
Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis

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Background: Sublingual swallow immunotherapy has been increasingly recognized as a safe and efficacious alternative to parenteral specific immunotherapy.

Objective: To determine the safety and efficacy of sublingual swallow immunotherapy ragweed allergen extract for rhinoconjunctivitis treatment starting just before and continuing through the ragweed pollen season.

Methods: This randomized, double-blind, placebo-controlled study was performed in children and adults with a documented history of allergic rhinoconjunctivitis during ragweed season at 9 Canadian allergy centers. Active treatment was standardized extract of ragweed allergen administered as sublingual swallow drops at increasing doses starting shortly before the pollen season and maintenance doses continued daily during the season. Primary efficacy variables were symptom and medication scores, and secondary variables included global evaluation of efficacy and immunologic measurements.

Results: Eighty-three patients were included in the safety analysis; 76 patients were included in the intent-to-treat analysis. Nine placebo recipients and 1 treatment recipient withdrew for lack of efficacy ($P = .004$). Nine patients in the treatment group withdrew because of adverse events, none serious ($P = .003$). Investigator evaluation of efficacy showed that significantly more patients improved and fewer deteriorated in the treatment group vs the placebo group ($P = .047$). Ragweed IgE and IgG4 levels increased significantly in treatment recipients vs placebo users ($P < .001$). Sneezing and nasal pruritus approached significant improvement in the treatment group vs the placebo group ($P = .09$ and $.06$, respectively). Quebec City experienced low pollen counts. Excluding Quebec City, significant improvement was seen for these 2 symptoms ($P = .04$).

Conclusion: Sublingual swallow immunotherapy seems to be safe and efficacious for ragweed rhinoconjunctivitis even when started immediately before the ragweed pollen season.

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INTRODUCTION

Specific immunotherapy (SIT) has been used extensively since 1911 for treating allergic rhinoconjunctivitis and asthma.^{1,2} The use of parenteral SIT is limited by the need for repeated injections under direct medical supervision and the risk of systemic reactions. This has contributed to a reduction in the use of SIT in the United Kingdom and has stimulated researchers to find alternatives to parenteral

SIT: hypoallergenic allergens and local administration routes. Sublingual swallow SIT (SLIT) has been shown to be safe and efficacious for many pollens and house dust mites.^{3–16}

In many parts of the United States, Canada, and Europe, pollen from ragweed (*Ambrosia*) often elicits severe rhinoconjunctivitis and asthma during the pollen season. In the northeast part of the United States and eastern Canada, the ragweed pollen season usually starts in early August and lasts until the first frost. Oral, usually encapsulated, ragweed has shown efficacy for ragweed SIT in North America.^{17–19} At the time of this study, there was no published study of the safety and efficacy of ragweed SLIT; 1 study¹⁶ has since been published using a combination of sublingual drops and maintenance sublingual tablets. Most trials using SIT, including SLIT, have used lengthy treatment protocols before onset of the pollen season and continuing throughout the pollen season, including the other ragweed study (preseasonal/coseasonal administration).^{1–16} We undertook this double-blind placebo-controlled study using a standardized glycerine sublingual swallow formulation of ragweed pollen (*Am-*

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brosia eliator) starting 2 weeks before and during the 2001 ragweed season at 9 Canadian allergy centers to evaluate the safety and efficacy of SLIT in treating seasonal allergic rhinoconjunctivitis due to ragweed allergen.

MATERIALS AND METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study using parallel groups of pediatric and adult patients performed in eastern Canada with the active product standardized ragweed allergen extract (*A eliator*) (Staloral; Stallergenes SA, Antony, France) administered by the sublingual swallow route (SLIT).

Participants

Patients of either sex, aged 6 to 58 years, with a history of previous seasonal allergic rhinoconjunctivitis during the usual ragweed pollen season and positive skin prick test reactions to ragweed (≥ 3 mm larger than the negative control) were included in this study. Exclusion criteria included symptomatic polysensitization; asthma not controlled with β -agonist therapy; current therapy with inhaled or oral corticosteroids, β -blocking agents, long-acting antihistamine agents, or cromones; and previous SIT of any kind. On recruitment, participants were randomized to receive either active treatment or placebo.

