

Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study

E. Nettis, M.C. Colanardi, A.L. Soccio, M. Marcandrea, L. Pinto,* A. Ferrannini, A. Tursi and A. Vacca†

Section of Allergy and Clinical Immunology, Department of Clinical Medicine, Immunology and Infectious Diseases, University of Bari, 70124 Bari, Italy

*Department of Respiratory Physiopathology, 'Miulli' General Hospital, Acquaviva delle Fonti, Italy

†Department of Internal Medicine and Clinical Oncology, University of Bari, Bari, Italy

Summary

Correspondence

Eustachio Nettis.

E-mail: e.nettis@allergy.uniba.it

Accepted for publication

3 November 2006

Key words

double-blind placebo-controlled study, natural rubber latex allergy, randomized controlled trial, sublingual immunotherapy

Conflicts of interest

None declared.

Background Natural rubber latex (NRL) allergy is a worldwide problem. Although prevention is sufficient to reduce sensitization, prolonged avoidance is needed to prevent resensitization or adverse reactions on re-exposure.

Objectives This double-blind, placebo-controlled study was conducted to determine the efficacy of sublingual immunotherapy (SLIT) with latex.

Methods Forty patients with NRL allergy were enrolled. At diagnosis, 30 presented urticaria and 10 asthma. Patients were evaluated on their clinical history and an allergological assessment: skin prick test with latex extract, serum-specific IgE and provocation tests. Patients were subdivided by complaint (asthma or urticaria), and randomized to receive SLIT with latex extract (ALK-Abelló, Lainate, Milan, Italy) or placebo.

Results The evaluable population consisted of 35 patients, 18 treated with SLIT and 17 with placebo. The results show that 12 months of SLIT improved the symptoms score and reduced the medication score in all subjects. The subjective evaluation was corroborated by improved bronchial and glove provocation test results. The latex-specific IgE levels increased slightly in the SLIT group, and skin sensitization was reduced at the end of the trial in all the patients treated with SLIT. The immunotherapy was not complicated by any severe adverse reactions.

Conclusions This is the first double-blind, placebo-controlled evaluation of the efficacy of SLIT with latex extract conducted in adult patients allergic to NRL. SLIT with latex can be proposed for subjects with latex allergy, especially those for whom complete avoidance of latex exposure may be very difficult or even impossible. More studies are needed to evaluate the efficacy of SLIT in the treatment of subjects with latex allergy who are sensitized to inhalant allergens.

Natural rubber latex (NRL) allergy is encountered worldwide, although its true prevalence in the general population is estimated at only about 1%. It is recognized as a major occupational problem among healthcare workers, as sensitization is observed in 5–17% of those exposed.^{1–3} Outside the healthcare environment, the people at highest risk of sensitization due to repeated contact include glove-wearing kitchen workers, housekeeping personnel,⁴ workers at plants manufacturing latex products,⁵ gardeners,⁶ hairdressers⁷ and subjects who have undergone multiple operations.⁸

Assessment in the 1990s of the results of primary prevention showed that removal of powdered latex gloves from

some areas of a hospital or the introduction of low-protein and/or powder-free gloves was followed by a decline or cessation of latex sensitization.^{9–12} Secondary prevention in sensitized/allergic individuals requires avoidance of all exposure to NRL products because their further use, or bystander exposure from other sources such as coworkers, could maintain or worsen the sensitization and lead to potentially life-threatening reactions. It has been demonstrated that prevention in the work environment is sufficient to reduce sensitization.^{13–16}

Even so, prolonged avoidance is needed to prevent resensitization or adverse reactions on re-exposure. The benefits of prevention are, in fact, limited to the duration of avoidance.

Immunotherapy against latex has recently been proposed. This double-blind, placebo-controlled study was conducted to determine the efficacy of sublingual immunotherapy (SLIT) with latex extract.

Materials and methods

Forty patients with latex allergy (11 men and 29 women) aged 18–47 years (mean $\pm$ SD 38.1 ± 6.4) were enrolled. At diagnosis 30 presented urticaria and 10 asthma. Positive results were obtained to a glove use test and a latex bronchial provocation test in the two groups, respectively. Patients sensitized to inhalant allergens were excluded, to rule out any interference of allergies to pollen or house mites, for instance, or of intake of any other drug, with the evaluation of symptoms.

