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Sublingual immunotherapy not effective in house dust mite–allergic children in primary care

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Keywords
adolescent; allergic rhinitis; child; house dust mite; immunotherapy; primary care; sublingual.

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Abstract

Background: Sublingual immunotherapy (SLIT) as a therapy for the treatment of allergic rhinitis in children might be acceptable as an alternative for subcutaneous immunotherapy. However, the efficacy of SLIT with house dust mite extract is not well established.

Objective: To investigate whether SLIT in house dust mite–allergic children recruited in primary care is effective and safe.

Methods: Children aged 6–18 years (n = 251) recruited in primary care with a house dust mite–induced allergic rhinitis received either SLIT or placebo for 2 years. Symptoms and medication use were assessed throughout the study. Primary outcome parameter was the mean total nose symptom score (scales 0–12) during the autumn of the second treatment year. Safety was assessed by recording any adverse event.

Results: Overall, the mean nose symptom score ± s.d. after 2 years of treatment showed no significant effect of SLIT (symptom score intervention group 2.26 ± 1.84 vs. placebo group, 2.02 ± 1.67; p = 0.08). There were no significant differences in secondary outcomes, nor in subgroup analyses. The number of patients reporting adverse events was comparable between both groups.

Conclusions: Sublingual immunotherapy with house dust mite allergen was not better than placebo in reducing rhinitis symptoms in house dust mite–allergic children in primary care. SLIT as administered in this study can be considered safe.

Allergic rhinitis is a common disorder in children. House dust mite (Der. p1 and Der. f1) is the most frequent indoor allergen causing this condition (1, 2). Unlike grass and tree pollen, house dust mites are present all year around with a peak in autumn (1, 2). National and international guidelines have recently been developed to improve the management of patients with allergic rhinitis (3–6).

Allergen immunotherapy is available in different modes of administration (7). Subcutaneous immunotherapy (SCIT) has been the most applied route for several decades and is effective in adults, but carries a risk of severe side effects (8, 9). For children, there are important advantages of using sublingual immunotherapy (SLIT) as a treatment. SLIT has a convenient form of administration and a good safety profile which allows home administration (10–13).

Specific immunotherapy might prevent the onset of asthma and new sensitizations and may accelerate the remission of asthma in children with allergic disease (14–18). Immunotherapy is recommended in the ARIA guidelines for patients with more severe disease, for those not responding to usual treatments, and for those refusing usual treatment (5, 6).

Clinical trials determining the efficacy of SLIT involving children have almost exclusively been performed in referral centers (19–22). SLIT may also be an effective treatment in primary care, as allergic rhinitis is mostly diagnosed and treated in primary health care. Only one study with SLIT in
children recruited in a primary care setting has been performed, and this concerned grass pollen–related rhinoconjunctivitis (23).

Evidence for the efficacy of SLIT in children with house dust mite–induced allergy remains inconclusive (24–26). A recent meta-analysis of SLIT house dust mites for respiratory allergy in both adults and children concluded that there is promising evidence of efficacy for SLIT, using mite extract in allergic patients (adults and pediatric population analyzed together). However, analyses in the pediatric population were based on a very small population and conclusions should therefore be interpreted with caution (27).

Our aim was to evaluate the efficacy and safety of 2 years of treatment with SLIT with house dust mite allergen, compared with placebo treatment, in 6- to 18-year-olds in primary care with house dust mite–induced allergic rhinitis.

**Methods**

**Study design**

The study was a randomized, double-blind, placebo-controlled trial, investigating the efficacy of 2 years of sublingual immunotherapy with SLIT with house dust mite allergen (SLIT-HDM) compared with placebo in 6- to 18-year-old children with allergic rhinitis and a proven house dust mite allergy in primary care. Patients entered the study during September–December in 2005 or in 2006. Written informed consent was obtained from parents of all children and from children aged 12–18 years. The study was approved by the Ethical Review Board of Erasmus Medical Center. A detailed description of the design of the study has been published elsewhere and is summarized below (28). The trial was registered as ISRCTN91141483 (Dutch Trial Register).