Treatment

During a 17-day dose progression phase, the patients received a daily dose of 0.5 to 300 IR (index of reactivity dosage) as drops (10-, 100-, and 300-IR/mL concentra-

tions; Table 1). A concentration of 100 IR is defined as the concentration that elicits a wheal with a mean diameter of 7 mm in 30 allergic patients who underwent skin prick testing; 100 IR contained 116 μ g of Amb a 1 major antigen and 300 IR contained 314 μ g of Amb a 1. Drops (0.05 mL per drop) were administered first thing in the morning before eating, drinking, or brushing teeth and were held sublingually for 2 minutes and then swallowed. The dose was escalated as seen in Table 1. To be evaluated for efficacy, patients had to reach a daily dose of at least 100 IR (116 μ g of Amb a 1), with the objective of reaching 300 IR (314 μ g of Amb a 1) daily in maintenance therapy. Treatment was maintained at the highest tolerated dose (minimum: 100 IR and 116 μ g Amb a 1; maximum: 20 drops daily, 1 mL, 300 IR/mL, and 314 μ g of Amb a 1) during a maintenance phase corresponding to the pollen season. Therapy began between July 16 and July 31, 2001, with the pollen season starting July 30 to mid-August and lasting until October 2001. Throughout the trial, visits were scheduled for efficacy and safety assessments. Patients were requested to complete a diary card daily to record the parameters needed to calculate a symptom score and a medication score. Because this was the first SLIT trial performed in Canada, all patients received an adrenaline pen (EpiPen; Dey Laboratories, Napa, CA) to have on hand with dose administration and were instructed in its use. The first dose of the therapy was administered in the physician's office.

Study Variables

The symptom score was evaluated on the basis of daily recording of rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus, and nasal obstruction) and conjunctivitis symptoms (eye redness, pruritus, and watering) according to a scale from 0 to 3 (0 indicates no symptoms; 1, symptoms present but not bothersome; 2, symptoms bothersome; and 3, symptoms very bothersome). The total rhinitis score was the sum of the individual scores for sneezing, rhinorrhea, nasal pruritus, and nasal obstruction. The total conjunctivitis score was the sum of the individual scores for eye redness, ocular pruritus, and watering of eyes. The number of days with asthma was recorded also. The medication score was evaluated on the basis of daily recording of relief medication use (10-mg tablets of loratadine, eye drops of olopatadine, and metered-dose inhaler puffs of salbutamol). The medication score was the sum of the individual scores for loratadine ($\times 2$), olopatadine, and salbutamol.

The primary efficacy variables were the symptom and medication scores. The secondary efficacy variables included overall evaluation of efficacy by the investigator and immunologic measurements (ragweed specific IgE and IgG4). The safety evaluation was based on the recording of adverse events as reported by the patients or observed by the investigators. Pollen grain counts were performed weekly between

Table 1. Dose Progression and Maintenance Phases*

Phase	Concentration, IR/mL	Drops, No.
Dose progression phase		
Day 1	10	1
Day 2	10	3
Day 3	10	6
Day 4	10	10
Day 5	100	1
Day 6	100	3
Day 7	100	6
Day 8	100	10
Day 9	300	1
Day 10	300	3
Day 11	300	6
Day 12	300	10
Day 13	300	12
Day 14	300	14
Day 15	300	16
Day 16	300	18
Day 17	300	20
Dose maintenance phase		
Daily throughout the pollen season	300	20

Abbreviation: IR, index of reactivity dosage.

* One milliliter equals 20 drops.

