

ORIGINAL ARTICLE

# Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study

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## ABSTRACT

**Background:** Natural rubber latex (NRL) allergy remains an important allergic disease triggering urticaria, asthma, angioedema and anaphylaxis. Specific immunotherapy can help to solve problems related to NRL allergy. So far, no controlled clinical trials have been performed in children suffering from NRL allergy.

**Objectives:** To evaluate the safety and efficacy of sublingual immunotherapy (SLIT) with a commercial NRL extract in children with NRL allergy.

**Research design:** Randomized, double-blind, placebo-controlled, 12-month trial.

**Patients and methods:** Twenty-six children (aged 4–15 years) with NRL allergy, who had cutaneous and/or respiratory symptoms, including oral allergy syndrome to fruits containing cross-reactive allergens, were recruited. Twelve children were randomized to SLIT with a commercial NRL extract and eight to placebo (3:2). An additional six children with NRL allergy served as untreated controls.

**Main outcomes measures:** A glove use test was utilized to monitor skin and systemic symptoms triggered by NRL exposure at baseline and 3, 6, 9 and 12 months later. Oral allergy symptoms were also monitored.

**Results:** No side effects related to treatments were observed in any patient. A significant improvement of symptom score in treated patients in comparison with baseline values was observed at 3 months ( $p = 0.01$ ) and consolidated after 1 year of treatment ( $p = 0.0005$ ). In comparison with placebo, significant improvements were observed starting at 9 months from study start ( $p = 0.015$ ) and at 12 months ( $p = 0.005$ ). The number of foods triggering oral allergy symptoms increased in placebo and control subjects, but not in active treated patients ( $p = 0.05$ ).

**Conclusion:** Latex SLIT was safe and efficacious in paediatric patients with NRL allergy.

## Introduction

Immediate-type (IgE-mediated) hypersensitivity to natural rubber latex (NRL) is recognized as a public health concern and a clinically important issue. After exposure, NRL products can trigger both type I (urticaria,

angioedema, asthma and anaphylaxis) and type IV, (contact dermatitis) allergic reactions. The prevalence of allergy to NRL is common among healthcare professionals<sup>1</sup> but also in children undergoing multiple operations.

Exposure to the antigen mainly occurs through the respiratory mucosa and the skin. Clinical

manifestations of type I NRL hypersensitivity could range from urticaria to angioedema, rhinoconjunctivitis, asthma or anaphylactic shock.

In the last decade, in industrialized Countries, a latex allergy epidemic among healthcare workers has broken out and then relatively receded. This behaviour can be interpreted as the consequence of the adoption of precaution measures in response to an increase in viral infection (hepatitis, HIV) in the late Eighties<sup>2</sup> and by the preventive measures to reduce latex exposure afterwards<sup>3</sup>.

Different proteins present in various NRL products are implicated in causing allergy in distinct risk groups<sup>4</sup>. Recent estimations indicate that NRL is used, alone or combined with other substances, in the manufacturing of more than 40 000 different objects for technical, professional and everyday-life use<sup>5</sup>.

In addition, a significant association between latex sensitization and the presence of one or more positive skin prick test responses to aeroallergens and/or food allergens has been demonstrated<sup>6,7</sup>. Atopic patients are reported to be more susceptible to latex allergy than non-atopic individuals<sup>8,9</sup>.

Prevention is considered the first step in the treatment of NRL allergy. Nevertheless, since latex allergens are very common in both professional and private environments, strict avoidance measures can hardly be achieved and kept. Encouraging results have been obtained with NRL-specific immunotherapy by subcutaneous<sup>10,11</sup>, percutaneous<sup>12</sup> and sublingual routes<sup>13,14</sup>, but the number of patients studied until now remains relatively low, in particular as far as paediatric subjects are concerned.

No controlled randomized trials have been performed so far in children with NRL allergy. We have, therefore, conducted a double-blind, placebo-controlled trial to evaluate the safety and efficacy of sublingual immunotherapy (SLIT) with a standardized NRL extract in a population of paediatric patients sensitized to latex who had cutaneous and, in some cases, respiratory symptoms.