Patients were recruited at the Department of Allergy and Clinical Immunology of Bari Polyclinic. The study was approved by the Ethics Committee of the University of Bari and all patients gave their written informed consent. Patients were evaluated on the basis of their clinical history and an allergological assessment: skin prick test (SPT) with latex extract, serum-specific IgE (CAP-FEIA; Pharmacia, Uppsala, Sweden) and provocation tests. They were free from other respiratory allergies, had not received specific immunotherapy in the previous 5 years, and had no other significant disorders or chronic/severe asthma.

Patients were subdivided into two groups: those with asthma and those with urticaria, and were randomized by a computer-generated list to receive SLIT with latex extract or placebo. The latex extracts used for immunotherapy and placebo were manufactured and provided by ALK-Abelló (Linate, Milan, Italy).

Allergological evaluation

Skin prick tests

SPTs were performed with ALK-Abelló latex extract, undiluted and diluted 1 : 1000, 1 : 100, 1 : 10 in a glycerol-saline solution. Additional SPTs were performed with food and common inhalant allergens. The food extracts included avocado, banana, pineapple, kiwi and chestnut (Stallergènes, Paris, France; Lofarma, Florence, Italy). The inhalant extracts included *Dermatophagoides pteronyssinus* and *D. farinae*, grass pollen, olive pollen, cypress pollen, *Parietaria*, *Artemisia vulgaris*, cat dander, dog dander, *Alternaria tenuis* and *Aspergillus*. Histamine dihydrochloride (10 mg mL^{-1}) was used as positive control, and physiological saline as negative control. An SPT was considered positive if the mean diameter of the weal was 3 mm larger than the weal of the negative control. The latex SPT was performed at baseline and after 6 months and 12 months.

Serum-specific IgE

Measurement of serum-specific IgE to NRL (Pharmacia CAP system, RAST FEIA, Uppsala, Sweden) was carried out under

standard conditions, as recommended by the manufacturer. A positive RAST was defined as a value $> 0.35 \text{ kU L}^{-1}$. This test was performed at baseline and after 6 months and 12 months.

Glove provocation test

The same batch of NRL gloves was used for the glove use test at baseline and after 12 months (Le Petit; Grandate, Como, Italy). A fingertip cut from a glove was placed on one finger for 30 min. If the reaction was negative, a whole glove was then worn for 30 min. If the reaction was still negative, the whole glove was worn for 60 min.¹⁶

A vinyl glove was used as control. A positive response was recorded when itching, redness or contact urticaria appeared on the finger or hand, or systemic reactions developed. Symptoms were scored 1 for local itching without any other manifestations, 2 for redness, 3 when weals became apparent, and 4 if any systemic reaction appeared. The glove use test was performed at baseline and after 12 months.

Latex bronchial provocation test

This was performed according to Pisati *et al.*¹⁷ Patients were initially exposed to 2 mL of glycerol-saline solution nebulized in a 7 m^3 challenge room up to 15 min to ensure that fluctuations of forced expiratory volume in 1 s (FEV_1) were $< 10\%$. On the next day, ALK-Abelló latex was firstly nebulized in the same room. The patients then entered and remained there for 15 min, except in the event of earlier onset of wheezing and a $\geq 15\%$ fall in FEV_1 with respect to the baseline value. After exposure, FEV_1 was monitored at 5, 10, 15, 30, 60, 90 and 120 min; if the fall in FEV_1 was $< 15\%$, the patient underwent the next scheduled nebulization. Each time, 2 mL of solution was delivered and the concentration of nebulized extract was increased 10-fold. The initial concentration was a 10-fold dilution of the predetermined skin-test endpoint in the individual undergoing challenge, and the highest concentration was the undiluted extract. If any nebulization caused a $\geq 15\%$ fall in the FEV_1 , no further exposure was conducted and FEV_1 was monitored hourly for 8 h, and finally after 24 h. FEV_1 measurements were carried out at the same pre-established times when the highest concentration was reached without a $\geq 15\%$ fall. A latex bronchial provocation test was performed at baseline and after 12 months.

Immunotherapy protocol

Treatment consisted of five concentrations of ALK-Abelló latex: 5×10^{-8} , 5×10^{-5} , 5×10^{-2} , 5 and $500 \mu\text{g mL}^{-1}$ (Table 1). The placebo preparation was identical to the active treatment in terms of composition, appearance, presentation, taste and colour. A 4-day sublingual induction phase was followed by a 12-month maintenance phase consisting of three administrations per week. In view of the doses employed, dose increments were supervised in hospital in the presence of a physician.