N=83 screened patients			
N=83 randomized patients (P=40 / T=43)			
n=57 completed patients (P=29 / T=28)		n=26 withdrawn patients (P=11 / T=15)	
n=56 P=29 / T=27 Included in ITT population	n=1 No diary card (T) Safety population	REASONS:	P T
		Inefficacy	n=9 n=1
		Adverse event	n=0 n=6
		Personal reason	n=0 n=3
		Lost to follow-up	n=0 n=1
		Noncompliance	n=1 n=0
		Adverse event + inefficacy	n=0 n=2
		Adverse event + lost to follow-up	n=0 n=1
		Inefficacy + personal reason	n=1 n=0
		Personal reason+ lost to follow-up + other	n=0 n=1
		POPULATIONS:	P T
		Safety (last visit = V1 or V2 ; no efficacy criteria)	n=1 n=5
		ITT (last visit > V1 ; presence of efficacy criteria)	n=10 n=10

POPULATIONS:	
Safety analysis: n=83 (P=40 / T=43)	
ITT analysis: n=76 (P=39 / T=37)	

Figure 1. Disposition of patients. P indicates placebo group; T, treatment group; ITT, intent-to-treat; V1, visit 1; V2, visit 2.

July 30 and October 7, 2001, by Aerobiology Research Laboratories (Nepean, Ontario, Canada).

Statistical Analysis

Statistical analysis of the efficacy variables used the 2-sample *t* test for normal distribution data and the 2-sample Wilcoxon test for nonparametric distribution data. Analysis of the safety variables was descriptive.

Ethics

To be included, patients (or their legal guardians if children) had to have signed informed consent forms after being informed about the nature of the trial, its aim, the methods and means to be used, the duration of the study, and the possible hazards related to administration of the study product. The study was reviewed and approved by institutional review boards from the appropriate jurisdictions. The study was conducted in accordance with the Note for Guidance on Good Clinical Practices (CPMP/ICH/135/95) and the ethical principles of the Declaration of Helsinki.

RESULTS

Participant Characteristics and Disposition

Of the 83 individuals screened, all were randomized (43 to receive active treatment with SLIT and 40 to receive placebo). Fifty-seven individuals, 28 in the treatment group and 29 in the placebo group, completed the study (Fig 1). The 2 groups did not differ in terms of demographic variables, history or severity of *Ambrosia* allergy, or medical history. Some patients were also allergic to trees, grasses, cats, dogs, birch, house dust mites, *Alternaria*, or mold, but their ragweed seasonal symptoms were not believed to be affected by these allergies.

All 83 screened participants took at least 1 dose of their study treatment and were included in the safety analysis. The intent-to-treat cohort for efficacy analysis included all randomized participants who took at least 1 dose of 100 IR of the study medication and for whom at least 1 primary efficacy criterion was available. The 76 patients in the intent-to-treat population (37 in the treatment group and 39 in the placebo

Table 2. Demographic Characteristics of the Intent-to-Treat Population

	Placebo group (n = 39)	Treatment group (n = 37)
Sex, M/F, No.	22/17	23/14
Age, mean (range), y	34.77 (16–56)	37.84 (14–58)
Age < 18 y, No.	1	1
History of SAR, y	17.13	18.70
Asthma, No. (%)	6 (15.4)	9 (24.3)
Asthma medications, No.	5	6
Ragweed SPT reaction, mm*	8.92/25.95	9.32/24.89
Ragweed IgE, kU/L	16.91	15.89

Abbreviations: SAR, seasonal allergic rhinitis; SPT, skin prick test.

* Mean wheal/flare.

group) consisted of 45 males (59%) and 31 females (41%), with a mean $\pm$ SD age of 36 ± 11 years (range, 14–58 years; 1 participant in each group was <18 years; Table 2).

Safety Results

Of the 15 patients who dropped out of the active treatment group, an adverse event contributed to the premature withdrawal in 9. Of the 11 patients who did not complete placebo treatment, the cause of premature withdrawal was inefficacy in 9 (Fig 1). Significantly more patients withdrew from the placebo arm because of lack of efficacy ($P = .004$). Significantly more patients withdrew from the active treatment arm because of adverse events ($P = .003$).

In the safety cohort, which includes all the randomized patients, 30 patients receiving SLIT (70%) vs 16 receiving placebo (40%) reported at least 1 adverse event. No adverse events were considered to be serious, and no systemic reactions were recorded. In the active treatment group, most of the adverse events were related to local intolerance (tongue itch/swelling, 9 patients; throat itch, swelling, or tightness, 13 patients; and nausea, 9 patients). Of patients who withdrew in the treatment arm, most did so because of tongue itch or nausea. No patient required the use of adrenaline. A total of 74 patients reached a dose of 300 IR on at least 1 occasion. Ten patients (in the treatment group) had to reduce the dose of medication to between 100 and 300 IR, and 1 patient reduced the dose to 90 IR. No patient experienced urticaria. Adverse reactions were not predicted by ragweed antibody titers or skin prick test results before therapy.

