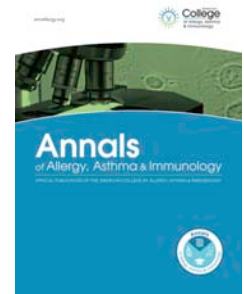


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Intralymphatic immunotherapy for mountain cedar pollinosis:

A randomized, double-blind, placebo-controlled trial.

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Keywords: cedar, pollen, allergic rhinitis, allergen, immunotherapy, intralymphatic, intranodal, ILIT, rhinoconjunctivitis

Abbreviations: AAAAI, American Academy of Allergy, Asthma, & Immunology; AE, adverse event; CRF, case report form; DMS, daily medication score; DSS, daily symptom score; EAAAI, European Academy of Allergy & Immunology; EDC, electronic data capture; FDA, Food & Drug Administration; GCP, International Conference on Harmonization Guideline for Good Clinical Practice; IgE, immunoglobulin E; IND, investigational new drug application; IRB, institutional review board; MQT, modified quantitative test; NRS, numeric rating scale; PEQ, patient experience questionnaire; PGI-I, patient global impression – improvement; ppm, particles

per cubic meter; SAE, serious adverse event; TCS, total combined score; WAO, World Allergy Organization.

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Background : Allergen immunotherapy can provide long-term benefits, including symptomatic relief and reduced disease progression, but requires a lengthy regimen that presents barriers to patient adherence. Thus, there is a need for improved approaches to immunotherapy. Recently, several clinical trials have reported successful results from intralymphatic immunotherapy.

Objective: To evaluate the efficacy, safety and tolerability of intralymphatic immunotherapy for allergies caused by mountain cedar pollen in a proof-of-concept study.

Methods : Twenty-one patients with allergic rhinoconjunctivitis due to mountain cedar pollen were randomized to receive three monthly intralymphatic injections of allergenic extract or placebo prior to the 2018-2019 mountain cedar pollen season. Safety was monitored during treatment thru the end of pollen season using structured and spontaneous reports. Clinical efficacy information was collected using a daily electronic diary of symptoms and allergy medication. Allergen-specific serum IgE was assessed before treatment and at the end of the study.

Results: There were no serious adverse events or systemic reactions in either group. Four patients experienced mild injection-site reactions. Patients receiving intralymphatic immunotherapy experienced a significant improvement in allergy symptoms and medication use relative to patients receiving placebo ($p < 0.001$) and the active treatment group had lower average total combined scores on 20 of 27 days during peak pollen season ($p < 0.05$). There was not a significant difference between groups in changes to mean mountain cedar-specific serum IgE levels.

Conclusion: In this proof-of-concept trial, intralymphatic immunotherapy was well tolerated and reduced the symptoms and medication use associated with allergic rhinoconjunctivitis caused by mountain cedar pollen.

INTRODUCTION

For more than 100 years, allergen immunotherapy has been used to reduce the symptoms of atopic disease. Although there are many treatments available, immunotherapy remains the only disease-modifying treatment, inducing tolerance to the allergen and reducing the IgE-mediated immune response, leading to a reduction in disease symptoms and slowing the progression of allergic disease from rhinitis to asthma.¹ However, the years-long series of treatments creates barriers to patient adherence, including the cost and time required to complete therapy.

Intralymphatic immunotherapy is the administration of allergen immunotherapy as a three-injection series of low-dose allergenic extracts directly into a lymph node. The first clinical trial of this procedure was reported more than a decade ago.² Since then, several additional randomized, controlled trials of intralymphatic immunotherapy have been reported for a variety of allergens. These trials generally demonstrated more rapid tolerization at lower doses than subcutaneous immunotherapy with similar safety and tolerability.³ Because intralymphatic immunotherapy offers the potential benefits associated with allergen immunotherapy at lower doses and with fewer injections over a shorter period, it may provide a clinically useful treatment for patients.

In Texas, pollen from *Juniperus ashei*, commonly called mountain cedar, has been recognized as an important cause of seasonal allergies for more than 100 years. The mountain cedar pollinates heavily during the winter months, with the season normally occurring from December to March and pollen counts that can exceed 10,000 particles per cubic meter. Cedar pollen can travel long distances on the strong northern wind fronts prevalent during Texas's

winter season, which may be due in part to the high carbohydrate content compared to other seasonal aeroallergens. This property leads to highly fluctuating levels during the peak season, but due to the absence of other, confounding outdoor aeroallergens during the winter months in central Texas, mountain cedar allergies have been a useful model for investigating seasonal allergy treatments.⁴

During the 2018-2019 mountain cedar pollen season, we conducted the first proof-of-concept study of intralymphatic immunotherapy for mountain cedar pollinosis. This was a randomized, double-blind, parallel-group, placebo-controlled study. The objectives were to evaluate the efficacy, safety and tolerability of intralymphatic immunotherapy in adults with mountain cedar allergies.

METHODS

Study Design

The study was a randomized, double-blind, parallel-group, placebo-controlled study. The study protocol was approved by the Integreview IRB (Austin, TX) and registered with ClinicalTrials.gov prior to enrollment of the first patient. Enrolled subjects returned daily electronic diaries following completion of treatment through the end of the 2018-2019 mountain cedar allergy season. An end-of-study visit in the clinic was completed for all enrolled subjects between March and April of 2019 with the last end-of-study visit completed on April 23, 2019.