## Materials and methods

### Patients and study design

The study design was a randomized double-blind, placebo-controlled, 12-month trial on paediatric patients (aged 4–15 years) with clinical signs of allergy to NRL, eligible for sublingual immunotherapy (SLIT). The study start was in autumn 2003, after local Ethics Committee approval. A total of 86 patients, attending our clinic with a suspected NRL allergy were screened. Twenty-six patients were recruited. On the basis of a computer-generated random allocation list, 20 patients

were assigned either to the SLIT (active) group ( $N = 12$ ) or to the control group ( $N = 8$ ) (3:2). Six additional patients were monitored as a further control group. The parents gave their informed consent before the children started the trial after being informed of the possible alternatives, such as allergen avoidance or symptomatic medication. Patients were selected according to the following inclusion criteria: age above 4 years and below 16 years with a clinical history of urticaria, rhinoconjunctivitis and/or asthma due to sensitization to NRL. History of anaphylactic shock, immunosuppressive treatment, severe immunological diseases (i.e. leukaemia, LES) and dermatographism were considered exclusion criteria. In all patients contact with NRL from different sources triggered symptoms. In 11 cases this was due to contact with latex gloves, in eight cases contact with balloons, in two cases wearing a bathing cap, in one case contact with an orthodontic device, and in one case contact with a film for food preservation. Moreover, in one child, symptoms were triggered by entering a room for the storage of tyres and in two children a reaction occurred during surgery for correction of urogenital (one patient) and oesophageal (one patient) malformations. Eighteen patients went through surgery more than once and two of these had spina bifida. No obvious exposures were known for eight patients. Fourteen patients suffered oral allergic syndrome and/or systemic allergic reactions to one or more vegetables. Of these, 11 had a documented latex–fruit syndrome. Twelve children also had a food allergy to one or more of the following foods: egg, milk, wheat, fish, shellfish. All these food allergies were clinically severe enough to prompt a specific exclusion diet. Patients' characteristics are shown in Table 1.

### Outcomes measures

The outcomes of this study were the safety and efficacy of sublingual immunotherapy after 1 year. Safety was evaluated clinically. The main hypothesis of the trial was to evaluate if specific sublingual immunotherapy could increase tolerance to structured use and rubbing test with NRL containing gloves. The following secondary outcomes were also considered: (1) conventional skin prick tests with an NRL extract, prick-by-prick with NRL-containing gloves and serum NRL-specific IgE in order to check for variations, if any, in the IgE responses to the allergen; (2) skin prick tests with inhalant and with food allergens, which are known to be associated with sensitization and allergy to NRL; (3) prick-by-prick tests with vegetables, which display a clinical and/or immunological cross-reactive behaviour with NRL allergens; (4) changes in severity of symptoms of the oral allergic syndrome, which is associated in most patients with NRL allergy.

**Table 1.** Patients' characteristics at baseline

|                                        | Active, N = 12 | Placebo, N = 8 | Control, N = 6 |
|----------------------------------------|----------------|----------------|----------------|
| Age, years, mean (range)               | 10.3 (5–14)    | 11.0 (5–14)    | 10.7 (4–15)    |
| Sex (female/male)                      | 4/8            | 4/4            | 4/2            |
| Clinical symptoms to latex exposure    |                |                |                |
| Rhinoconjunctivitis, N (%)             | 12 (100%)      | 4 (50%)        | 4 (66%)        |
| Asthma, N (%)                          | 10 (83%)       | 3 (37%)        | 3 (50%)        |
| Urticaria, N (%)                       | 4 (33%)        | 6 (100%)       | 4 (66%)        |
| Food symptoms, N (%)                   | 8 (66%)        | 2(25%)         | 4(66%)         |
| Patients with a positive skin test to: |                |                |                |
| Inhalant                               | 9 (23)         | 6 (15)         | NA             |
| Food                                   | 5 (7)          | 2 (2)          |                |
| Serum IgE, kU/L , mean (SD)            | 28 (32)        | 23 (24)        | 13 (11)        |

Note: numbers of individuals with positive skin tests to inhalant and food allergens at recruitment are also reported (the number in parenthesis is the cumulative number of skin tests positive to inhalant or food allergens, respectively)

N.A.: not available

Details of these tests are reported in the following paragraphs.