Efficacy Results

Primary efficacy variables. All centers considered, there was a trend nearing statistical significance favoring immunotherapy for sneezing and nasal pruritus ($P = .09$ and $.06$, respectively). In one center, Quebec City, a low pollen peak was observed (including 21% of patients who completed the study; Fig 2). A secondary analysis was undertaken that excluded Quebec City. This showed a significant effect in the active treatment SLIT group for 2 primary efficacy variables: sneezing and nasal pruritus ($P = .04$ for both). There were small improvements in rhinorrhea and nasal obstruction,

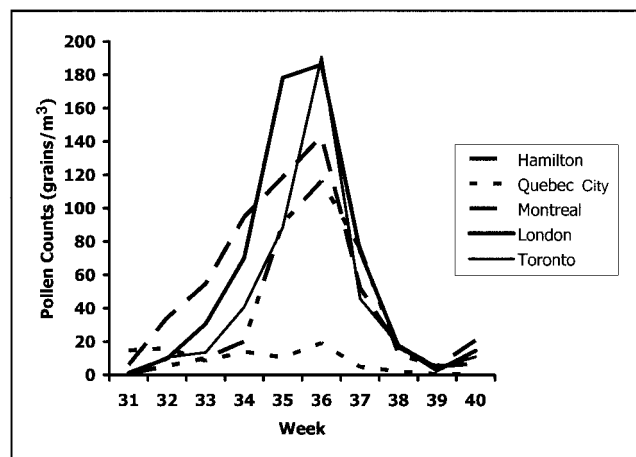


Figure 2. Ragweed (*Ambrosia*) pollen counts: 2001.

which were not statistically significant ($P = .16$ and $.55$, respectively). There was no difference in total conjunctivitis scores ($P = .35$) or medication scores ($P = .36$; Table 3).

Secondary efficacy variables. Investigator global evaluation significantly favored active treatment ($P = .047$). Ragweed specific IgE levels were significantly increased in the active treatment group (before treatment: 15.8 kU/L; after treatment: 41.1 kU/L) vs the placebo group (before treatment: 16.9 kU/L; after treatment: 22.5 kU/L; $P < .001$). Similarly, ragweed specific IgG4 levels were significantly increased in the active treatment group after immunotherapy (before treatment: 899 μ g/L; after treatment: 5,981 μ g/L) vs the placebo group (before treatment: 382 μ g/L; after treatment: 439 μ g/L; $P < .001$).

DISCUSSION

This randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of potent standardized ragweed extract (*Ambrosia*; dose, 100–300 IR; 116–314 μ g of Amb a 1) administered by the sublingual swallow route (SLIT). Primary efficacy parameters were symptom and medication scores computed from the patient daily record. Therapy was started only 2 weeks before the pollen season, with most patients barely reaching the maintenance dose at the time of pollenosis, and was stopped at the end of the ragweed pollen season (immediate preseasonal/coseasonal). Although originally planned to include 100 patients for a longer duration before the pollen season, with late approval of the study, only 83 patients were recruited and randomized, and therapy before the pollen season was limited to 2 weeks. Despite this limiting the power of the trial and the potential time to achieve efficacy of therapy, significant benefit was seen. Investigator evaluation was significantly in favor of the treatment group, and there was a significant increase in ragweed specific IgE and IgG4 levels in the treatment group. There was improvement in nasal pruritus and sneezing in all patients analyzed that approached significance and showed sig-

Table 3. Rhinitis, Conjunctivitis, and Medication Scores during the Ragweed Pollen Peak*

