

Intralymphatic immunotherapy in pollen-allergic young adults with rhinoconjunctivitis and mild asthma: A randomized trial

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Study outline

All eligible allergic patients at the allergy clinics at the Karolinska University Hospital in Solna/Huddinge, Stockholm, Sweden, were screened and enrolled in the study during the inclusion period January 1, 2013, and December 31, 2015. Inclusion criteria were age 16 to 45 years, confirmed allergy to birch and/or timothy grass pollen together with rhinoconjunctivitis and mild asthma (controlled asthma [asthma control test score > 19] and a positive methacholine challenge), and otherwise healthy. Exclusion criteria were troublesome allergy to mites and animal dander, disease in the upper airways including sinusitis and nonallergic rhinitis, uncontrolled asthma, pregnancy, breast-feeding, other illnesses, and drug abuse. Unfortunately, the required number of patients (60 according to the power calculation; see the Statistical Analysis section below) was not reached because of narrow inclusion criteria. The study was randomized, double-blind, placebo-controlled, and performed between 2013 and 2017. Before each treatment period, an assistant prepared sealed opaque envelopes for both active and placebo treatments to achieve a final 1:1 ratio. After the first year of the study, it was revealed that 3 actively treated patients had to be excluded and therefore, patients were randomized 2:1, active:placebo, for the remainder of the study to achieve the 1:1 ratio. The envelopes were randomly mixed, and an independent nurse drew 1 envelope for each patient and prepared the medical product according to the envelope at all 3 injection visits. The active allergen extracts could not be distinguished from placebo. Using this method, all the participants, physicians who administered the interventions, and study staff who evaluated the outcomes remained blinded until the follow-up visit after the first pollen season was completed.

Assessment of clinical parameters

Clinical parameters were evaluated before the start of the treatment, in the fall after the first pollen season, and in the fall after the second pollen season (active group only). Treatment effect was evaluated by asking the patients to compare their allergic symptoms during the last pollen season with the pollen season before treatment on a visual analogue scale ranging from 0 (unchanged symptoms, no improvement) to 10 (total symptom relief, complete recovery). Asthma control 4 weeks before follow-up was estimated with the asthma control test, where a score of 19 or less suggests poorly controlled asthma.^{E1} Quality of life was assessed using the Juniper Asthma Quality of Life Questionnaire, giving a score ranging from 1 to 7, and a change in score of 0.5 points is considered clinically relevant.^{E2} Modified SSs and MSs^{E3} were calculated taking into account the frequency: daily (4 points); every second day (3 points); 1 to 3 days per week (2 points); occasionally (1 point); never (0 points), for the following symptoms: blocked nose, rhinorrhea, fatigue, sneezing, and asthma symptoms, and for the following medications used: local and systemic antihistamines, nasal steroids, asthma medication, and eye drops. A maximum score of 20 points for symptoms and 16 points for medication could be obtained.

Nasal provocation tests (NPTs) were performed with a commercially available birch or grass extract, Aquagen 100,000 SQ-E/mL (ALK-Abelló, Copenhagen, Denmark), according to a modified Lebel protocol.^{E4} One spray dose, 0.1 mL of the extract (10,000 SQ-E), was deposited in each nostril. Symptoms during NPTs were scored according to the Lebel scoring scale before and 5, 15, and 30 minutes after administration by a trained research nurse. The scoring system identifies nasal, eye, and ear symptoms: rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, watery eyes, and itchy ears, each graded on a scale from 0 to 3

points, and a total score was summarized after subtracting the starting score (maximum score is 54 + the number of sneezes).

Fraction of exhaled nitric oxide, FEV₁, and forced vital capacity were measured according to international guidelines.^{E5} Bronchial hyperresponsiveness to a challenge with methacholine was assessed, and the dose of methacholine causing a 20% reduction in FEV₁ (PD₂₀) was calculated.^{E6}

Assessment of serum antibodies

Blood was taken at each visit, and serum and plasma were collected for immunological analyses. Allergen-specific IgE level was measured by ImmunoCAP (Phadia, Thermo Scientific, Uppsala, Sweden) for birch (t3) and timothy grass (g6) pollen according to the manufacturer's instructions. A cutoff level ≥ 0.35 kU_A/L was considered positive. In addition, IgG to birch/timothy grass pollen and IgG₄ to birch/timothy grass pollen were measured by ImmunoCAP, with the cutoff 2 mg/L for IgG and 0.05 mg/L for IgG₄.

Outcomes

The primary outcome of the study was the change in symptoms score after NPT. The secondary outcomes were SSs and MSs, changes in response to a bronchial challenge with methacholine (PD₂₀), treatment effect measured on a visual analogue scale, changes in quality of life, changes in allergen-specific serum immunoglobulin levels, incidence of adverse events, changes in asthma symptom scores, changes in pulmonary function measurement (FEV₁ and forced vital capacity), and changes in airway inflammation assessed by fraction of exhaled nitric oxide.

Adverse events and patient analysis

Four patients were removed or left the study before analysis of results; 3 patients (active group) were excluded after the first treatment period because of deviations from the treatment protocol, and 1 patient (placebo) left the study after the first treatment period, before the follow-up (see [Fig E1](#)).

No adrenaline was needed during the study. In total 91 injections were given, 55 with active treatment and 36 with placebo. A total of 69 mild side effects (pain, redness, itch or swelling at injection site, sneezing, and tiredness) within 24 hours after injection were reported. Fifty-nine of these were reported from 13 patients receiving active treatment, and 10 from 5 placebo-treated patients. In the active group, 1 patient suffered from generalized urticaria 15 minutes after injection and 1 patient reported increased asthma symptoms the day after injection.

Eleven patients (6 receiving active and 5 placebo treatments) did not have full analysis data sets. In the active treated group, 1 patient reported side effects after the first treatment period (eczema) and declined the booster dose. This patient completed the follow-up after the first pollen season and is included in the analysis. One patient was diagnosed with sarcoidosis 3 months after the booster injection. After careful medical investigation by a physician in respiratory medicine, no causal relationship could be established. The patient participated in the final follow-up but did not take part in NPT and methacholine challenge and is not included in the analysis of spirometry and quality of life for that time point. In addition, 1 patient did not perform the NPTs and 3 did not answer the symptoms and medication questionnaires. In the placebo-treated group, 1 patient did not perform the NPT at the follow-

up after the first pollen season, another did not perform the spirometry measurements at the follow-up after the first pollen season, and 3 patients did not answer the symptoms and medication questionnaires.

Statistical analysis

A power calculation was performed with a 2-sample *t* test for the primary outcome variable of NPT response. We expected 30% improvement in nasal symptoms in the active group at the NPT 6 to 9 months after treatment compared with the placebo group, based on a previous study,¹⁷ and we assumed a mean of 18 in the placebo group and a mean of 14 ± 5.5 in the active group. Aiming at a power of 0.80 and using a type 1 error rate α level of .05, the calculated sample size was 60 in total. Data are presented as median \pm interquartile range. Mann-Whitney *U* test was used for comparisons between placebo and active treatments. Wilcoxon matched pairs signed rank test was used within the active and placebo groups to compare before treatment to after the first pollen season and after the second pollen season. A *P*value ≤ 0.05 was considered significant. Data were analyzed using Graphpad Prism v 8.0.2 (Graphpad Software, La Jolla, Calif; www.graphpad.com).