Table 1 Treatment schedule

Day	Vial	Protein concentration ($\mu\text{g mL}^{-1}$)	Drops	Cumulative dose (μg)	Interval between doses
Induction phase					
1	0	5×10^{-8}	1	2×10^{-5}	15 min
			10		15 min
	1	5×10^{-5}	1		15 min
			10		15 min
2	2	5×10^{-2}	1	2.2	15 min
			10		15 min
	3	5	1		15 min
			10		15 min
3	4	500	1	400	15 min
			2		15 min
			3		15 min
			4		15 min
			10		15 min
4	4		25	500	15 min
Maintenance phase					
	4		5	100	2 days

SLIT with latex extract was administered to the patient by the same doctor. Maintenance doses were self-administered at home in accordance with the detailed instructions provided by the physician. The drops were always held under the tongue for 3 min before being swallowed. Patients recorded all doses in a diary.

Safety of immunotherapy

Patients were asked to keep a record of any side-effect or suspected adverse event that might be related to SLIT, together with its time of onset and treatment (if any). Reactions were classed as systemic (asthma, rhinitis, urticaria, angio-oedema, generalized itching, diarrhoea and vomiting) and local (oral itching/swelling, oedema of the tongue). Patients were instructed to contact the centre if they needed medical advice. All patients were included in the side-effect analysis.

Latex avoidance

After enrolment and before the beginning of immunotherapy, all patients were informed of the hazards of NRL allergy and given oral instruction on preventive measures, as well as a written handout. They were particularly advised to avoid exposure to NRL in occupational settings and, whenever possible, at home and to use gloves made of vinyl, polyurethane and neoprene. Instruction comprised information on latex-containing products frequently used in daily life (such as clothes, condoms, air mattresses) and latex-free alternatives. Patients were instructed to inform physicians of the requirement to perform any necessary surgical and medical procedures in a latex-free environment. Risk factors, signs and symptoms of latex allergy ranging from contact urticaria to anaphylactic shock were explained. Particular emphasis was laid on the hazardous forms of exposure, such as anaesthesia, condoms and other forms of mucosal contact, and avoidance

of cross-reacting foods (kiwi, chestnut, banana, avocado and pineapple) was recommended.

At diagnosis, five healthcare workers were employed in the operating room, two in the emergency room, two in the obstetric and gynaecology unit, and two in the cardiology unit. After diagnosis, of the 11 healthcare workers, nine changed department, while two (belonging to the SLIT group) changed their job title: three subjects now worked in a central administration office, three in the ambulatory of a neurology unit, two in the administration office of a cardiology unit, one in a spirometry laboratory, and two in a hospital pharmacy. After diagnosis, two hairdressers (one from each group) stopped working.

Diary cards

Patients recorded their daily symptoms: bronchial (cough, wheezing and shortness of breath), ocular (swelling, itching, and watery eyes), nasal (itching, sneezing, congestion and rhinorrhoea) and skin related (itching, redness and weals) on a scale ranging from 0 (absent) to 3 (severe), as well as their daily use of medication: one point for antihistamines, one point for inhaled β_2 -agonists, two points for topical corticosteroids and three points for oral corticosteroids. All patients received appropriate on-demand therapy to control their allergic symptoms in case of exposure to latex or ingestion of cross-reactive foods. The total symptoms and medication scores were calculated as means per week. The efficacy of the treatment was assessed after 6 and 12 months by calculating the mean scores for weeks 24–26 and weeks 51–53, respectively, while the baseline evaluation was referred to the 3 weeks before starting the immunotherapy or placebo.

At baseline, 6 months and 12 months, patients also completed a 10-cm visual analogue score (VAS) indicating the overall severity of their latex allergy over the previous days, from 0 (none) to 10 (worst).

Statistical analysis

The significance of differences in age, sex, baseline characteristics and test results was compared using the Mann–Whitney test and χ^2 test for categorical data. For the efficacy analyses and comparison of the VAS in each study group and at different visits, the Wilcoxon matched-pair test was used. To compare the efficacy and the VAS in the two groups at different visits the Mann–Whitney test was performed. $P < 0.05$ was taken as significant.

Results

The 40 patients were randomized, 20 were treated with SLIT (14 women and six men) and 20 with placebo (15 women and five men). The two groups were matched for age and sex, serum concentrations of latex-specific IgE and SPT results. Two patients in the SLIT and three patients in the placebo group discontinued treatment within the first 8 weeks owing to noncompliance ($n = 3$), lack of efficacy ($n = 1$) and change of residence ($n = 1$).