### ***Skin tests with allergenic extracts***

Sensitization to NRL was assessed by a serum IgE (Pharmacia, Peapack, USA) level > 0.7 kU/L (which is defined as the lower cut-off of the class II range of positivity with the highest specificity according to Saxon<sup>15</sup>) and by a positive skin prick test for latex. The latter was performed with a commercially available skin prick test solution containing an NRL extract standardized at 500 µg/mL of total protein and corresponding to 30 Histamine Equivalent Prick test Units (HEP) (ALK Abellø, Milano, Italy)<sup>15</sup>. Sensitizations to the following inhalant and food allergens were also tested by skin prick test: *Dermatophagoides pteronyssinus* and *farinae*, cat, dog and horse dander, *Alternaria alternata*, *Cladosporium herbarum*, *Phleum pratense*, *Parietaria judaica*, *Artemisia vulgaris*, *Platanus acerifolia*, *Cupressus arizonica*, *Olea europaea*, cow milk, albumen, tomato, peanut, codfish and wheat. All allergen extracts were commercially available purified preparations from ALK Abellø. The skin prick test for NRL and other allergens was performed and interpreted according to the EAACI guidelines<sup>17</sup>.

### ***Prick-by-prick tests with fresh vegetables and with NRL containing gloves***

Skin tests with fresh vegetables were done by using the prick-by-prick technique with the following foods which are clinically implicated in the latex–fruit syndrome (cross-allergy) and for which there is evidence of immunological cross-reactivity (cross-antigenicity) with inhibition techniques<sup>18</sup>: kiwi, banana, pineapple, avocado, peach, passion fruit, mango, chestnut, potato, buckwheat, dill, fig, carrot, sweet pepper, tomato,

oregano and sage. Moreover, other fruits were included, that on the basis of our experience and of previous observations<sup>19</sup> can be considered cross-antigenic but not inducing cross-allergy (melon and papaya). Finally, a third group was considered (orange, apple, grapes, eggplant, walnut, pear, apricot, blackberry, watermelon and almond) for which only cross-sensitization at the skin test level is observed.

The prick-by-prick test with a latex containing glove was performed by running the lancet through the glove laid on the forearm surface. Also prick-by-prick tests were interpreted according to the EAACI guidelines<sup>17</sup>.

### ***Evaluation of tolerance to fruits***

A careful medical history was collected at each visit, where the eating behaviour for the above reported list of 29 vegetables was investigated. The possible answers to questions were that the vegetable was either ‘non-tolerated’ (for oral allergy syndrome, or more severe reactions), ‘tolerated’ or ‘not taken’. In the ‘not taken’ group were included foods excluded for personal taste preferences and/or for the fear of suffering adverse reactions and/or for unavailability at the season of visit.

### ***Glove use and rubbing test***

This technique has been first described by Turjanmaa and co-workers<sup>20</sup> and was applied with modifications aimed to maximize the sensitivity of the assay to NRL-dependent type-I reactions. Briefly, patients were asked to wet their hands with water and to put on one latex glove (Touchy gloves, International PBI, Milan, Italy) for 10 min. Then the glove was removed and the face was rubbed twice with the external part and twice with the internal part of the glove. Fifteen minutes later local (itching, erythema, wheals) and general symptoms (rhinitis, asthma) were

evaluated. Each symptom was scored according to values indicated in Table 2. Scoring did not take into account the severity of each symptom but attributed to the symptom itself an absolute value incorporating the assessment of severity. In the absence of an international validated score tool, the scoring system utilized in the present study was developed in our clinic.