**Patients**

Children aged 6–18 years with at least a 1-year history of allergic rhinitis were invited by their general practitioner. Children aged 6–18 years with at least a 1-year history of allergic rhinitis were invited by their general practitioner according to the following predefined criteria. Children were enrolled only if they had IgE antibodies ≥0.7 kU/l to house dust mite (CAP-Phadiatop®; Pharmacia Diagnostics AB, Uppsala, Sweden). HDM CAP-class 2: 0.7–3.5 kU/l; class 3: 3.5–17.5 kU/l; class 4: 17.5–50 kU/l; class 5: 50–100 kU/l; class 6: >100 kU/l); did not use nasal steroids in the month before the start of baseline measurements; had a retrospective nose symptom score of at least 4 of 12 points during the last 3 months; and provided written informed consent.

Patients were excluded when they had been treated with immunotherapy in the previous 3 years; had severe asthma (defined as requiring 800 mcg of budesonide or equivalent other inhaled corticosteroid daily); or had required >3 courses of oral prednisone/prednisolone, or one or more hospital admissions for asthma in the previous year; had a sensitization to pets present at home at entry in the study (IgE antibodies ≥0.7 kU/l); or had a planned surgery of the nasal cavity.

**SLIT**

In the currently marketed Oralgen® House Dust Mite (Oralgen Mijten®, Artu Biologicals, Lelystad, The Netherlands), the content of active substance is declared as biological units (BU), based on in vivo standardization compared to the *D. pter* house dust mite in house reference extract of the manufacturer. To assess the concentration of *Der. p1* and *Der. f1* (mcg/ml) in the study medication, three vials of the active study drug and placebo medication were analyzed. Concentration of *Der. p1* and *Der. f1* was determined by making use of the *Der. p1* and *Der. f1* ELISA kit (Indoor Biotechnologies, Warminster, UK) according to the supplier’s instructions. Participants received an aqueous extract of house dust mites (*D. pter, Dermatophagoides pteronyssinus*) in a glycerinated isotonic phosphate-buffered solution (Oralgen Mijten®) or placebo treatment consisting of the glycerol-containing solvent only. Treatment started on day 1 with 0.05 ml (1 drop) corresponding with 35 BU; the dose was increased by 1 drop per day until day 20 (20 drops = 1 ml = 700 BU). After this dose escalation phase, the maintenance dose was 20 drops twice weekly. The drops were administered sublingually and kept there for at least 1 min before being swallowed. These instructions were given and monitored during home visits by research assistants of Erasmus Medical Center.

**Outcome measures**

The primary outcome measure for efficacy was the difference in total daily mean nose symptom score based on four nose symptoms (rhinorrhea, blocked nose, sneezing, and itching) between the groups receiving house dust mite allergen extract and placebo, after 2 years of treatment in the period September through December. The intensity of these symptoms was subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints, and 3 = serious complaints; the maximum score was 12. The scores were assessed daily by the patient and recorded in a diary. The period of assessment of all outcome measurements was a baseline period of 1 month before randomization and 3 months in the period September through December after 1 and 2 years of treatment.

Secondary outcome measures were the differences in the following measures after 2 years of treatment of the active study drug and placebo:

- the proportion of ‘well days’;
- the proportion of symptom-free days;
- the proportion of days with rescue medication (medication combined);
- the proportion of days with levocetirizine tablets;
- the proportion of days with xylomethazoline nasal spray;
- the proportion of days with levocabastine eye drops;
- total mean symptom score for nose and eye (symptoms combined);
- total mean eye symptom score;
- rhinoconjunctivitis-specific quality of life;
- patients’ rating of benefit of treatment after 2 years.
A ‘well’ day was defined in two different ways: (i) as a day without nose symptoms and without rescue medication and (ii) as a day with minimal nose symptoms (maximum 2 points and per symptom not more than 1 point) and without rescue medication.

A symptom-free day was defined in two different ways: as a day with a total nose symptom score of 0 and as a day with a combined nose and eye total symptom score of 0.

Rescue treatment (levocetirizine tablets, xylometazoline nasal spray, and levocabastine eye drops) and other medication were documented in a patient diary throughout the 2-year period.

For the eye symptom score, the following symptoms were scored: tearing, itching, and redness. The intensity of these symptoms was assessed according to the same grading scale as for nose symptoms.

Rhinocconjunctivitis-specific quality of life (QoL) was assessed through the validated Pediatric (6–11 years) and Adolescent (12–17 years) Rhinocconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively). The score ranged from 0 (i.e., not troubled) to 6 (i.e., extremely troubled), with lower scores indicating a better QoL (29, 30).

Patients were asked for their overall evaluation of the treatment effect after 2 years based on the following scale: 1 = much worse, many more complaints; 2 = worse, more complaints; 3 = no difference, similar complaints; 4 = a bit better, less complaints; 5 = much better, hardly any complaints; 6 = no complaints any more.