The evaluable population thus consisted of 35 patients. Their demographic and baseline characteristics were also well matched. Dropouts were excluded from the analysis because of their short treatment duration.

Allergological evaluations

Skin prick tests

At diagnosis all patients had positive SPTs with NRL extract and there was no significant difference between the SLIT and the placebo group. At 6 months, in the SLIT group there was a significant difference in terms of a stronger concentration of latex extract needed to produce a positive weal, as compared with the baseline response. In addition, there was a significant decrease in mean weal diameter in patients with the same end-point titre as compared with baseline (mean diameter 6.9 mm vs. 4.1 mm, range 3.5–8.5 mm vs. 3.0–6.5 mm; $P < 0.05$).

At 12 months, the significant concentration difference persisted and there was a further difference in mean weal diameter in patients with the same end-point titre (mean diameter 7.7 mm vs. 3.2 mm, range 6.5–8.5 mm vs. 3.0–3.5 mm; Fig. 1). In the placebo group, skin reactivity to the extract was significantly decreased only at 12 months ($P < 0.05$).

Comparison between the two groups thus showed a nonsignificant difference in terms of a decrease of latex SPT positivity, evaluated as an increased concentration by at least 10-fold, after 6 months and after 12 months of treatment ($P > 0.05$ and $P = 0.05$, respectively).

At diagnosis, there were no IgE-positive results in the inhalant extracts, whereas 10 of 35 patients (29%), including four in the SLIT group, had one or more positive IgE tests to cross-reactive food extracts.

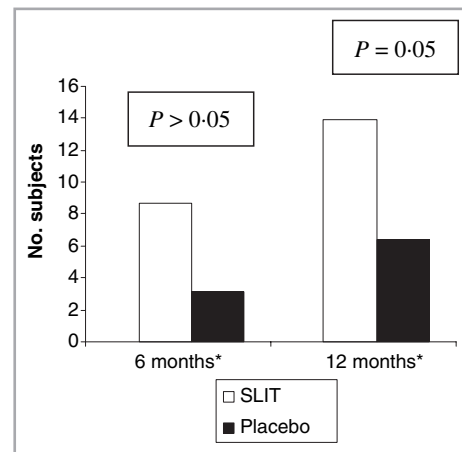


Fig 1. Decrease of latex skin prick test positivity, evaluated as an increased concentration by at least 10-fold needed to trigger a reaction, after 6 months and after 12 months of treatment.

*As compared with baseline, two subjects in the sublingual immunotherapy (SLIT) group yielded negative results, one at the 6-month evaluation and one at 12 months.

Serum-specific IgE

There were no significant changes in specific latex serum IgE concentrations either in the SLIT group or the placebo group. At 6 months, a nonsignificant increase in IgE levels from 16.7 to 19 kU L⁻¹ was observed in the SLIT group; the levels decreased to 17.2 kU L⁻¹ at 12 months. Specific IgE was not detectable in one patient.

In the placebo group, a nonsignificant decrease was found both at 6 months and at 12 months (16.1 kU L⁻¹ at baseline, 15.2 kU L⁻¹ at 6 months, 11.9 kU L⁻¹ at 12 months).

Glove provocation tests

Initially, 28 subjects (80%) (14 in each group) had a local latex reaction: 12 with the fingertip, 16 with the whole glove. All reactions appeared within 60 min. There were no significant differences between the groups (reaction onset after a mean of 42.3 min vs. 45.4 min in the SLIT and placebo group, respectively; $P > 0.05$). Eight of 28 patients (29%) (four placebo and four SLIT) experienced a systemic reaction. At 12 months a longer exposure was needed to provoke a reaction in the SLIT group (mean 85 min; $P < 0.05$): only two of 14 patients (14%) had a reaction in the first 60 min compared with 60–120 min in the other 12 of 14 (86%). There was also a significant decrease in the mean score (3.4 vs. 1.8; $P < 0.05$). A systemic reaction developed in only two cases.