### Active treatment

SLIT-LATEX (ALK-Abellø), a commercially available NRL extract for sublingual administration, was used. The extract was prepared by neutralization, semi-purification and concentration of an ammoniated NRL suspension and biologically standardized, as described elsewhere<sup>16</sup>. The treatment was prepared in five vials containing dilutions of the NRL extract in glycerosaline solution, phenol (0.3% W/V) as a preservative and human serum albumin (0.04% W/V) in all vials except in the most concentrated. All doses of the build-up phase were administered in a hospital setting with

the availability of complete resuscitation equipment and trained personnel, keeping the patient under constant observation after each administration and for at least 30 min after each day's last administration. Patients were instructed to keep the allergen solution in the mouth for at least 3 min and then to swallow (sublingual-swallow technique). The protein concentration of each vial in µg/mL and the treatment schedule used is detailed in Table 3. The build-up phase was completed in 4 days according to a rush schedule. After the build-up phase patients followed the maintenance schedule, consisting of two drops of the maximum concentration (resulting in 40 µg of NRL per administration) once daily for a total of 12 months. During the first week of the maintenance phase, doses were dispensed at the hospital, where patients remained under medical surveillance for at least 30 min after administration. The corresponding placebo had a similar aspect and taste as the active vaccine. Maintenance administrations were performed at home by each patient, whose parents had been

**Table 2.** Symptom score applied to the glove use and rubbing test

| Symptom (yes/no)        | Score | Symptom (yes/no)       | Score |
|-------------------------|-------|------------------------|-------|
| Skin of the hand        |       | Upper respiratory      |       |
| Erythema                | 0/1   | Sneezing               | 0/1   |
| Itching                 | 0/1   | Rhinorrhoea            | 0/1   |
| Wheal                   | 0/2   | Nasal obstruction      | 0/1   |
| Oedema                  | 0/2   | Nasal itching          | 0/1   |
| Skin of the face        |       | Lower respiratory      |       |
| Erythema                | 0/1   | Cough                  | 0/1   |
| Itching                 | 0/1   | Stridor                | 0/2   |
| Wheal                   | 0/2   | Mouth and throat       |       |
| Oedema                  | 0/2   | Itching                | 0/1   |
| Urticaria               | 0/3   | Burning                | 0/1   |
| Eyes                    |       | Feeling a foreign body | 0/2   |
| Conjunctivitis          | 0/2   | Vomit                  | 0/3   |
| Itching, tears, burning | 0/1   |                        |       |

**Table 3.** Treatment schedule of build up phase

| Day | Minute | Vial concentration (µg/mL) | Drops | Administered dose (µg) | Cumulative dose (µg) |
|-----|--------|----------------------------|-------|------------------------|----------------------|
| 1   | 0      | $5 \times 10^{-8}$         | 1     | $2 \times 10^{-9}$     | $2 \times 10^{-9}$   |
|     | 15     | $5 \times 10^{-8}$         | 10    | $2 \times 10^{-8}$     | $2 \times 10^{-8}$   |
|     | 30     | $5 \times 10^{-5}$         | 1     | $2 \times 10^{-6}$     | $2 \times 10^{-6}$   |
|     | 45     | $5 \times 10^{-5}$         | 10    | $2 \times 10^{-5}$     | $2 \times 10^{-5}$   |
| 2   | 0      | 0.05                       | 1     | 0.002                  | 0.002                |
|     | 15     | 0.05                       | 10    | 0.02                   | 0.022                |
|     | 30     | 5                          | 1     | 0.2                    | 0.222                |
|     | 45     | 5                          | 10    | 2                      | 2.222                |
| 3   | 0      |                            | 1     | 20                     | 22.2                 |
|     | 15     |                            | 2     | 40                     | 62.2                 |
|     | 30     | 500                        | 3     | 60                     | 122.2                |
|     | 45     |                            | 4     | 80                     | 202.2                |
| 4   | 60     |                            | 10    | 200                    | 402.2                |
|     | 0      | 500                        | 25    | 500                    | 902.222              |

Maintenance phase: two drops (40 µg) from vial number 4, once daily. Concentrations (µg/mL) and amounts of administered treatment (µg) refer to NRL proteins

instructed on how to proceed in the case of adverse effects and specifically asked to immediately report any adverse reaction or discomfort to the doctor.