Study Subjects

Participants were recruited through radio advertisements and among patients seen at participating clinics in central Texas. All patients provided written informed consent and all procedures were conducted according to good clinical practice guidelines. Adult patients with a history of seasonal allergic rhinitis and conjunctivitis due to mountain cedar pollinosis, confirmed using subcutaneous and intradermal testing, were included. Allergic rhinitis, stable allergic asthma, eczema or food sensitivities were allowed, but other clinically or medically significant co-morbidities were excluded particularly those requiring concomitant medications that could reduce the effectiveness of rescue treatments for anaphylaxis or alter immune response, such as immunosuppressants or systemic corticosteroids. Other exclusions were pregnant or lactating females, patients that had previously completed immunotherapy for mountain cedar pollinosis, patients in whom injection into suitable inguinal lymph nodes was not possible and anyone who planned to leave the central Texas area for a significant period during the pollen season.

Allergen Testing

Aeroallergen sensitivity was conducted using skin prick testing to estimate a range of reactivity followed by an intradermal test to define the degree of allergic sensitivity. With a history of winter allergies, these tests provide useful information on the appropriate starting dose for immunotherapy. Positive and qualifying results were defined as a wheal greater than or equal to 3 millimeters larger than control. The protocol allowed for enrollment of hypersensitive patients, defined as a wheal for allergenic extract greater than for the positive control.

Treatment

Intralymphatic immunotherapy was delivered as a series of three injections at four week intervals of 0.1 mL of a commercially-available, FDA-approved allergenic extract (Mountain Cedar Pollen, ALK-Abelló, Inc., Port Washington, NY) or diluent as placebo control (sterile saline solution containing 0.4% phenol as a preservative with matched glycerin concentration; ALK-Abelló, Inc., Port Washington, NY) . Following receipt of the IND, both stock solutions were prepared and labeled under the supervision of the investigators and were visually identical. Preparation, labeling and storage was in accordance with the AAAAI Practice Management Resource Guide, 2014 edition, Allergen Immunotherapy Extract Preparation Manual and guidance from the manufacturer.

Randomization and Blinding

Patients were randomized in a 1:1 ratio in the REDCap Cloud EDC system using a block randomization with random block sizes of two and four. All the participants, physicians who administered the interventions, and study staff who interacted with the patients and monitored the data remained blinded throughout the study. Following database lock, the study was unblinded on April 29, 2019.

Intralymphatic Injections

Injections were made using a 1-mL hypodermic syringe with a 25-gauge needle and given every four weeks prior to the start of the cedar allergy season. The injection site was prepared for aseptic injection into a superficial inguinal lymph node using ultrasonography. After each injection, subjects were monitored for one hour with vital signs checked at 15-minute intervals, and adverse events recorded using the total safety score worksheet.⁵

Briefly, local reactions are scored as 1 point, mild systemic reactions (WAO grades 1 and 2) are scored as 2 points, moderate systemic reactions (WAO grade 3) are scored as 3 points, and severe reactions (WAO grade 4+) are scored as 4 points. Patients that experienced a treatment-emergent adverse reaction were monitored in the office until stable. All patients were instructed to report delayed-onset hypersensitivity reactions to the study staff during the subsequent 24 hours.

Rescue Medications

All patients were provided with a daily oral antihistamine (cetirizine HCl), nasal glucocorticosteroid spray (fluticasone), and prescription antihistamine eye drops (olopatadine HCl). Subjects were instructed to use the oral antihistamine daily and the corticosteroid and ophthalmic antihistamine only as needed for symptom control. Asthmatic patients were allowed to use their inhaler as needed, and inhaler use was tracked in the electronic diary.

Outcome Measures

Total Combined Score. The EAAAI,⁷ and FDA,⁸ recommend that allergic rhinitis and conjunctivitis be measured using a composite measure of symptoms and medication use. Symptom and medication use were assessed using the TCS delivered as a daily electronic diary generated and emailed to each subject from the REDCap EDC system. The TCS is the sum of the daily symptom score and daily medication score.⁶ Symptoms including runny nose, stuffy nose, sneezing, itchy nose, gritty/itchy eyes, and watery eyes were scored on a 0 – 3 point scale corresponding to no symptoms, mild, moderate, or severe symptoms for a total daily symptom score range of 0 – 18 for each subject. The daily medication score asked

each patient if they used an oral antihistamine (6 points), antihistamine eye drops (6 points), and a nasal corticosteroid (8 points) for a total daily range of 0 – 20. Thus, a total combined score could range from 0 – 38 each day but based on the instruction that patients should use a daily oral antihistamine, the expected score of a fully compliant patient without symptoms would be six.

NRS-11. The numerical rating scale (NRS-11) is an 11-point scale (0-10) for pain. Immediately and 30 minutes after each intralymphatic injection, patients were asked to rate their discomfort on a scale from 0 (“no pain”) to 10 (“most pain imaginable”).

Serum IgE. Blood samples were obtained prior to treatment and at the end-of-study visit, which was 4-8 weeks after the end of pollen season. Approximately 3 mL of venous blood was collected into a serum separating tube and allowed to clot in an upright position for at least 30 minutes prior to centrifugation. Samples were stored and shipped under refrigeration for allergen specific IgE testing by Clinical Pathology Laboratories (Austin, Texas) using Immucap fluoroenzymeimmunoassay.

Statistical Analysis

Statistical analysis was performed with R Studio Version 1.1.456 software (RStudio, Inc.) following a statistical analysis plan that was written for this study prior to the unblinding of the data. The primary and secondary efficacy endpoints were pre-specified.