In the placebo group, the mean score decrease (3.5 vs. 2.9) was not significant, whereas there was a significant increase in the exposure time as compared with baseline (mean 45.4 min vs. 61.5 min). However, this increase was lower than the corresponding increase in the SLIT group ($P < 0.05$). In five of 14 subjects (36%) the reaction developed between 30 and

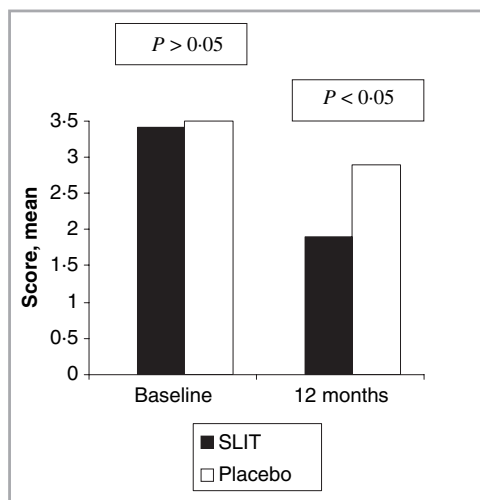


Fig 2. Changes in the glove use test score in the sublingual immunotherapy (SLIT) and placebo groups.

60 min and in nine of 14 (64%) between 60 and 120 min. Three of the four patients who had initially displayed a systemic reaction continued to do so at 12 months. At the 12-month evaluation there was a significant difference in the scores between the two groups (Fig. 2).

Latex bronchial provocation test

At the initial examination, this test was positive in four patients in the SLIT group and three subjects in the placebo group. In the SLIT group, one patient reacted to the 1 : 100 dilution, FEV₁ decreasing 5 min after exposure, two reacted to the 1 : 100 dilution, FEV₁ decreasing 30 min after exposure, and one patient reacted to the 1 : 1000 latex dilution, FEV₁ decreasing 15 min after exposure.

In the placebo group, one patient reacted to the 1 : 100 dilution, FEV₁ decreasing 10 min after exposure, one reacted to the 1 : 100 dilution, FEV₁ decreasing 15 min after exposure, and one patient reacted to the 1 : 1000 dilution, FEV₁ decreasing 10 min after exposure.

At 12 months, a stronger concentration was needed to provoke a $\geq 15\%$ FEV₁ fall in the SLIT group: two of three patients previously positive at 1 : 100 now displayed a $\geq 15\%$ FEV₁ fall at 15 and 30 min after exposure to the 1 : 10 dilution, and the other patient at 30 min after exposure to the 1 : 1 dilution. The fourth patient (previously positive at 1 : 1000) now displayed a FEV₁ decrease at 15 min after exposure to the 1 : 100 dilution.

Two of the positive patients in the placebo group displayed a longer interval between exposure and the FEV₁ fall: their reaction to the 1 : 100 dilution occurred after 30 min, whereas in the third patient it occurred after 15 min at 1 : 100 dilution (Table 2). There were no $> 10\%$ falls of FEV₁ following exposure to the glycerol-saline solution, either at baseline or at 12 months. The number of patients is too limited for reliable statistical analysis to be performed.

Safety of immunotherapy

Four of 35 patients (11%) [three of 18 in the SLIT group (17%) and one of 17 in the placebo group (6%)] developed adverse reactions. Two patients in the SLIT group reported mouth itching and burning and the third reported an episode of swelling of the lips. These side-effects occurred during the induction phase and regressed spontaneously. In the placebo group, one patient reported an asthma episode.

Diary cards

Symptoms scores and medication scores, assessed at baseline and reported as the mean of the three previous weeks, were not significantly different between the two groups ($P > 0.05$). At 6 months, the total symptoms score had decreased by 57.4% in the SLIT group and 38.9% in the placebo group ($P > 0.05$). These decreases were significant as compared with baseline ($P < 0.05$). After 12 months, the score had decreased by 88.7% and 43% as compared with baseline, in the active and placebo groups ($P < 0.05$); again, this value was significant with respect to the 6-month value only in the SLIT group ($P < 0.05$) (Fig. 3). Comparing the two treatment groups, a

Patient	Baseline		12 months	
	Positive dilution	Exposure (min)	Positive dilution	Exposure (min)
SLIT group				
1	1 : 100	5	1 : 10	15
2	1 : 100	30	1 : 10	30
3	1 : 100	30	1 : 1	30
4	1 : 1000	15	1 : 100	15
Placebo group				
1	1 : 100	10	1 : 100	30
2	1 : 100	15	1 : 100	30
3	1 : 1000	10	1 : 100	15

SLIT, sublingual immunotherapy with latex extract.

