Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care

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Background: Sublingual immunotherapy (SLIT) is considered safer and more convenient than subcutaneous therapy and therefore has been proposed as especially suitable for children and in primary care. Most efficacy studies in children lack power to be conclusive, and all have been performed in referral centers.
Objective: To investigate the efficacy of SLIT with grass pollen allergen in children and adolescents with rhinoconjunctivitis in a primary care setting.
Methods: Youngsters aged 6-18 years with hay fever were enrolled from general practices and randomly assigned to receive placebo or grass pollen mix for 2 years. The primary outcome was the mean daily total symptom score (scale 0-15) comprising sneezing, itching nose, watery running nose, nasal blockage, and itching eyes during the months May-August of the second treatment year.
Results: Out of 204 youngsters randomized, 168 entered the intention-to-treat analysis (91 verum, 77 placebo). The mean daily total symptom score did not differ between participants allocated to verum and those allocated to placebo (difference for verum minus placebo: −0.08, 95%CI, −0.66-0.50; $P = .78$). No differences were found for rescue medication–free days, disease-specific quality of life, and overall evaluation of the treatment effect. Local side effects were more frequent in the verum group (39% vs 17% of participants; $P = .001$).
Conclusion: Sublingual immunotherapy with grass pollen in a primary care setting is not effective in children and adolescents.
Clinical implications: Currently, SLIT cannot be recommended for general practitioners as a therapeutic modality in youngsters with grass pollen allergy. (J Allergy Clin Immunol 2007;119:892-8.)

Key words: *Immunotherapy, sublingual, grass pollen, allergic rhinitis, child, adolescent, primary care*

Abbreviations used

AdolRQLQ:	Adolescent Rhinoconjunctivitis Quality of Life Questionnaire
ANCOVA:	Analysis of covariance
ARIA:	Allergic Rhinitis and its Impact on Asthma
BU:	Biological units
ISAAC:	International Study of Asthma and Allergies in Childhood
PRQLQ:	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy

In recent years sublingual immunotherapy (SLIT) has been proposed as an alternative to subcutaneous immunotherapy (SCIT). Owing to a convenient administration form and good safety profile,[1,2] SLIT is particularly suitable for children. The evidence on the efficacy of SLIT in children is still inconclusive. Recent meta-analyses showed conflicting results, hampered by the significant heterogeneity in allergens, duration of treatment, and outcome measures of the included studies.[3-5] The absence of serious side effects enables the administration of SLIT in primary care settings. Prescription of immunotherapy by general practitioners has the additional advantage of favoring introduction at an earlier stage of the disease, thereby potentially preventing the onset of asthma and the development of new sensitizations.[6,7] From that perspective, SLIT is ideal to treat children seen in primary care. However, until now all clinical trials involving children have been performed in referral centers only.

We therefore designed a large randomized, double-blind, placebo-controlled trial in a primary care setting to evaluate the efficacy and safety of SLIT in children and adolescents with a grass pollen–induced allergic rhinoconjunctivitis.

METHODS

Design

Using a randomized, double-blind, placebo-controlled trial design participants entered the trial and started treatment after the grass

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pollen season either in September-October 2001 or in September-October 2002. At the end of the trial 2 years later (in 2003 and 2004, respectively) data were pooled. The ethics committee of the Dutch health authorities and the Erasmus MC-University Medical Center approved the study protocol. Written informed consents were obtained.

Participants

Youngsters aged 6 to 18 years with an International Classification of Primary Care code of R97 (hay fever/allergic rhinitis)[8] were invited by their general practitioner and screened by a research assistant. Inclusion criteria were IgE antibodies to grass pollen ≥0.7 kU/L and a history of rhinoconjunctivitis, assessed by a retrospective symptom score: participants scored 5 symptoms (sneezing, itching nose, watery running nose, nasal blockage, and itching eyes) during the previous grass pollen season (May-August) on a 0-3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe; maximum total score = 15). Participants with a retrospective total symptom score ≥5 were included. Exclusion criteria included the use of daily pulmonary inhaled glucocorticoids during ≥3 months in the preceding year, immunotherapy in the preceding 3 years, sensitization to pets in the family home (specific IgE ≥0.7 kU/L), nasal abnormalities requiring surgery, and contraindications for immunotherapy.[9]

Additionally, IgE antibodies to house dust mite, birch, and cat were determined to assess possible multisensitization. Specific questions on wheezing and dry cough at night from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire[10] established the presence of lower airway symptoms during the last 12 months.