Safety analysis included all participants who received at least one dose of study intervention regardless of whether they provided any diary data. Safety analyses were intended to include descriptive statistics rather than formal hypothesis testing for

noninferiority due to the small overall sample size. The study included a formal stopping rule in the event two systemic allergic reactions were detected. Efficacy analyses were on the per protocol dataset, which included participants who received three study treatment injections and completed at least 50% of expected electronic diary responses during the allergy season, with no major protocol violations. Of note, all enrolled patients met the criteria for inclusion in both the safety and per protocol analysis populations. The analysis period was the peak mountain cedar pollen season in the local area, defined as the period when the first cedar pollen count was above 100 ppm (corresponding to “high” on the AAAAI’s NAB scale) to the last date pollen was above 100 ppm followed by more than five (5) consecutive days with a count below 100 ppm. We selected five days for cedar due to the labile nature of cedar pollen and the associated tendency of pollen counts to fluctuate widely depending on wind speed and direction.

The primary efficacy analysis was the between group comparison of the daily average TCS during peak pollen season. The pre-specified analysis was linear regression ANOVA or non-parametric testing if the conditions for ANOVA were not met. Although the data displayed both high skewness and significantly different between group variances, following log transformation, the assumptions for ANOVA testing were met and the results were in agreement with non-parametric testing using the Mann-Whitney U test. The secondary efficacy endpoint was the percentage of days during peak allergy season for which the group average TCS score was lower in the immunotherapy group versus placebo control. A binomial exact test of difference of proportions (Clopper-Pearson) was used for this comparison using the Holm-Bonferroni correction for multiple tests. Other efficacy tests were intended as exploratory in nature, including changes in IgE, sensitivity analyses for

baseline covariates and the PGI-I. Changes in serum IgE were analyzed using Welch's 2-sample t-test. A p-value of 0.05 or less was considered statistically significant.

Sample Size

The initial sample size was planned based on a χ^2 test of between group differences on TCS during peak pollen season with the assumption that the test would be two-sided, the significance threshold would be set at 0.05, and that the between group average difference in TCS during peak pollen season would be 8.0 points with a pooled standard deviation of 9.0 points. Planning assumptions for effect size and variance, and dosing were based on extrapolation from previous intralymphatic immunotherapy studies with other seasonal aeroallergen extracts.

Under these assumptions, the study was planned with a target enrollment of 96 subjects to achieve a 99% chance of detecting differences if the assumed effect size was true. We further assumed a 12% screen failure rate and planned to enroll 110 subjects. However, following discussions with the FDA and receipt of the IND, the aim of the study was changed to proof-of-concept. With only 6 weeks available for enrollment in order to administer the study treatments prior to the anticipated start of allergy season, enrollment was stopped after 26 subjects were screened. In the final analysis plan, reflecting the reduced sample size, Welch's two-sample t-test for the paired comparison replaced the χ^2 test used for initial power calculations.

RESULTS

Patients

An IND was granted on September 27, 2018, and screening and enrollment of subjects started the following day. In total, 26 patients were screened and 21 patients with allergic rhinitis and conjunctivitis due to mountain cedar pollen were enrolled. All 21 patients completed all three treatments and returned after the pollen season for an end-of-study assessment. A CONSORT diagram in Figure 1 shows the patient flow. Baseline characteristics and demographics were similar for both groups (Table 1). Using an ANCOVA model on measured baseline covariates, no significant covariate effects were identified showing that randomization resulted in balance between the treatment groups. No hypersensitive patients were enrolled.

Because of the intensity of cedar allergy season, there is extensive media coverage of cedar allergies and awareness in the region is high. While the study allowed recruitment and treatment at participating clinics throughout central Texas, all patients were treated at one clinic.

Safety

Patients were observed for 1 hour following intralymphatic injections, with the possibility of extended observation in the event of an unresolved adverse event. Monitoring included measurement of vital signs prior to, immediately after, and every 15 minutes thereafter. The total safety score worksheet was also used for each patient to evaluate adverse events of interest and grade those events according to the World Allergy Organization criteria. There were no serious adverse events or systemic reactions of any severity in either group.

There were three cases of local, injection-site redness reported on the total safety score worksheet, all of which occurred in the active immunotherapy group (out of 33 injections, a 9% rate). All were mild and resolved spontaneously without intervention. These events were considered related to treatment. Injection site redness and pain during subcutaneous immunotherapy are associated with glycerin dose and do not always indicate a localized immune reaction.⁹ Unlike most prior studies of intralymphatic immunotherapy, this study used a non-standard, glycerinated extract thus the redness may have been due to glycerin, but a mild local immune response cannot be ruled out. There was one local reaction of bruising at the injection site, which occurred in the placebo group (out of 30 injections, 3% rate). This event was mild, assessed as related to treatment and resolved spontaneously without intervention.

The total safety score across all patients for the active immunotherapy group was three versus one for the placebo group. The rate of localized injection site reactions for subcutaneous immunotherapy has been reported extensively in the literature and ranges from 10-80% of patients. Overall, the rate of mild, local reactions to intralymphatic immunotherapy in this study (9% of injections, 27% of patients receiving active immunotherapy intranodal injections) was similar to the lower end ranges reported elsewhere for subcutaneous immunotherapy.