## Statistical analysis

The statistical analysis was carried out on an intention-to-treat basis. On the basis of this preliminary analysis, comparisons of the results observed in different groups were then performed with Mann–Whitney statistic test. Wilcoxon signed rank test was used to compare data over time in the same group. Numbers of individuals and numbers of observations, which scored in the experimental groups either positive or negative at different times, were compared by the Fisher's exact test. The Chi-square 3X2 test was utilized to compare numbers of non-tolerated foods between the three groups. On the basis of previously published data<sup>14</sup>, sample size calculation was performed on the hypothesis to detect a difference in rubbing test score in comparison with baseline values of at least  $1.8 \pm 1.5$  after treatment with SLIT. With a statistical power of 80% and a type I error of 0.05, a total of 10 patients in the active arm were estimated to be enrolled in the trial. Sample size calculation was performed using the StudySize, computer program. Randomization was performed using a computer-generated randomization list (Arcus Quickstat) with a block of five patients in a 3:2 ratio. All statistical analyses and the sample size calculation were done with the BMPD statistical software package (BMPD Inc., Los Angeles, CA, USA). All statistical tests were two-sided with a significance level of 0.05.

## Results

All randomized patients concluded the 12-month treatment period and were evaluated for safety and efficacy. Their demographic characteristics are shown in Table 1.

### Safety

The treatment was well tolerated by all subjects included both in the active and placebo groups. There was no sign of local (buccolingual) or systemic side effects, including gastrointestinal symptoms or anaphylactic shock.

### Efficacy

#### Glove use and rubbing test

In the active treated group, in comparison with baseline values, a significant decrease (–82%) of the symptom

score of the glove use and rubbing test was observed at T4 (from  $8.8 \pm 5.0$  to  $1.6 \pm 1.0$ ) ( $p < 0.0005$ , Wilcoxon test). A significant reduction ( $p < 0.01$ ) was also observed starting from T1. In contrast, in the placebo group, no changes were observed at any of the considered times. In comparison with placebo, active treated subjects showed a significant reduction of the severity of triggered symptoms at T3 ( $p = 0.015$ ; Mann–Whitney test). This tendency was remarkably strengthened at T4 ( $p = 0.005$ ) (Figure 1). At the end of the trial all subjects (12/12; 100%) in the active group showed a reduction of 50% or more in the symptom score of the glove use and rubbing test in comparison with three out of eight (37%) in the placebo group.

### Skin tests

Table 4 reports the results of skin tests. No changes were observed in the three experimental groups in the wheal reaction to the conventional NRL skin prick test measured at study start as compared to any of the other considered times. Similarly, no changes were observed in the three experimental groups in the wheal reaction, measured by the glove prick-by-prick test at study start, at any of the considered times. No significant intra-group changes were observed, either in the number of individuals who displayed at least one positive skin prick test, or in the cumulative number of positive prick tests for inhalant and food allergens, respectively, when comparing T0 values with T4 values. The same applied to the cumulative numbers of positive prick-by-prick tests, when comparing T4 with T0. All subjects had more than one positive prick-by-prick test at T0, and this held true at T4. The

