



Latex immunotherapy: state of the art

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ABSTRACT

Objective: Latex allergy remains a significant problem, especially among certain professional categories, and specific immunotherapy has been suggested as a suitable therapeutic option. The objective of this article is to review the available literature on clinical trials of specific immunotherapy in latex allergy.

Data Sources: Literature databases (PubMed, Embase, Google Scholar) were searched for latex immunotherapy clinical trials.

Study Selections: Clinical trials (either open or randomized controlled) using subcutaneous or sublingual immunotherapy with latex extracts were selected. Only articles published in English in peer-reviewed journals were considered. Case reports quoted in the clinical trials were also described, when pertinent.

Results: Eleven clinical trials (3 with subcutaneous and 8 with sublingual immunotherapy) were identified. Two of the 3 randomized trials of subcutaneous immunotherapy reported some benefit in adults but a remarkable occurrence of side effects. Concerning sublingual immunotherapy (SLIT), there were 6 randomized placebo-controlled (1 in children), 1 randomized open, and 1 open trials. All but 1 trial reported positive results, and the safety profile was overall superior to injection immunotherapy. The overall quality of the study was moderate, and the number of subjects studied was low.

Conclusion: Although guidelines do not consider allergy to latex as an accepted indication to desensitization, SLIT can be offered, in addition to symptomatic treatment, to selected patients, when avoidance measures are not feasible or effective.

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Introduction

Latex juice is harvested from *Hevea brasiliensis* plants and contains rubber particles and luteoids suspended in an aqueous liquid called C-serum, whereas the luteoids contain another fluid called B serum.¹ Those suspensions, in turn, contain the allergenic proteins that are responsible, at various degrees, for immunoglobulin E (IgE) sensitization. The allergenic components are numbered from Hev b 1 to Hev b 13 and include genuine sensitizers, such as Hev b 1, Hev b 5, and Hev b 6, as well as cross-reacting proteins, such as Hev b 8 (profilin) or Hev b 12 (lipid transfer protein)² (Table 1). Those latter pan-allergens are usually responsible for the latex-fruit syndromes, which can involve banana, kiwi, apple, and other foods.

Latex-derived products are part of our everyday life. In fact, numerous latex-containing devices (household and professional gloves, balloons, pacifiers, baby bottle nipples, condoms, bathing

caps, orthodontic devices, sport equipment) are commonly used. Latex allergy has thus become a relevant health problem for the general population and an occupational hazard for health-related professions.³ The risk of sensitization is higher for housekeeping personnel, gardeners, hairdressers, and especially for health care workers or patients undergoing multiple surgeries, such as children with spina bifida or other congenital malformations (eg, of the urinary tract).¹ Liss et al⁴ performed an epidemiological study on a large number of health care workers (HCW), and found a prevalence of latex positivity of 12.1%, without significant differences among professional categories (physicians, nurses, laboratory workers, therapists, and technicians). This finding was subsequently confirmed by other authors.^{5,6} Latex is extracted from the sap of the *Hevea brasiliensis* tree and, after various industrial procedures, it can be prepared as different products.

The diagnosis of latex allergy is essentially based on a suggestive clinical history, positive skin prick test (SPT) with latex extract, the demonstration of latex-specific IgE, and positive results of various provocation tests (whole glove or glove finger wearing, rubbing

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Table 1
Latex allergens

Denomination	MW (kDa)	Description	Function
Hev b1	58 (tetramer)	Rubber elongation factor	Rubber biosynthesis
Hev b 2	34–36	β -1,3-Glucanase	Antifungal action
Hev b 3	24	Small particle protein	Rubber synthesis
Hev b 4	155	Helix lutoid component	Cyanogenic glucosidase
Hev b 5	15	Acid protein	Not defined
Hev b 6.01	20	Prohevein	Precursor
Hev b 6.02	4.7	Hevein	Antifungal action
Hev b 6.03	16	C terminal fragment	Not defined
Hev b 7.01	42	Patatin homologue from B-serum	Esterase
Hev b 7.02	42	Patatin homologue from B-serum	Esterase
Hev b 8	14	Profilin	Cytoskeletal structure
Hev b 9	50	Enolase	Metabolism
Hev b 10	16	Superoxide dismutase	Metabolism
Hev b 11	33	Chitinase	Metabolism
Hev b 12	9.3	Lipid transfer protein	Metabolism
Hev b 13	43	Early nodule-specific protein homolog	Metabolism

test). The first case of allergic reaction due to latex devices was described in 1979,⁷ and in the subsequent two decades, type I hypersensitivity reactions to natural rubber latex increased. Those consist of skin involvement (urticaria/angioedema), respiratory symptoms (asthma/rhinitis), and, more rarely, life-threatening reactions such as anaphylaxis. Allergic contact dermatitis to latex, less frequent, is sustained by a type IV immune reaction and is usually associated with chemical additives (thiurams, carbamates, benzothiazoles, or antioxidants) used during latex processing.