Vital signs and spontaneous adverse events were also collected. One subject in the active immunotherapy group experienced a transient elevation in blood pressure during post-injection monitoring, while another subject in that group experienced peri-procedural anxiety during two injection procedures. These events were mild and resolved spontaneously

without intervention during the post-injection monitoring period. These events were not considered drug related. It has been reported that about 24% of adult patients experience anxiety or fear of injections or injection-related pain.¹⁰ One finding of this study, that the authors have not seen reported elsewhere was that seven patients (out of 21, 33%) experienced mild feelings of pre-procedural anxiety, including slight elevation in vital sign readings. These feelings were present prior to treatment and thus were not considered adverse events. All subjects completed all three injections and no patients declined the study due to anxiety.

Tolerability

Tolerability of the intralymphatic injection procedure was also assessed using a validated rating scale for pain, the NRS-11. Immediately after the intralymphatic injection, both groups reported similar pain scores on the NRS-11 (placebo, mean = 0.5, SD= 0.5; active immunotherapy, mean = 0.5, SD= 0.5) on a zero to ten point scale with a score of zero meaning “no pain”. At the 30-minute post injection assessment all patients report a pain score of zero (data not shown).

Total Combined Score

All subjects completed at least 50% of expected diary entries, with overall electronic diary compliance at 87% for the study. Peak pollen season ran from December 13, 2018 thru Jan 10, 2019 (Figure 2). During this period there were several readings in the thousands (corresponding to “very high” levels) peaking above 10,000 ppm but interspersed with low or

zero readings. Overall, the 2018-19 season was mild-to-moderate in severity and both earlier and somewhat shorter than is typical.

The primary efficacy endpoint was the between group difference of the daily average TCS during peak pollen season (Figure 3). The daily mean TCS for the active immunotherapy group was 10.5 versus the mean for Placebo of 13.3 with a corresponding effect size of 2.8-point reduction (95% CI, 2.3 – 3.3) in daily average TCS score for immunotherapy patients. The pre-specified analysis was linear regression ANOVA. There was a significant between-group difference ($p < 0.001$), suggesting that the null hypothesis, that the groups were equivalent, may be rejected in favor of active immunotherapy. Non-parametric testing using the Mann-Whitney-test revealed a similar between group difference ($p = 0.001$). The TCS is the sum of the daily symptom score and daily medication score. The mean daily symptom score in the placebo group was 6.3 (SD= 3.0) versus a mean of 4.7 (SD= 2.7) in the active immunotherapy group. The mean daily medication score was 6.7 (SD= 5.2) in the placebo group versus 5.4 (SD= 2.8) in the immunotherapy group. No asthmatic patients in either group reported use of a rescue inhaler during the allergy season. This data suggest that the benefits of immunotherapy included both reduced allergy symptoms and reduced need for medication during peak pollen season. The secondary efficacy endpoint was the percentage of days during peak pollen season for which the average TCS was lower in the immunotherapy group than in the placebo group. This was the case on 20 of 27 days during peak pollen season (Figure 4). A binomial exact test of difference of proportions (Clopper-Pearson) reveals this to be significant ($p < 0.05$) favoring immunotherapy using the Holm-Bonferroni correction for multiple tests because the two outcomes are based on correlated data.

During the study, the average daily pollen count during peak season was 1,126 (SD= 2,152) ppm, while outside the peak pollen season, the average daily count was 22 (SD= 30) ppm. The daily average total combined scores for both groups during these periods are shown in Table 2. The active immunotherapy group had slightly higher average daily TCS scores outside peak pollen season, but lower scores during peak pollen season. Exploratory analysis of these differences in TCS using linear regression ANOVA and ANCOVA were significant ($p < 0.001$) for the effect of immunotherapy, the effect of the pollen season, and the interaction effect of immunotherapy and pollen season (Figure 5). Comparison of patient-level average TCS data was similar to the daily average TCS data: both groups of patients had nearly identical average total combined scores outside of peak pollen season (active immunotherapy = 7.4, SD= 4.1; placebo = 7.0, SD= 4.0). The average change in total combined score between non-peak and peak pollen season for each patient was plus 2.7 points (SD= 3.6) in the active immunotherapy group versus plus 6.3 (SD= 3.6) in the placebo group (Figure 6). A post-hoc analysis using Welch's 2-sample t-test comparing within patient change in average total combined score by group trended towards significance ($p = 0.07$).

Serology

Baseline serum IgE levels were similar in both groups and both groups included two patients with baseline values between 0.10 and 0.34 kU/L, which is considered borderline; however, all patients had a history of winter allergy complaints and a positive dermal test. Increases in allergen-specific serum IgE following allergen exposure during allergy season are to be expected. In the active immunotherapy group, cedar-specific serum IgE levels

averaged 1.62 kU/L (SD= 3.26 kU/L) prior to treatment and increased to an average of 3.10 kU/L (SD= 5.59 kU/L) at the end of the study, an increase of 148%. In the placebo group, baseline serum IgE levels were similar at 1.75 kU/L (SD= 1.53 kU/L) and increased to an average of 6.27 kU/L (SD= 9.64 kU/L) at the end of the study, an increase of 201%. The difference in increase between groups was not statistically significant (Welch's 2-sample t-test, $p = 0.31$). Results are shown in Figure 7 on a log scale.