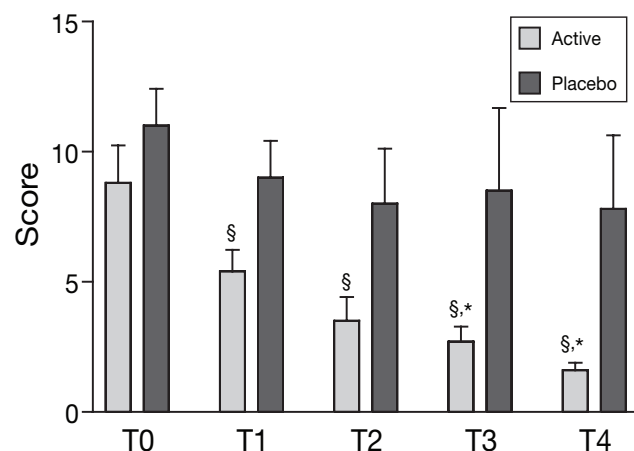


**Figure 1.** Scores of use and rubbing tests at study entry (T0), and after 3, 6, 9 and 12 months of immunotherapy with NRL (T1, T2, T3 and T4, respectively). Mean (SD) values. § $p < 0.01$ , Wilcoxon test (comparison with baseline values); \* $p < 0.02$ , Mann–Whitney test (comparison between groups)

**Table 4. Skin tests results**

|                                                   | T0        |           |           | T4        |           |           |
|---------------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
|                                                   | Active    | Placebo   | Control   | Active    | Placebo   | Control   |
| NRL skin prick test, mean (SD) diameter, mm       | 6.9 (2)   | 7.5 (1.9) | 7.4 (3.2) | 7.2(4.8)  | 7.6 (4)   | 7.6 (3.8) |
| Glove prick-by-prick test, mean (SD) diameter, mm | 3.5 (1.3) | 4.8 (2.3) | 3.3 (2.2) | 4.5 (1.9) | 6.3 (3.7) | 6.8 (4.9) |

number of tolerated vegetables was monitored at study start (T0) and at T4. In the placebo and control groups there was an increase in the number of non-tolerated vegetables. At T4 the numbers of non-tolerated foods were eight in the active group, 10 in the placebo group and 16 in the control group ( $p = 0.05$ ; 3X2, Chi square test (Figure 2).

### Serum IgE

Baseline values of specific serum IgE levels ( $28.69 \pm 32.15$ ,  $23.12 \pm 24.79$  and  $13.69 \pm 11.73$  kU/L, for the active, placebo and control groups, respectively) remained unchanged in the three groups at all considered times (e.g., T4:  $34.99 \pm 42.62$ ,  $29.22 \pm 23.49$  and  $49.39 \pm 38.83$  kU/L, the active, placebo and control group, respectively).

## Discussion

This study compares safety and efficacy of latex SLIT with placebo in sensitized children. To our knowledge, this is the first double-blind, placebo-controlled study published on latex SLIT in this particular patient population and confirms both excellent tolerance and successful desensitization that has been observed in previous trials in adult patients<sup>13,21,22</sup>.

No relevant side effects were observed during the trial, in agreement with the works from Patriarca's group on non-injective approaches in NLR allergy<sup>13,21–23</sup>.

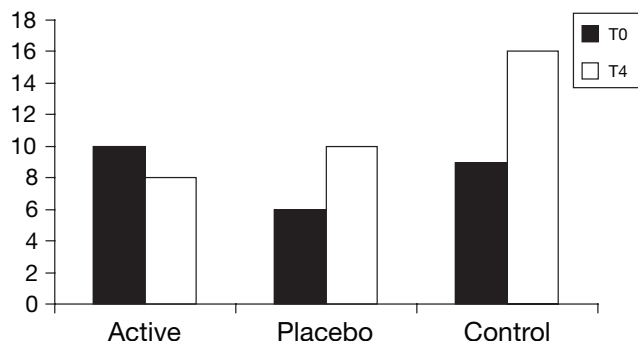


**Figure 2.** Changes in the number of vegetables triggering adverse reactions in the three cohorts of patients indicated in the legend. Foods were indicated as 'not tolerated' by means of clinical history and enumerated at study entry (T0) and after 1 year of immunotherapy with NRL (T4). On the y-axis the numbers of 'not tolerated' foods at T0 and T4