Intervention

Participants underwent verum treatment with a mixture of aqueous extracts of 5 grass pollen species (*Lolium perenne*, *Phleum pratense*, *Dactylis glomeratein*, *Anthoxantum odoratum*, and *Holcus lanatus*; Oralgen Grass Pollen; Artu Biologicals, Lelystad, The Netherlands) in a glycerinated isotonic phosphate-buffered solution. Placebo treatment consisted of the solvent. Treatment starting with a single drop containing 475 biological units (BU) of allergen was increased with 1 drop daily until day 20. The maintenance dose was 20 drops (9,500 BU; 21 μg equivalent Lol p 5) twice weekly for 2 years, resulting in a mean cumulative dose of 1,976,000 BU (4.5 mg equivalent Lol p 5). The drops were administered sublingually and kept there for at least 1 minute before being swallowed. A research assistant instructed the participants and provided written instructions. A pharmacist allocated medication in accordance with a computer-generated randomization list stratifying for symptom score and participating general practice. Participants, parents, investigators, and caregivers were unaware of the group assignment and could not make a distinction between verum and placebo treatment.

Outcome measures

The primary outcome in this study was the mean daily total symptom score comprising sneezing, itching nose, watery running nose, nasal blockage, and itching eyes in the second treatment year. The symptoms were scored on a 0-3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) and recorded on diary cards during the period May 1-August 31. Beforehand, several measures were taken to ensure that days with sufficient exposure to grass pollen would be analyzed (see Statistical Analysis). Daily pollen counts were obtained from the pollen-monitoring station in Leiden (Burkard pollen trap, Leiden University Medical Center). These counts represented the pollen exposure in the region where the participants were recruited and evaluated.

Secondary outcomes were the percentage symptom-free days, the percentage rescue medication–free days, the type of rescue medication used, disease-specific quality of life, overall evaluation of the treatment effect, and safety.

Rescue medication was recorded on diary cards during the period May 1 through August 31. Participants were provided with free cetirizine tablets, xylometazoline nose spray, and levocabastine eye drops. The use of other antiallergic drugs was allowed. Rescue medication was categorized as follows: cetirizine, xylometazoline, levocabastine eye drops, other oral antihistamines, nasal inhaled glucocorticoids, other nasal sprays, and other eye drops. Those days eligible for symptom score analysis were eligible for evaluation of rescue medication as well.

Rhinoconjunctivitis-specific quality of life was assessed with the validated Pediatric (6-11 years) and Adolescent (12-17 years) Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively)[11,12] at baseline and in June during the peak of the grass pollen season. The mean overall score and the mean score for the domains separately were calculated (scale 0-6, higher score represents lower quality of life).

At the end of the study, both participants and their parents evaluated the overall effect of the treatment on a 6-point scale (1 = much worse, 2 = worse, 3 = unchanged, 4 = better, 5 = much better, 6 = no complaints any more).

To evaluate side effects, participants recorded all complaints irrespective of the relationship with the study medication. The complaints were grouped as follows: oral pharyngeal irritation/swelling, gastrointestinal complaints, rhinitis, conjunctivitis, shortness of breath/cough, eczema/itch/rash, allergy (not specified), and other.

Compliance was determined by weighing the returned study medication and calculating the medication intake during the study period. The participant was considered compliant if the medication intake was ≥80% of prescribed.

A research assistant contacted the participants every 6 weeks during the 2-year follow-up either by visits (March-October) or by telephone.

Statistical analysis

The primary outcome was the mean daily total symptom score during the months May-August of the second treatment year. The sample size was based on an earlier trial among adults.[13] A difference in primary outcome between treatment groups of at least 30% was considered to be the minimal clinical important difference.[14] To detect a difference of 30%, 70 participants were required in each treatment group (2-sided $\alpha = 0.05$; power = 90%). To allow for dropouts, we aimed to randomize 100 participants to each group.

The protocol incorporated several measures to ensure that only days with sufficient exposure to grass pollen were analyzed. First, a minimum mean seasonal grass pollen count of 20-30 pollen grains/m^3 was required for the efficacy of grass pollen immunotherapy to emerge.[15] Therefore, if the mean daily pollen count was less than 25 pollen grains/m^3 during the period of May 15-June 30 of a particular year, that year was considered a lost season and would not be evaluated. Second, only those days that exceeded the median pollen count of that year were considered as pollen-relevant days and consequently evaluated. Finally, an often-used and straightforward intention-to-treat procedure, the last observation carried forward (LOCF) method, was used to impute missing data. Thus, if a participant left the study before the second year or the diary card assessed during the second year was incomplete (ie, <50% of pollen-relevant days were filled out), the first year would be analyzed, provided that the first year diary was sufficiently complete (ie, ≥50% of pollen-relevant days were filled out).

Univariate comparison of the primary outcome, all secondary outcomes, and compliance was done by the Mann-Whitney test or χ^2 test in case of percentages.

The main evaluation of the primary end point was done using analysis of covariance (ANCOVA) with the *a priori* defined covariates "age," "sensitization to house dust mite," "sensitization to birch