DISCUSSION

This proof-of-concept study was a randomized, double-blind, parallel-group, placebo-controlled clinical trial designed to examine the safety and clinical efficacy of intralymphatic immunotherapy for rhinoconjunctivitis due to mountain cedar pollen. The strengths of this investigator-initiated study include pre-specification of the endpoints, a high rate of daily diary compliance, independent data monitoring, and clinically and demographically balanced treatment groups. The objectives of this study, and subsequent results did not include a comparison of the efficacy or effectiveness of ILIT relative to other immunotherapies (i.e. SLIT).

Because treatments were to be completed prior to allergy season, one limitation of the study was the short duration available for enrollment, which led to a substantial reduction in the planned sample size. The TCS integrates both allergy symptom and medication use in accordance with guidelines for efficacy measures of allergy treatments, but has not been psychometrically validated, making the clinical interpretation of numeric differences difficult. Despite this, the treatment effect observed in this study, a between group difference of 2.8 points on the TCS favoring immunotherapy (-22%), was similar to the effects reported

in pivotal clinical trials of FDA-approved sublingual immunotherapies for rhinoconjunctivitis due to grass pollen (-26%),⁶ and house dust mite allergies (-16%).¹¹

Two subjects in the active immunotherapy group experienced a reduction in cedar-specific serum IgE and no subjects of the placebo patients experienced a reduction in cedar-specific serum IgE, which was supportive evidence for the clinical effects observed, but a larger sample size would be required to make a stronger conclusion about the immunological effect of the treatment.

No systemic reactions were observed in either group. The rate of local reactions in this study was similar to the lower end of localized injection site reactions for subcutaneous immunotherapy (9% of injections, 27% of patients receiving active immunotherapy intranodal injections).¹² These reactions were uniformly mild in nature and resolved spontaneously without treatment. This finding was consistent with reports from other clinical trials of intralymphatic immunotherapy showing local reactions to be rare and typically mild.

During careful monitoring of vital signs and through spontaneous reports from patients, we assessed other aspects of the safety and tolerability of the procedure. It has been reported that about 24% of adult patients experience anxiety or fear of injections or injection-related pain.¹⁰ One finding of this study, was that seven patients (out of 21, 33%) experienced mild feelings of pre-procedural anxiety accompanied by slight elevation in vital sign readings. These feelings were present prior to treatment and thus were not considered adverse events. All subjects in both groups completed all treatments and no patients declined the study due to anxiety. Across previous ILIT studies, we found only four reported cases of patients starting

but not completing the three-month treatment, a premature discontinuation rate below 4%. In contrast, the reported rate of premature discontinuation at four months for SLIT was 14%.¹¹

Consistent with reports from the original intralymphatic immunotherapy study,² the procedure was virtually pain free. There were no differences in pain measures reported between groups and all patients reported no pain 30 minutes post-treatment. At the end of the study, patients in both groups were generally satisfied with their treatment and would recommend it to a friend or family member (eFigure 1).

In summary, this proof-of-concept study demonstrates that a three-treatment series of intralymphatic immunotherapy injections with a non-standardized, glycerinated allergenic extract of mountain cedar pollen is well tolerated and can reduce the symptoms and medication use associated with allergic rhinitis and conjunctivitis due to mountain cedar pollinosis.

Group	Placebo	Active Immunotherapy
Enrolled Subjects	10	11
Gender		
Female	50% (5)	64% (7)
Male	50% (5)	36% (4)
Race		
Not Reported	60% (6)	82% (9)
White / Caucasian	40% (4)	18% (2)
Ethnicity		
Not Reported	70% (7)	91% (10)
Hispanic or Latino	20% (2)	0% (0)
NOT Hispanic or Latino	10% (1)	9.1% (1)
Age at Enrollment (in years)		
Mean (SD)	35 (12)	40 (13)
valid (missing)	10 (0)	11 (0)
History of Stable Asthma		
Yes	10% (1)	27% (3)
No	90% (9)	73% (8)
Other allergies		
FALSE	30% (3)	36% (4)
TRUE	70% (7)	64% (7)
Screening IgE (kU/L)		
Mean (SD)	1.7 (1.5)	1.6 (3.3)
valid (missing)	10 (0)	11 (0)

Abbreviations: SD, standard deviation; kU/L, kilo unit per litre

Table 1

Baseline patient characteristics and demographics.

Season	Pollen count		Active Immunotherapy	Placebo
		ppm	Daily average total combined score	
Non-Peak				
Mean (SD)	26 (30)	7.8 (1.2)	6.4 (2.3)	
Peak				
Mean (SD)	1,126 (2,152)	10.1 (2.7)	13 (3.9)	
Change	+ 1,100	+ 2.3	+ 6.6	

Abbreviations: SD, standard deviation; ppm, particles per cubic meter

Table 2

Daily average total combined scores by group compared against the daily average pollen count during non-peak and peak season. The difference between peak and non-peak season daily average TCS was significantly different between treatment groups ($p < 0.001$).

Figure 1

CONSORT Patient flow diagram.

Figure 2

The average daily total combined score during peak pollen season was lower in the immunotherapy group than the placebo group ($p < 0.001$).

Figure 3

On 20 of 27 days during peak pollen season the mean total combined score was lower in the active immunotherapy group than the placebo group ($p < 0.05$).