Health care workers with latex allergy are encouraged to use synthetic latex-free gloves, but such devices (vinyl, neoprene, nitrile, or polysoprene gloves) are often unacceptable to surgeons because they do not have the same features as latex gloves, or they are very expensive.³ In addition, avoiding latex-containing products is very difficult; thus, alternative sources as *Pathernium argenteum* have been proposed.^{8,9} This plant produces guayule latex, a rubber with low allergenicity, no cross-reactivity in subjects allergic to *Hevea brasiliensis* latex,¹⁰ and an effective barrier action against viral infections.¹¹

The administration of allergens at increasing doses (either subcutaneously or sublingually) results in a shift of T helper (Th) cell polarization from the Th2 (sustaining allergic reaction and inflam-

mation) to the Th1 cell phenotype.^{12,13} The Th2 to Th1 switch is essentially mediated by different populations of T regulatory cells (Tregs), which produce interleukin-10, tumor necrosis factor alpha, transforming growth factor-beta, and interferon-gamma.¹⁴ Although the mechanisms of action of specific immunotherapy (SIT) are not fully clarified, the clinical results are invariably the reduction of symptoms on allergen exposure and, consequently, a reduction in the need for rescue medications. The profound immunological changes induced by SIT also result in a long-lasting duration of the clinical effects (after the treatment is interrupted) and in modifications of the natural history of progression of the disease.¹⁵ The oral mucosa is highly vascularized, but macromolecules such as allergens have limited or no direct adsorption through it. Conversely, the oral mucosa contains numerous antigen-presenting cells but few inflammatory cells (mast cells, eosinophils). These features may contribute to the efficacy and safety of sublingual immunotherapy (SLIT).^{16,17}

Prevention (total avoidance) is the best approach for patients with latex allergy, but it is difficult to do, because totally avoiding contact with latex products at home or at the workplace is virtually impossible. Moreover, often health care or other workers do not want to change their employment. For these reasons, SIT may be regarded as a relevant therapeutic approach. We review herein the available clinical trials of latex immunotherapy, either subcutaneous (SCIT) or sublingual (SLIT).

Methods

Search strategy

The main medical databases (PubMed, Embase, Google Scholar) were searched for clinical trials of latex immunotherapy. Keywords were *latex* [AND] *immunotherapy*, with specific filters for “clinical trials” and “human”. Randomized controlled (either blinded or not) and open trials were included. The references listed in the article retrieved were also reevaluated for missing trials. The trials were evaluated by the authors, who extracted and tabulated the data. An evaluation of the methodological quality of the trials was done by applying the Jadad score. This system attributes 1 point to each of the following: presence of randomization, appropriateness of randomization, presence of blinding, appropriate description of blinding, description of dropouts. The Jadad score thus ranges from 5 (highest quality) to 0 (lowest quality). Case reports were included in this review, if of historical relevance or if containing novel aspects not covered in clinical trials. In total, 11 clinical trials (3 with SCIT and 8 with SLIT immunotherapy) were identified.

Table 2
Methodological characteristics of clinical trials with latex SCIT

Author, Year	Study design	JADAD score	A/P	Dropout	Age range (years)	Symptoms	Build-up duration	Build-up dose	Maintenance dose	Total duration
Leynardier, 2000	RDBPC	4	9/8	3 Placebo	22–41	Rhinitis (17/17) Ocular (16/17) Asthma (9/17) Angioedema (6/17)	2 days	5.8 IR (cumulative)	96 IR (cumulative)	1 year
Sastre, 2003	RDBPC	3	16/8	None	21–51	Rhinitis (17/24) Ocular (18/24) Asthma (15/24) Urticaria (24/24)	98 days	65 μ g Total protein (cumulative) Target: 20 mcg protein	5 $\pm$ 3 to 186 $\pm$ 14 μ g protein cumulat. according to max tolerated dose	6 months
Tabar, 2006	RDBPC	4	11/12	3 Active 2 Placebo	24–58	Rhinitis (22/23) Conjunctivitis (23/23) Asthma (20/23) Itching (18/23) Urticaria (18/23) Hand eczema (4/23) Angioedema (7/23)	2 days	16.6 IR (cumulative)	80 IR (cumulative)	1 year

Abbreviations: A, active; P, placebo.