Safety was assessed by recording any adverse event. In addition, exploratory analyses were performed for separate nose and eye symptoms, and asthma symptoms after 2 years of treatment. Asthma symptoms were wheezing/dyspnea and dry cough during the night. The intensity of these symptoms was assessed according to the same grading scale as described earlier.

Compliance

Compliance was determined by weighing the returned study medication. Compliance was calculated over the complete study period.

Populations for analysis

The primary analysis was conducted on the intention-to-treat (ITT) population that included all patients who took at least one dose of study medication and who had evaluable diary data after either 1 or 2 years of treatment (i.e., symptom scores for relevant outcome measure filled out for at least 50% per diary period). The per-protocol (PP) population included all patients who completed the study according to the protocol and had no major protocol violations. The major protocol violations were as follows:

- compliance to medication <80%, that is, using <80% of prescribed study medication over the total study period;
- withdrawal from study; loss to follow-up. In case major events occurred during the study period, which necessitated withdrawal from the study, or loss to follow-up/drop-out for other reasons, diary card data were evaluated up to the day of drop-out. Patients were requested to agree with further follow-up according to the study protocol;
- diary of second year filled out <50% of days. In the period of evaluation (diary period after 2 years), the percentage of days at which the daily symptoms were properly recorded should be at least 50.

The safety population included all patients who received at least one dose of the investigational product.

Statistical analysis

A detailed description of the sample size calculation of the study has been published elsewhere (28). We aimed at a sample size of 128 patients in each study group, allowing for 25% loss to follow-up.

Statistical comparison between the active study drug and placebo of the mean daily nose sum score after 2 years was made using repeated-measurements ANOVA (SPSS version 15, SPSS Inc, Chicago, IL). Five covariates were included in this analysis: baseline symptom score at entry into study; age of patients at entry into study; gender; house dust mite CAP-class at entry into study (classes 2–6); and cohort (patients started in 2005 or 2006).

In addition, the year of evaluation after the start of treatment (first year and second year) was included in the model (YEAR). Baseline symptom score and age were entered as continuous covariates (both retaining 1 decimal), gender as dichotomous (male/female), HDM CAP-class as dichotomous (class 2 = 0 and classes 3–6 = 1), and cohort as dichotomous (cohort 1 and cohort 2). YEAR represents a fixed factor (first year of evaluation = 1 and second year of evaluation = 2). In this model, the nose sum score at baseline and after 1 and 2 years was analyzed as square-root-transformed variables to obtain approximate normal distributions.

Additional details of the statistical analysis are provided in the Data Supplement S1.

Subgroup analysis

We compared the effect of placebo and the active study drug within planned subgroups of patients with a baseline mean total nose symptom score of <3 and ≥3; patients with a RAST class of 2 and above 2; and monosensitized and polysensitized patients. No subgroup analyses were performed to explore whether certain patients benefit more from treatment than others.

Results

Demographic and baseline characteristics

A total of 500 children were screened and 257 patients were randomly assigned to receive either SLIT or placebo therapy. Of the 257 randomized patients, 251 comprised the safety population, 226 the ITT population, and 185 patients the PP population.

Fig. 1 shows the flow of patients during the study. The baseline demographic and clinical characteristics of each
At baseline, all characteristics were well balanced between treatment groups; mean age of the patients was 11.7 years and 60% were boys. Mean nose symptom scores at baseline were 3.20 and 3.19 for the active study drug and placebo, respectively; 28% of children had a mean baseline score of 4 or higher, and 17% had a baseline score of 5 or higher. Only 19% of the patients were mono-sensitized. The total duration of treatment was $739 \pm 61$ days in the active study drug group and $735 \pm 70$ days in the placebo group. The proportion of patients taking $\geq 80\%$ of the calculated dose was 81% in the placebo group and 86% in the active group ($p = 0.38$).

### Secondary efficacy measures

At 2-year follow-up, analysis of all secondary outcomes showed no significant differences between placebo and the active study drug for any of these parameters (Table 3). For separate symptoms, no differences were found, except for dyspnea/wheeze, an exploratory efficacy measure showing a
significant difference after 2 years of treatment favoring the placebo group ($p = 0.010$).

Quality of life did not differ between groups in total scores for the PRQLQ and AdolRQLQ ($p = 0.41$ and $p = 0.84$) or for the separate domains of these questionnaires.