Table 2 Latex bronchial provocation test at baseline and after 12 months of treatment

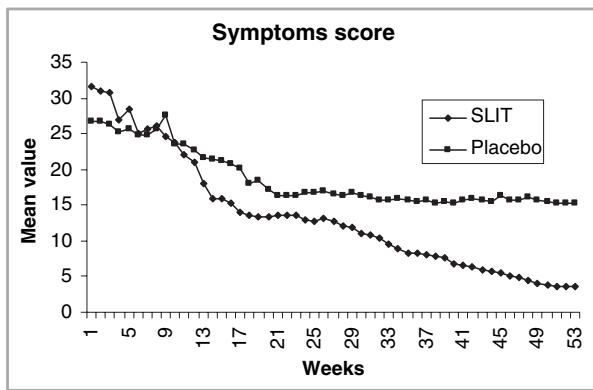


Fig 3. Symptoms score in relation to time (53 weeks). SLIT, sublingual immunotherapy.

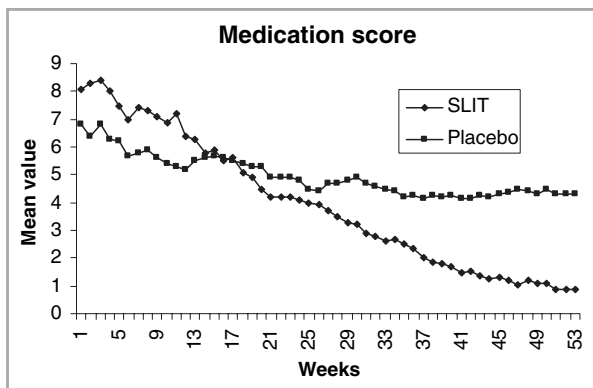


Fig 4. Medication score in relation to time (53 weeks). SLIT, sublingual immunotherapy.

statistically significant difference was present at the 12-month assessment (15.3 vs. 3.6; $P < 0.05$).

After 6 months, the medication score was significantly reduced by 48.2% in the SLIT group, and a significant reduction was also noted in the placebo group ($P < 0.05$). There was no significant difference between the two groups ($P > 0.05$). Instead, at 12 months the score was significantly reduced in the SLIT group (−88.9%) with respect to the baseline, the 6-month assessment and the 12-month assessment values in the placebo group ($P < 0.05$) (Fig. 4). In contrast, in the placebo group, there was no statistical difference at the 12-month assessment as compared with the 6-month, whereas there was a significant difference between the 12-month evaluation and baseline.

There was a significant improvement in the VAS in the SLIT group: a mean decrease by 49.4% after 6 months and 74.1% after 12 months ($P < 0.05$). These percentages falls were greater (but reaching statistical significance only after 12 months) than the corresponding decreases as compared with baseline in the placebo group, which were 42.2% and 44.8%, respectively.

Discussion

This is the first double-blind, placebo-controlled evaluation of the efficacy of SLIT conducted in adult patients allergic to NRL, with cutaneous and respiratory manifestations. Our results show that 12 months of SLIT improved the symptoms score and reduced the medication score in the treated subjects.

A self-evaluation of efficacy is not proposed in many trials. We used a VAS, which is a crude and subjective criterion. We therefore correlated it with other parameters and found a correlation between the VAS and the global symptoms and medication score. The subjective evaluation was also corroborated by the improved bronchial and glove provocation test results.

The NRL-specific IgE levels did not change significantly in either group, confirming previous results obtained in trials with NRL subcutaneous immunotherapy and SLIT performed in children.^{18,19} The slight increase in the SLIT group contrasts with the decrease in the placebo group, as reported in other studies.²⁰ It may thus be deduced that there is no uniform correlation between latex-specific IgE and the symptoms and medication scores in these groups.

Skin sensitization was reduced in all the patients in the SLIT group at the end of the trial: 15 of 18 (83%) showed at least a 10-fold reduction of SPT reactions to NRL extract, whereas three of 18 (17%) showed a decrease only in the SPT weal mean diameter. However, although SPT results are regarded as a parameter of immunotherapy efficacy, skin and mucosal mast cells do not appear to behave in a similar fashion.

The glove use test and bronchial provocation test are valid ways of quantifying NRL sensitivity, and have thus been used, with some modifications, in other studies of the efficacy of latex immunotherapy.^{18,21,22} Our findings demonstrate an increased threshold dose in the bronchial test and a more prolonged exposure time (more frequent in the SLIT group) to trigger a reaction, substantiating the efficacy of the immunotherapy.

