 (27.4)	12 (30.0)	2 (2.2)
Induration	14 (14.7)	1 (2.5)	1 (1.1)
Bruising	13 (13.7)	5 (12.5)	28 (30.1)
Nodule	12 (12.6)	2 (5.0)	7 (7.5)
Erythema	8 (8.4)	3 (7.5)	0 (0.0)
Irritation	3 (3.2)	5 (12.5)	0 (0.0)
Movement impairment	3 (3.2)	2 (5.0)	0 (0.0)
Rash	1 (1.1)	2 (5.0)	1 (1.1)
Headache	17 (17.9)	9 (22.5)	22 (23.7)
Nasal congestion	6 (6.3)	1 (2.5)	4 (4.3)
Rhinorrhea	4 (4.2)	2 (5.0)	6 (6.5)
Sneezing	4 (4.2)	1 (2.5)	7 (7.5)
Upper respiratory tract infection	3 (3.2)	3 (7.5)	2 (2.2)
Nausea	1 (1.1)	3 (7.5)	3 (3.2)
Pharyngolaryngeal pain	1 (1.1)	2 (5.0)	0 (0.0)
Influenza like illness	0 (0.0)	2 (5.0)	0 (0.0)

group increased 6-fold from pretreatment to approximately 3 weeks after treatment, whereas they remained almost unchanged in the placebo group. These results indicate a strong induction of a

specific immune response over time. Although IgG levels have not been shown to correlate directly with clinical effect, an increase in IgG levels has been shown to accompany successful immunotherapy.^{10,11,26,45} The increases in ragweed-specific IgG₁ and IgG₄ levels were even more dramatic (8- and 21-fold increases from baseline to after treatment, respectively). Other conventional clinical field studies have shown the benefit of MATA MPL ultrashort-course therapy throughout the following pollen season with grass allergen^{23,26} and with Ragweed MATA MPL.⁴⁶

Ragweed MATA MPL was very well tolerated in this study. The most frequent AEs (irrespective of relationship to study drug) were injection-site reactions (mostly pruritus, swelling, and pain), whereas the most frequent nonlocal AE was headache. Local AEs were more common in the 2 active treatment groups compared with the placebo group, which is not unexpected because injection-site reactions are known to be common during SIT. In contrast, nonlocal AEs were comparable between the placebo and active treatment groups. The majority of AEs were mild in severity. Interestingly, there was no consistent trend with regard to the frequency of adverse reactions with administration of increasing dose strengths. No severe systemic AEs, serious AEs, or deaths occurred during the study, and no subject discontinued from the study because of a treatment-related AE.

One concern regarding several recent studies of sublingual immunotherapy (with a high incidence of oral pruritus) is whether the AE profile potentially compromises blinding. However, whereas sublingual immunotherapy is a daily therapy and is therefore taken at the same time as the symptoms are being assessed, Ragweed MATA MPL is a preseasonal treatment completed before the posttreatment assessment period, and hence

the adverse experiences arising from injections would therefore be temporally remote to the recording of symptoms. In this study, considering the nature of the AEs reported, each common event (>10%) was reported in both the active treatment and placebo groups, and none were exclusive to the active treatment. Occasionally, AEs were reported more commonly in the placebo group (eg, local injection-site bruising and headache), although pruritus and swelling were reported more frequently in the active treatment groups. Therefore it is important to note that although the incidence of pruritus and swelling was very similar in both the Ragweed MATA MPL and Ragweed MATA groups, the clinical outcomes of TSS and EEC-RQLQ measurements were notably different. Hence the Ragweed MATA group acts as a positive control with respect to AEs to show that clinical improvement is not associated with adverse experiences.

The primary objective of the study was to assess the efficacy of Ragweed MATA MPL compared with placebo (the standard comparator for SIT studies). Ragweed MATA was included as a safety reference to an equivalent formulation without the MPL adjuvant. No significant differences in safety profile were apparent between Ragweed MATA MPL and Ragweed MATA, showing that MPL is well tolerated. Although the number of patients receiving Ragweed MATA was not prospectively powered for statistical comparison of efficacy, such analyses were conducted *post hoc*, showing that the change from baseline in TSS approached statistical significance ($P = .067$), whereas with Ragweed MATA MPL, the responder rate was 63.3% of subjects compared with 37.9% of subjects receiving placebo ($P < .0001$) and 40.0% of subjects receiving Ragweed MATA ($P = .018$), showing a statistically significant difference. The improvements in the TSS, responder rate, and quality of life were shown to be more pronounced in the Ragweed MATA MPL group compared with the Ragweed MATA group, indicating the additional benefit of MPL over treatment without the adjuvant.

In conclusion, ultrashort-course SIT with only 4 injections of Ragweed MATA MPL over 3 weeks efficiently reduced allergy symptoms, improved quality of life, and increased ragweed-specific IgG, IgG₁, and IgG₄ levels in subjects with moderate-to-severe SAR ascribed to ragweed pollen exposure 3 weeks after the completion of the treatment course. The study did not demonstrate any safety or tolerability concerns for Ragweed MATA MPL. Ultrashort-course SIT might offer several potential benefits to both patients and allergists. Its convenience over traditional SIT likely leads to improved compliance²⁶ and the ability to start and complete annual treatment closer to the start of the pollen season, thereby avoiding the risks associated with coseasonal administration. Moreover, the reduced commitment for an effective treatment might permit more patients to access immunotherapy.

Clinical implications: Patients with moderate-to-severe ragweed pollen allergy can be treated effectively with only 4 injections of Ragweed MATA MPL. The treatment is well tolerated.

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TABLE E1. Nonlocal AEs experienced by more than 1 subject that were related to study medication*: ITT set

	Ragweed MATA MPL (n = 95)	Ragweed MATA (n = 40)	Placebo (n = 93)
Headache, no. (%)	5 (5.3)	2 (5.0)	8 (8.6)
Rhinorrhea, no. (%)	2 (2.1)	1 (2.5)	2 (2.2)
Urticaria, no. (%)	3 (3.2)	1 (2.5)	
Fatigue, no. (%)	1 (1.1)	1 (2.5)	1 (1.1)
Sneezing, no. (%)	1 (1.1)		3 (3.2)
Eye pruritus, no. (%)	1 (1.1)		1 (1.1)
Dizziness, no. (%)		1 (2.5)	2 (2.2)
Pain in extremity, no. (%)			2 (2.2)

*This includes AEs with at least a possible relationship to the study medication.

TABLE E2. Adverse reactions: ITT set

Category	Ragweed MATA MPL (n = 95)	Ragweed MATA (n = 40)	Placebo (n = 93)
Patients with no reaction, no. (%)	9 (9.5)	4 (10.0)	47 (50.5)
Patients with reaction, no. (%)	86 (90.5)	36 (90.0)	46 (49.5)
Local reaction, no. (%)	77 (81.1)	33 (82.5)	32 (34.4)
Mild, no. (%)	54 (56.8)	19 (47.5)	32 (34.4)
Moderate, no. (%)	18 (18.9)	13 (32.5)	0 (0.0)
Severe, no. (%)	5 (5.3)	1 (2.5)	0 (0.0)
Systemic reaction, no. (%)	9 (9.5)	3 (7.5)	14 (15.1)
Mild, no. (%)	8 (8.4)	3 (7.5)	13 (13.9)
Moderate, no. (%)	1 (1.1)	0 (0.0)	1 (1.1)
Severe, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Adverse reactions that occurred within 24 hours of the injection and were considered possibly, probably, or definitely related to the study medication were included in the summary. Subjects reporting more than 1 adverse reaction are only counted once (under the greatest reported severity).