The overall evaluation of the treatment effect by the patients did not differ between groups (Table 4, $p = 0.31$).

### Subgroup analyses

None of the analyses showed a difference between the active study drug and placebo within any of the subgroups (Table 5). Reduction in the nose symptom score was larger in patients with a higher baseline score as compared to a low baseline score, but this difference was not significant ($p = 0.079$).

### Safety

A total of 251 patients were analyzed for safety. The number of patients who reported adverse events was comparable between both groups (Table 6). No difference was seen in local oral pharyngeal irritation/swelling in both groups. The most commonly reported adverse event was nasal complaints. Nine patients, six on the active study drug and three on placebo, reported a serious adverse event: generalized eczema; asthmatic complaints; hospitalization for appendicitis ($2\times$); in hospital observation of asthma complaints ($2\times$); planned surgery to replace brain drain; meniscus operation; and in hospital observation of constipation. None of these serious adverse events were considered to be related to the study drug.

### Der p1 and Der f1 concentration

A mean concentration of 2.03 mcg/ml Der p1 and no detectable Der f1 was found in active study drug vials. No Der p1 or Der f1 was detected in the placebo vials. For the active study drug group, the total cumulative dose in a fully compliant patient over the 2-year period was estimated at 435 mcg Der p1.

### Discussion

This is the first large study conducted with house dust mite SLIT in allergic children in primary care. We found no...
significant effects of SLIT compared with placebo on our primary outcome, daily mean nose symptom score, or the secondary end-points, except for a significant worsening of one individual efficacy measure, dyspnea/wheezing, in the SLIT group.

**Strengths**

The study was designed to comply with current guidelines for the design, analysis, and reporting of studies assessing the efficacy of immunotherapy (31–34). It had a baseline assessment; was placebo-controlled, double-blind, and randomized; had an adequate sample size and sufficient duration of treatment. Patients were selected according to predefined clinical criteria, and the primary and secondary outcomes were clearly defined. The baseline assessment occurred between September and December; moreover, the outcomes after 1 and 2 years of treatment were also assessed during this period, that is, when house dust mites are most prevalent (35–37).

The safety of SLIT in children has been confirmed in trials, systematic reviews, and meta-analyses (10–13, 22, 23). In our study, SLIT proved to be safe. We found a remarkable similarity in the proportion of patients with placebo and active study drug treatment reporting local symptoms. A possible explanation is that the activity of the allergen extract administrated was insufficient to generate local side effects.

The ARIA guidelines state that monosensitized subjects have more benefit from a single-allergen SLIT treatment than polysensitized subjects (5, 6). In our study, we included both mono- and polysensitized participants. About 81% of the participants were polysensitized. In contrast to our results, two recent trials suggested the benefit of single-allergen SLIT in polysensitized patients (38, 39). Different pollen seasons can cause symptoms owing to overlap, and various perennial allergens could be responsible for different outcomes in the evaluation of efficacy (32). This is of importance in clinical practice because the majority of patients with allergy are polysensitized. Further studies are needed to establish whether single-allergen SLIT is useful in polysensitized patients.

Our study had an unusually high compliance rate. Previous study showed that monitoring frequency is correlated with compliance (40). We think that this may indeed have been the case in the present study and that the high compliance was caused by the intensive monitoring scheme. Over the 2 years of treatment, the total number of planned contacts was 13 home visits and 23 telephone calls, if possible all by the same research nurse.

**Limitations**

The cumulative dose in our study after 2 years of treatment was estimated at 435 mcg of Der p1, which seems relatively

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### Table 4 Overall evaluation of the treatment effect

<table>
<thead>
<tr>
<th></th>
<th>Active study drug, n (%)</th>
<th>Placebo, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much worse, many more complaints</td>
<td>0 (0)</td>
<td>2 (1.8)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Worse, more complaints</td>
<td>5 (4.8)</td>
<td>2 (1.8)</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>No difference, similar complaints</td>
<td>39 (37.1)</td>
<td>34 (31.2)</td>
<td>73 (34.1)</td>
</tr>
<tr>
<td>Slightly better, less complaints</td>
<td>35 (33.3)</td>
<td>39 (35.8)</td>
<td>74 (34.6)</td>
</tr>
<tr>
<td>Much better, hardly any complaints</td>
<td>23 (21.9)</td>
<td>30 (27.5)</td>
<td>53 (24.8)</td>
</tr>
<tr>
<td>No complaints any more</td>
<td>3 (2.9)</td>
<td>2 (1.8)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>105</td>
<td>109</td>
<td>214</td>
</tr>
</tbody>
</table>