In the placebo group, there was a decrease in both the subjective and the objective parameters used to evaluate NRL allergy. This could be explained by the fact that because latex allergy can be life threatening, and all patients had reported adverse reactions, sometimes severe, to NRL at the beginning of the study, we had carefully instructed them about how to avoid exposure to latex. As in previous studies, prevention induced a reduction of sensitization, but not enough to impede resensitization or adverse reactions on re-exposure.¹⁶

We studied a selected, small group of subjects with latex allergy, i.e. monosensitized patients, excluding individuals sensitized to inhaled aeroallergens. This could represent a selection bias in the study because it is well known that atopy is considered a risk factor for latex allergy. However, this allowed us to refer the improvements in the medication score and symptoms score, and the differences between the two study groups, only to the immunotherapy and to latex avoidance.

Both in the SLIT group and the placebo group, the fact that symptoms were present and medication was necessary throughout the study implies that latex avoidance was not

strictly adhered to, especially in non-healthcare environments. The fact that the efficacy measures showed a significant difference between the two treatment groups only at 12 months could suggest that up to 6 months, the effects of latex avoidance and latex-specific immunotherapy are similar, while in later months the beneficial effects should be attributed predominantly to the immunotherapy.

The efficacy of immunotherapy in this setting has not received much attention.^{18,21–24} Initially, case reports showed that both subcutaneous immunotherapy and SLIT were very effective and all exposure tests yielded negative results.^{21,22} Controlled studies using subcutaneous protocols and rush SLIT have since been performed.^{18,23,24} Studies of subcutaneous immunotherapy have confirmed its feasibility as a means of inducing tolerance, especially in severely affected subjects, including healthcare workers, for whom no other causative treatment can be offered, and allergen avoidance is not always possible. However, these studies are burdened by a high rate of adverse events due to the use of unfractionated latex extracts. In any event, life-threatening reactions are very rare, and none was observed in our study.

Rolland *et al.*²⁵ have proposed the selection of hypoallergenic preparations for subcutaneous immunotherapy to avoid the risk of adverse events. They describe the progress made in developing hypoallergenic preparations of the major latex allergens Hev b 5 and Hev b 6·01. Future immunotherapy should target allergenic components known to cross-react with homologous proteins in fruits and vegetables, to prevent adverse reactions on exposure to these substances. The finding that Hev b 6·01 is one of the most important allergens in healthcare workers was confirmed by Sastre *et al.*²⁶ In addition, they reported a significant negative correlation between the maximum tolerated dose and specific IgE to Hev b 6·01 at baseline, so the levels of specific IgE to Hev b 6·01 might predict the maximum tolerated dose of allergen during immunotherapy.

The only previous study among adults which used a sublingual route, as we have done, was conducted in 12 patients, but was not a double-blind, placebo-controlled trial.²³ Even so, it showed that during 3 months of follow up there were no adverse events and all patients developed a clinical tolerance to NRL, characterized by a surprising reduction by 100% of reactions to cutaneous, mucous and sublingual challenge. SPT variations were not evaluated. On the other hand, surprisingly, serum-specific IgE decreased in 58·3% of patients. However, this was observed in a 3-month study and cannot be compared with our 12-month trial.

In conclusion, SLIT reduces the symptoms in patients with NRL allergy. As this therapy is not complicated by severe adverse reactions, a build-up phase, conducted under medical supervision, can safely be followed by continuation of therapy at home. It can thus be proposed for subjects with NRL allergy, especially those for whom complete avoidance to latex exposure may be very difficult. Nevertheless, in any case, all latex-allergic subjects should be strongly advised of the extreme importance of avoiding exposure to latex. More studies are needed to evaluate the efficacy of SLIT in the

treatment of latex allergy subjects sensitized to inhalant allergens.

Acknowledgments

This study was partly funded by a grant from the 'Regione Puglia' which was used to buy treatments from ALK-Abelló. The authors wish to thank Dr. ssa Silvia Pecora for her corporation.