Publications of clinical trials with SCIT for latex allergy (Tables 2 and 3)

The first administration of SCIT to latex was anecdotally reported in 1999.¹⁸ The patient was a 31-year-old woman employed as a radiology technician, who displayed symptoms caused by her professional exposure to latex devices. Allergy to latex was confirmed by CAP-RAST and SPT, and an ammoniated latex extract was prepared (ALK-Abellò, Madrid, Spain). It was given at increasing doses, starting from 0.3 mL of 0.1 µg/mL solution of the latex proteins. During the buildup phase, the injection of 0.50 mL induced a systemic reaction (urticaria, erythema, eye congestion, dysphonia, hoarseness, and dyspnea), which was successfully managed by medical therapy. SCIT was then continued at a lower dose (0.35 mL) until a maintenance dose of 0.40 mL was reached. During the maintenance phase, only 1 episode of immediate local reaction was recorded. The authors outlined that SCIT was highly effective, because in a 5-month treatment (cumulative dose, 7.19 µg proteins), the cutaneous response to commercial latex extract was decreased, and clinical symptoms and response to specific provocation tests improved.

One year later, Leynadier et al¹⁹ performed a randomized, multicenter, double-blind, placebo-controlled trial in 17 patients (16 HCW) with latex allergy (cutaneous, respiratory, and ocular symptoms) and professional exposure. In 9 subjects, a latex extract (Stallergènes SA, Antony Cedex, France) standardized in index of reactivity (IR) was injected, according to a 2-day rush protocol, whereas 8 patients received placebo. The dose-progression (injections of increasing doses from 0.01 IR/mL to 10 IR/mL) was followed by a 12-month maintenance with the maximum tolerated dose (1–2 µg, according to patients' tolerance). The efficacy and safety of the treatment were evaluated by recording symptom and rescue medication usage at 6 and 12 months, as well as by conjunctival provocation test. The comparison between the active and placebo groups at 6 and 12 months showed a clear clinical benefit in the active-treated patients. The frequency of local and systemic adverse reactions was higher in the active group, even during the maintenance phase. A second randomized, double-blind, placebo-controlled study on latex SCIT was conducted by Sastre et al²⁰ in 2003, which included 24 patients (19 HCW). The active group received increasing doses of an extract of latex containing 0.002 µg/mL to 20 µg/mL of proteins. The extract was standardized in vivo (5 histamine equivalent prick = 20 µg protein). The authors assessed symptom and medication score, titrated skin prick test, specific reactivity (challenge chamber), methacholine reactivity, glove wearing and rubbing tests, and specific IgE. No change in symptom/medication scores or methacholine reactivity was seen, whereas specific reactivity, skin reactivity, and glove use test improved in the active group. A high rate of side effects occurred: systemic reactions occurred in 8% of the doses and 69% of patients.

A high frequency of side effects was also highlighted by Tabar et al,²¹ who used the same latex extract used in 1 of the previous

studies¹⁹ (Stallergènes SA) for 12 months. In contrast with the previous reports,^{19,20} this trial failed to demonstrate a clinical benefit of latex SCIT, probably because of biases in patients' enrollment and low maintenance doses.

In general, the results obtained with SCIT latex immunotherapy show an important imbalance between the benefits obtained and the risk of systemic side effects; thus, this route of administration has been virtually abandoned.²²

Publications of clinical trials with SLIT for latex allergy (Tables 4 and 5)

According to the results obtained with respiratory allergens, SLIT appears to be safer than SCIT, in both adults and children.^{16,23} The favorable safety profile of SLIT allows shortening or abolishing the induction phase, as recently described in some "big trials." On this ground, SLIT has been suggested as a suitable approach for latex allergy.

In 2001, Nucera et al²⁴ described 1 case of successful SLIT in a 23-year-old medical student with latex allergy. A glycerol-saline solution of latex (Alk-Abellò) was delivered with a sublingual-spit technique, completing the buildup in 3 days, reaching a cumulative dose of 500 µg of proteins without side effects. A maintenance dose of 100 µg/day was then administered. After the rush desensitization, contact and mucous latex challenges turned negative, thus suggesting the efficacy and safety of this route. Afterwards, some other studies were conducted with a more rigorous methodology to confirm this anecdotal positive result, and various schedules of administration were tested.