### Table 5 Primary outcome: results of subgroup analyses after 2 years of treatment

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Treatment effect</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Baseline mean total nose symptom score &lt;3</td>
<td>0.057</td>
<td>−0.122 to 0.236</td>
</tr>
<tr>
<td>RAST class</td>
<td>HDM CAP-class 2</td>
<td>0.125</td>
<td>−0.196 to 0.446</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Monosensitized</td>
<td>0.108</td>
<td>−0.260 to 0.477</td>
</tr>
<tr>
<td></td>
<td>Polysensitized</td>
<td>0.113</td>
<td>−0.032 to 0.259</td>
</tr>
</tbody>
</table>

---
low compared with most other studies (27). This could be a possible explanation for the absence of an effect of SLIT compared with placebo, which has consequences for the generalizability of our findings.

A lack of similar studies makes it difficult to compare findings and doses between studies. If we compare HDM-SLIT studies with children and a diagnosis of allergic rhinitis (and/or asthma), different cumulative doses and different outcomes in efficacy are reported. Hirsch et al. (41) reported a cumulative dose of 570 mcg for a duration of 1 year, concluding that SLIT over 12 months with the fivefold Der p1 dose of subcutaneous IT was well tolerated, but no consistent clinical benefit or immunologic change compared with placebo could be found. Bahcecil et al. (42) reported a cumulative dose of 560 mcg over 6 months; their results suggest that SLIT may be a useful alternative or additional therapy in the treatment of children with asthma/rhinitis caused by HDM. Pham-Thi et al. (43) performed a study in children with house dust mite-induced allergic asthma for 18 months with a cumulative dose of 6900 mcg Der. p1 and 14,700 mcg Der. f1 and found no evidence for the efficacy of HDM-SLIT.

Transparency in the total doses of major allergens and the immunologic activity of an allergen preparation should be encouraged, and this information should be made available by manufacturers. Also, in most studies, failure to report the total dose of major allergens in standardized units hampers comparability (44, 45).

A relevant question is: was the disease severity of the present study population enough to allow the detection of treatment effects? It is known that about 90% of the patients consulting a GP have moderate to severe disease (46, 47). In our population, the baseline symptom scores were considerably lower than the retrospective symptom scores assessed at inclusion. However, compared with other studies, our patients’ symptom scores at baseline were similar or even higher (43, 48).

Most studies performed in referral centers reported symptom scores only after treatment (21, 49) and the symptom scores in our study were comparable to those. Thus, there was substantial room for improvement, and it is unlikely that the absence of effect can be explained by low initial symptom scores in the study population.

As all children were treated for two years, this should be sufficient to show an effect. Apart from the low SLIT dosage, mentioned elsewhere, another possible explanation for a lack of effect may be the regimen of twice-weekly dosing during the maintenance phase. An animal study suggested that reducing dosing intervals may improve immunologic outcomes (50). However, the regimen in our study was in accordance with the manufacturer’s guidelines and we adhered to these guidelines.

Calculation of mean scores in a fixed time period does not take into account the wide variation in day-to-day symptoms. Therefore, additional end-points have been proposed to evaluate the efficacy of immunotherapy (51). In the current study, however, primary and secondary outcomes did not differ between the active study drug and placebo group.

We found a statistically significant difference for the dyspnea/wheeze score after 2 years of treatment in an exploratory analysis, favoring the placebo group. The absolute difference between group means was small, only 0.10 on a 0–4 point scale; hence, the clinical relevance of this result is questionable.

In the Netherlands, patients are often referred to an allergologist for indication and treatment with SCIT or SLIT (3, 4). Recent articles also address the importance of primary care in the treatment for and management of allergic rhinitis (52–54). The World Allergy Organization proposed more collaboration between primary care and allergologists for an optimal delivery of SLIT in the community setting. GPs should be trained for the early detection, diagnosis, management of and treatment for allergic disorders (33). For these reasons, we considered it important to perform our study in a population that was seen in primary care. The effectiveness of SLIT for house dust mite allergy in such a population is highly relevant, as marketing efforts of SLIT manufacturers have specifically targeted this group over the past decade.

Conclusion

HDM-SLIT with a relatively low dosage was not effective in this primary care population of children with allergic rhinitis. SLIT was in general safe and well tolerated.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

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References


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Sublingual immunotherapy in primary care