Figure 4

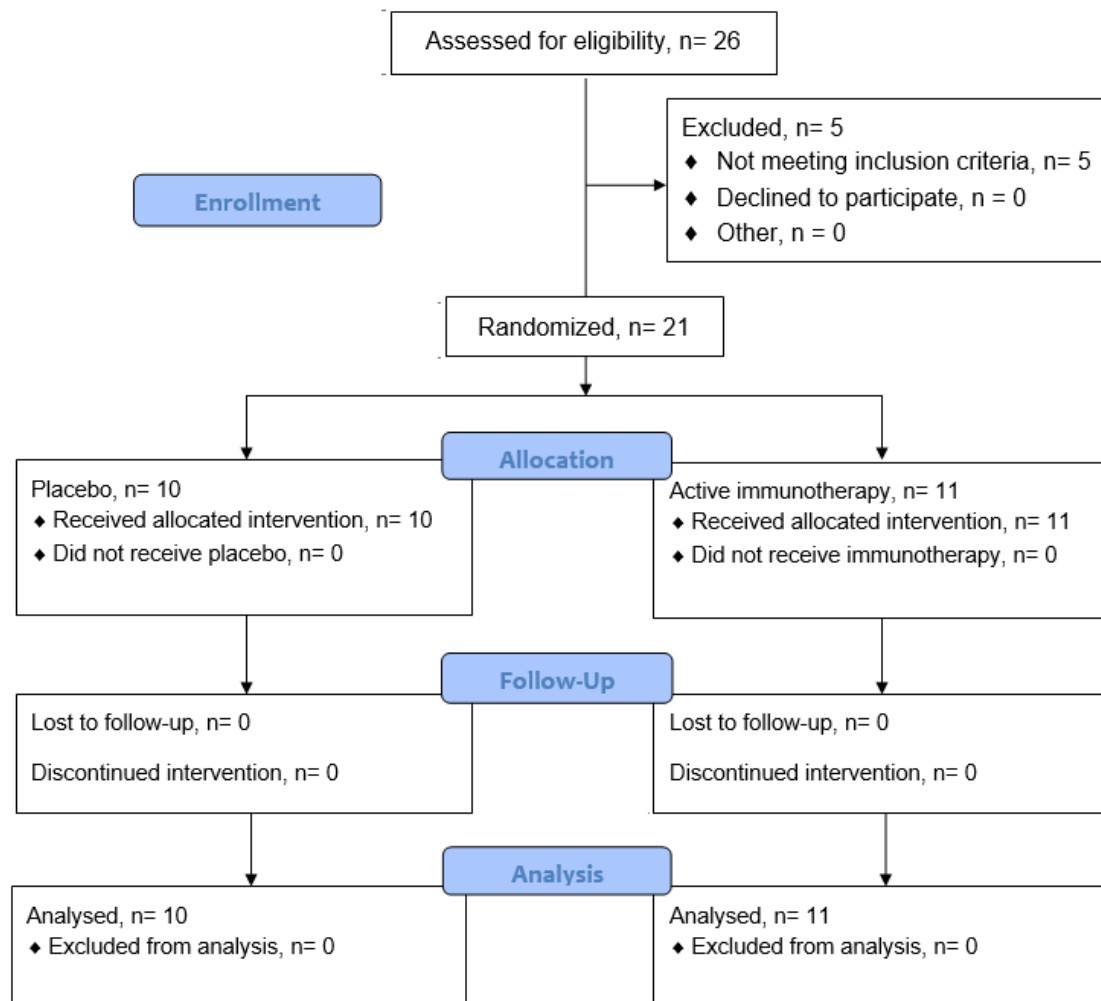
Active immunotherapy attenuated increases in the daily average total combined score for patients during the peak pollen season compared to the placebo group ($p < 0.001$).