In contrast, in studies carried out in adults with NRL allergy, immunotherapy was associated with an incidence of reactions in 8–24% of the population<sup>14</sup>. Several biological and clinical parameters were evaluated in patients included in this study. Levels of specific IgE to NRL did not vary between groups or within groups at different times from study start, confirming previous results obtained in a trial with NRL subcutaneous immunotherapy<sup>24</sup>. Moreover, no statistically significant modifications were observed in the three experimental groups regarding skin reactivity to NRL as measured by means of a skin prick test with a purified extract or as a prick-by-prick with a latex glove. Probably, an end-point dilution technique would be required to further evaluate this aspect. In fact, a reduction of NRL skin test reactivity was documented with this skin-test method in a previous NRL subcutaneous immunotherapy trial<sup>23</sup>.

Latex SLIT induced a significant improvement in the use test scores, confirming the efficacy of this treatment on cutaneous symptoms, which was also reported in adult patients<sup>14</sup>.

Some limitations have to be taken into account in evaluating our study. First, data regarding the effect of immunotherapy on clinical evolution of latex allergy and on quality of life of the enrolled patients are lacking. The score system we have used to evaluate the rubbing and glove use tests was developed in our clinic and it is not a validated one. However, a search of the international literature reveals that a validated tool to score the rubbing or the glove use test is not available. Our study does not provide data regarding safety on a long term (i.e. > 12 month) basis. Furthermore, we have not performed, for ethical reasons, provocative tests to evaluate airways response to NRL inhalation. In a study on adult healthcare workers the severity of nasal and bronchial symptoms was reduced following subcutaneous NRL immunotherapy<sup>11</sup>, a similar trend was observed in a different cohort<sup>24</sup> trial. In our study, we did not have data on clinical symptoms following real-life NRL exposure, since in paediatric patients allergen avoidance is more easily achieved. However, results of the use test clearly demonstrated that a significant reduction of symptom scores was achieved as early as 3 months after immunotherapy started. This is in agreement with data on NRL immunotherapy in adult patients where the glove-use test improved significantly after only 10 weeks of treatment<sup>14</sup>.

Oral allergy symptoms were reported to have improved following SLIT with a cross-reactive allergen, although these beneficial effects are variable and patients usually relapse with their food sensitization after immunotherapy discontinuation<sup>25</sup>. More recently, Hansen *et al.* reported that immunotherapy to birch was not accompanied by a significant decrease in the allergy to apple as compared to placebo<sup>26</sup>. In this study, we have shown that a pattern compatible with an overall improvement of food allergy to cross-reacting foods was reached following 1 year of SLIT with NRL. In contrast to active treated subjects, placebo and control groups showed an increase in the number of non-tolerated vegetables. Moreover, a trend towards the reduction in prick-by-prick positive scores for fresh vegetables was observed in treated subjects. Taken together these data allow speculation that latex SLIT could also improve oral allergy when allergen components which are both cross-antigenic (i.e. cross-reactive on the basis of formally proven immunological mechanisms) and cross-allergic (i.e., cross-reactive on the basis of clinical data)<sup>19</sup> are concerned. However, larger studies are needed in order to assess this particular aspect.

Marcucci *et al.*<sup>27</sup> recently evaluated food–pollen cross-reactivity by nose–mouth cross-challenge in patients with oral allergy syndrome and found that the cross-reactivity between food and pollen, when evaluated at the shock organ, was not clinically evident. They suggest that different immunological mechanisms likely act in the nose and in the mouth to determine local symptoms. Thus, immunological cross-reactivity can not explain the whole phenomenon of oral allergy to vegetables containing proteins which are homologues to inhalant allergens. It is likely that target-organ related factors play a crucial role, which needs further investigation. NRL-specific immunotherapy should no longer be considered as an experimental treatment and should be utilized in patients with severe symptoms for whom allergen avoidance cannot be warranted.

## Conclusion

Our data support the concept that SLIT for NRL allergy is a promising safe and efficacious treatment for allergic children, as it was previously reported for adults. These data need to be confirmed in larger cohort studies with a longer follow-up in view to assess the efficacy and safety of latex sublingual immunotherapy in the long term.

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