Symptom	Placebo group	Treatment group	P value
Rhinitis			
Sneezing score			
Mean $\pm$ SD	1.34 $\pm$ 0.67	0.99 $\pm$ 0.64	.04
Range	0.11–2.71	0–2.46	
Rhinorrhea score			
Mean $\pm$ SD	1.36 $\pm$ 0.67	1.10 $\pm$ 0.81	.16
Range	0–2.71	0–2.63	
Nasal pruritus score			
Mean $\pm$ SD	1.15 $\pm$ 0.73	0.79 $\pm$ 0.65	.04
Range	0–2.54	0–2.00	
Nasal obstruction score			
Mean $\pm$ SD	1.19 $\pm$ 0.90	1.07 $\pm$ 0.79	.55
Range	0–2.91	0–3.00	
Total rhinitis score			
Mean $\pm$ SD	5.03 $\pm$ 2.54	3.95 $\pm$ 2.45	.09
Range	0.83–10.31	0–8.89	
Conjunctivitis			
Ocular redness score			
Mean $\pm$ SD	0.66 $\pm$ 0.70	0.57 $\pm$ 0.64	.54
Range	0–2.43	0–1.83	
Ocular pruritus score			
Mean $\pm$ SD	0.99 $\pm$ 0.67	0.82 $\pm$ 0.77	.28
Range	0–2.40	0–2.82	
Eyes watering score			
Mean $\pm$ SD	0.73 $\pm$ 0.65	0.57 $\pm$ 0.58	.41
Range	0–2.24	0–1.82	
Total conjunctivitis score			
Mean $\pm$ SD	2.38 $\pm$ 1.92	1.96 $\pm$ 1.90	.35
Range	0–7.15	0–6.06	
Medication			
Total medication score			
Mean $\pm$ SD	1.26 $\pm$ 1.24	1.05 $\pm$ 1.60	.36
Range	0–4.38	0–8.55	

* Quebec City, Quebec, was excluded from this analysis.

nificance when patients from the geographical area that had a low pollen count were excluded from analysis ($P = .04$ for both). Medication scores did not show significance, but medication intake was low. Significantly more patients in the placebo group dropped out of the study because of lack of efficacy (9 patients in the placebo group vs 1 patient in the treatment group). No serious adverse events were encountered, although significantly more patients withdrew for adverse events in the treatment group vs the placebo group. Adverse events were mostly rhinoconjunctivitis, mouth and throat irritation, and gastrointestinal as a whole, as seen previously.^{3–16}

Oral SLIT has shown significant benefit for grass, tree, and other pollens and for house dust mites for rhinoconjunctivitis and asthma and has been reviewed recently in several publications, including Cochrane analysis.^{3–16} No ragweed studies have been included in these reviews, and no North American studies were included for analysis. A recent study¹⁶ showed improvement with ragweed SLIT performed in France and indicated a dose response of 100 to 300 IR. The cumulative

median dose in this study reached 17,450 IR in 2½ months, whereas it reached 23,000 IR in 7½ months in the study by Andre et al.¹⁶ We present the first North American ragweed SLIT trial showing significant improvement in ragweed rhinoconjunctivitis and demonstrating significant improvement starting as little as 2 weeks before onset of the pollen season. The dropout rate in this study was higher than that in the study by Andre et al.¹⁶ and may have been because of the inexperience of the Canadian investigators in using SLIT (the investigators in the study by Andre et al had previously used other SLIT therapies). It is not known whether starting near the onset of the pollen season contributed to more dropouts than in the study by Andre et al, but this was apparently not seen in the study by Vervloet et al.²⁰ We did not exclude patients with oral allergy syndrome from participating, and we did not investigate whether such patients would be predisposed to gastrointestinal adverse events; therefore, this aspect needs further investigation. Although we show that starting SLIT near the onset of a pollen season seems to be efficacious, it may be that the earlier a patient starts therapy

before the pollen season and the greater the dose administered, the better the response.¹⁶ Other researchers are investigating rush SLIT²⁰ and optimal timing and dose of SLIT. We support the concept that patients who are late in seeking immunotherapy may still be eligible for SLIT and may experience benefits during the same season, but this observation needs confirmation by larger clinical studies.

In conclusion, sublingual swallow immunotherapy (100–300 IR) seems to be safe and efficacious for the treatment of ragweed rhinoconjunctivitis even when starting therapy near the onset of the pollen season.

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