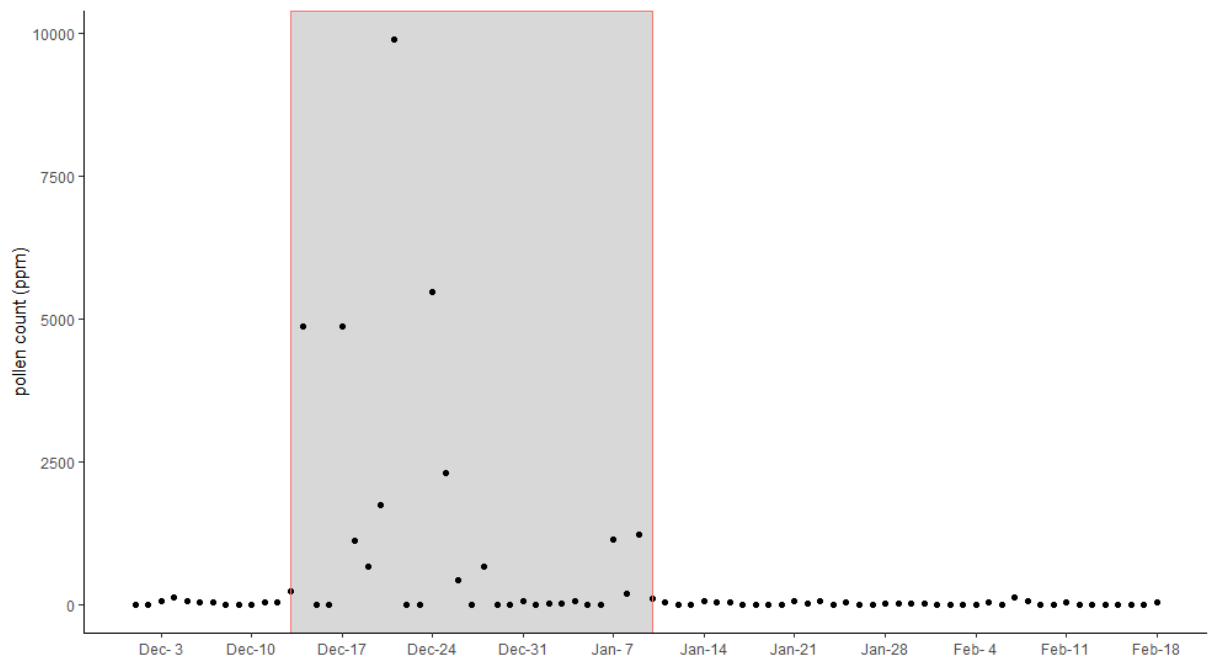
Figure 5

Active immunotherapy attenuated increases in the average total combined score for patients during the peak pollen season compared to the placebo group ($p = 0.07$).

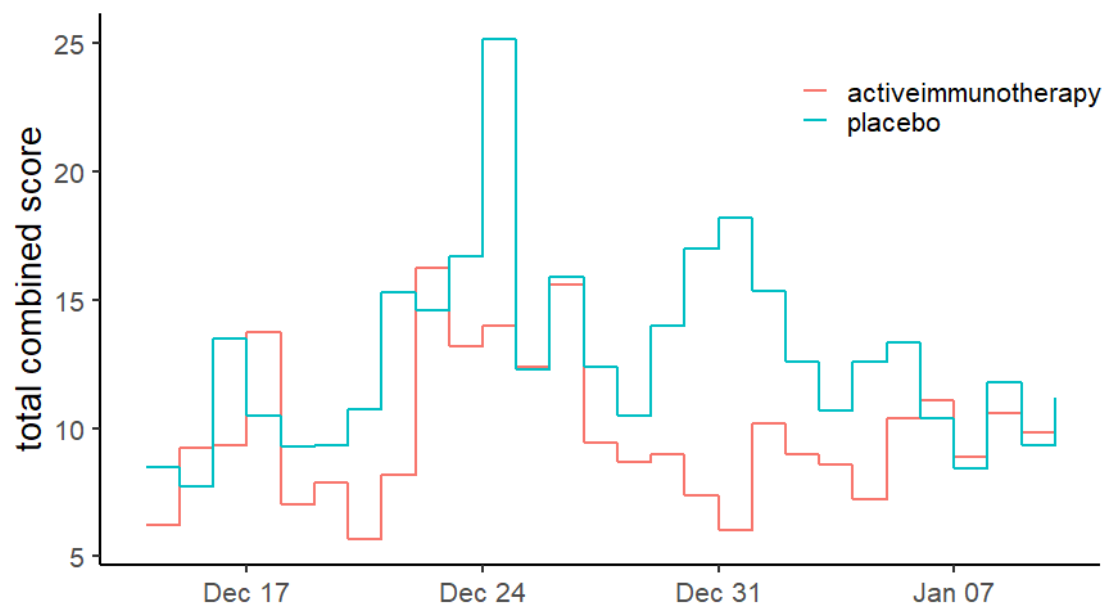
Figure 6

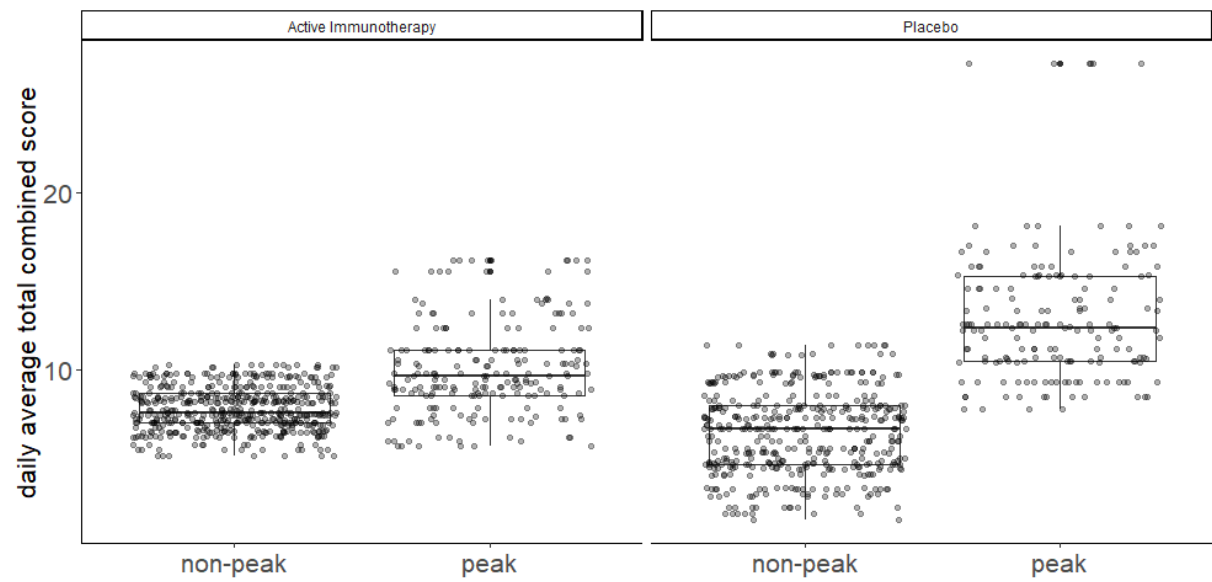
Cedar-specific serum IgE (in kU/L) levels were similar in both groups prior to treatment and at the conclusion of the study.