References

- Charous B. The puzzle of latex allergy: some answers, still more questions. *Ann Allergy* 1994; **73**:277–81.
- Vandenplas O, Charous B, Tarlo S. Latex allergy. In: *Asthma in the Workplace* (Bernstein D, Bernstein I, Chan-Yeung M, Malo JL, eds), 2nd edn. New York: Marcel Dekker, 1994; 425–44.
- Nettis E, Assennato G, Ferrannini A, Tursi A. Type I allergy to natural rubber latex and type IV allergy to rubber chemicals in health care workers with glove related skin symptoms. *Clin Exp Allergy* 2002; **32**:441–7.
- Sussman GL, Lem D, Liss G, Beezhold D. Latex allergy in house-keeping personnel. *Ann Allergy Asthma Immunol* 1995; **74**:415–18.
- Tarlo SM, Wong L, Roos G, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol* 1990; **85**:626–31.
- Carrillo T, Blanco C, Quirarte J *et al.* Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol* 1995; **96**:699–701.
- Nettis E, Dambra P, Soccio AL *et al.* Latex hypersensitivity: relationship with positive prick test and patch test responses among hair-dressers. *Allergy* 2003; **58**:57–61.
- Nettis E, Dambra P, Soccio AL *et al.* Type I allergy to natural rubber latex and type IV allergy to rubber chemicals in children with risk factors. *Contact Dermatitis* 2001; **44**:181–2.
- Sussman GL, Liss GM, Deal K *et al.* Incidence of latex sensitisation among latex glove users. *J Allergy Clin Immunol* 1998; **101**:171–8.
- Turjanmaa K, Reinikka-Railo T, Reunala T, Palouso T. Continued decrease in natural rubber latex (NRL) allergen levels of medical gloves in nationwide market surveys in Finland and co-occurring decrease in NRL allergy in a large university hospital. *J Allergy Clin Immunol* 2000; **104**:S373 (Abstract).
- Tarlo SM, Easty A, Eubanks K *et al.* Outcomes of a natural rubber latex control program in an Ontario teaching hospital. *J Allergy Clin Immunol* 2001; **108**:628–33.
- Liss GM, Tarlo SM. Natural rubber latex-related occupational asthma: association with interventions and glove changes over time. *Am J Ind Med* 2001; **40**:347–53.
- Allmers H, Brehler R, Chen Z *et al.* Reduction of latex aeroallergens and latex specific IgE antibodies in sensitised workers after removal of powdered natural rubber latex gloves in a hospital. *J Allergy Clin Immunol* 1998; **102**:841–6.
- Hamilton RG, Brown RH. Impact of personal avoidance practices on health care workers sensitised to natural rubber latex. *J Allergy Clin Immunol* 2000; **105**:839–41.
- Turjanmaa K, Kanto M, Kautianen H *et al.* Long-term outcome of 160 adult patients with natural rubber latex allergy. *J Allergy Clin Immunol* 2002; **110**:S70–4.
- Nettis E, Colanardi MC, Ferrannini A. Type I latex allergy in health care workers with latex-induced contact urticaria syndrome: a follow-up study. *Allergy* 2004; **59**:718–23.

- 17 Pisati G, Baruffini A, Bernabeo F, Stanizzi R. Bronchial provocation testing in the diagnosis of occupational asthma due to latex surgical gloves. *Eur Respir J* 1994; **7**:332–6.
- 18 Sastre J, Fernandez-Nieto M, Rico P *et al.* Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2003; **111**:985–94.
- 19 Bernardini R, Campodonico P, Burastero S *et al.* Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. *Curr Med Res Opin* 2006; **22**:1515–22.
- 20 Bousquet J, Scheinmann P, Guinnee MT *et al.* Sublingual–swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites. A double-blind, placebo-controlled study. *Allergy* 1999; **54**:249–60.
- 21 Nucera E, Schiavino D, Buonomo A *et al.* Latex rush desensitization. *Allergy* 2001; **56**:86–7.
- 22 Pereira C, Rico P, Lourenco M *et al.* Specific immunotherapy for occupational latex allergy. *Allergy* 1999; **54**:291–3.
- 23 Patriarca G, Nucera E, Pollastrini E *et al.* Sublingual desensitization: a new approach to latex allergy problem. *Anesth Analg* 2002; **95**:956–60.
- 24 Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. *J Allergy Clin Immunol* 2000; **106**:585–90.
- 25 Rolland JM, Drew AC, O'Hehir RE. Advances in development of hypoallergenic latex immunotherapy. *Curr Opin Allergy Clin Immunol* 2005; **5**:544–51.
- 26 Sastre J, Raulf-Heimsoth M, Rihs HP *et al.* IgE reactivity to latex allergens among sensitized healthcare workers before and after immunotherapy with latex. *Allergy* 2006; **61**:206–10.