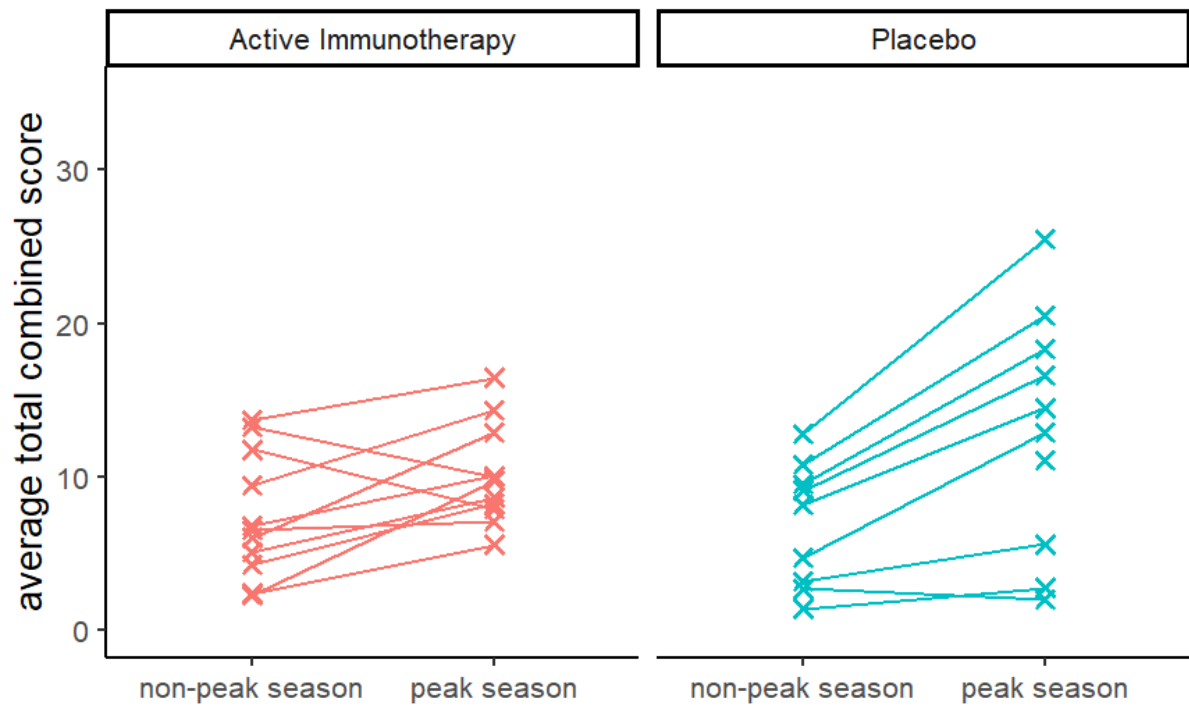
**Figure 1**

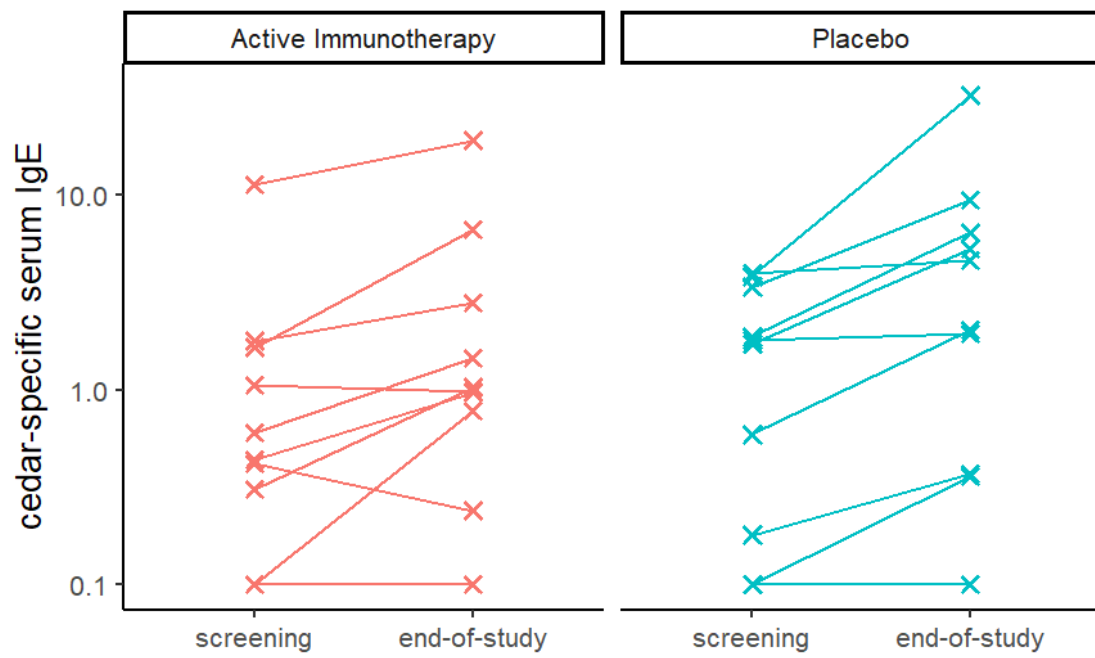
**Figure 2**



**Figure 4**

**Figure 5**

**Figure 6**

**Figure 7**

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