Patriarca et al²⁵ studied 24 patients (16 HCW) with latex allergy mainly attributable to the use of latex gloves. The active group (12 patients) received, being hospitalized, increasing doses of latex extract in 4 days. On day 4, patients received 500 µg of latex proteins in a single dose, without side effects. The maintenance phase was continued at home with 5 drops of 500 µg/mL solution 3 times per week. Glove use, oral challenge, and conjunctival challenge were evaluated. During maintenance, only 2 patients had mild immediate adverse reactions (no treatment needed). Three months after starting SLIT, only patients receiving active treatment were able to wear latex glove for 6 hours and to hold a latex-glove finger in their mouth for 1 hour without symptoms. Moreover, in 7 of 12 SLIT patients a decrease of latex-specific IgE was seen.

An open design study by Cisterò Bahima et al²⁶ enrolled 26 patients allergic to latex treated with SLIT-LATEX (Alk-Abellò), a commercial extract for sublingual administration. The treatment involved 5 increasing concentrations of extract (from 5×10^{-8} µg/mL to 500 µg/mL), to be given in 4 days in a hospital setting, according to a rush schedule provided by the manufacturer. The maintenance dose administered at home was 5 drops of the highest concentration, corresponding to 100 µg latex proteins 3 times/week for 9 weeks. A significant improvement in skin reactivity at the glove-use test and rubbing-test was recorded, with no change

Table 3
Outcomes and results in the clinical trials with latex SCIT

Author, Year	Outcomes	Main results	Safety
Leynadier, 2000	CLINICAL: Symptom score (nose, eye, skin, asthma), medication score PROVOCATION: Conjunctival challenge	CLINICAL: Decrease in rhinitis, ocular, and skin symptoms but not asthma symptoms. Decrease in medication score. PROVOCATION: Decrease in conjunctival reactivity	Systemic reaction in 47% injections in active group and 13% in placebo. Severe systemic reactions in 4/9 active patients.
Sastre, 2003	CLINICAL: Symptom and medication scores. Titrated SPT. PROVOCATION: Specific and nonspecific bronchial chall. Glove and rubbing test. SEROLOGICAL: Specific IgE	CLINICAL: No change in symptoms, medications and SPT PROVOCATION: No change in nonspecific bronchial reactivity. Decrease in specific reactivity, glove use and rubbing tests. SEROLOGICAL: No change in IgE	Systemic reactions in 8% doses and 69% patients in the active group. No anaphylaxis
Tabar, 2006	CLINICAL: Symptom and medication scores. SPT PROVOCATION: Conjunctival Challenge. SEROLOGICAL: specific IgE- IgG4.	No significant change in all parameters between groups during the treatment period	Systemic reactions in 81.8% patients in active group and 16.7% in placebo group. No anaphylactic shock

Table 4
Methodological characteristics of the SLIT trials

Author, Year	Study design	JADAD score	A/C	Dropout	Age range (years)	Symptoms	Build-up duration	Build-up dose	Maintenance dose, (Timing)	Total duration
Patriarca, 2002	RDBPC	3	12/12	No	8–64	Astma (17/24), rhinitis (10/24), urticaria (18/24)	4 days	904.8 µg cumulative	300 µg/week (each other day)	3 mo
Cistero, 2004	Open	1	26	No	15–45	Respiratory symptoms (23/26), cutaneous symptoms (26/26), anaphylaxis (3/26)	4 days	902.2 µg cumulative	300 µg/week (each other day)	2.5 mo
Nettis, 2007	RDBPC	4	20/20	2 A 3 C	18–47	Urticaria (30/40) Asthma (10/40)	4 days	902.2 µg cumulative	300 µg/week (each other day)	1 year
Nucera, 2008	Random open	2	12 11	2 in 2 day group	5–64	Urticaria-angioedema (14/23), eczema (1/23), asthma (10/23), itching erythema (6/23), rhinoconjunctivitis (8/23)	2 days vs 3 days	502 µg cumulative	–	Only safety of the build up only
Nettis, 2010	RDBPC	4	12/9	No	20–49	Latex-induced contact urticaria (21/21)	3 days	591.2 µg	300 µg/week (each other day)	Only safety of the build up
Bernardini, 2006	RDBPC	4	12/8	No	4–15	Rhinoconjunctivitis (16/20), asthma (13/20), urticaria (10/20)	4 days	902.2 µg	210 µg/week (daily)	1 year
Buyukozturk, 2011	RDBPC	4	8/4	3 A	26–32	Skin (9/12), rhinitis (7/12), ocular (9/12), asthma (4/12), systemic (5/12)	4 days	Not Stated	300 µg/week (each other day)	1 year
Gastaminza, 2011	RDBPC	4	14/14	1 C 1 st year 3A 5C 2 nd year	24–57	Urticaria (21/28), rhinoconjunctivitis (19/28), asthma (8/28), anaphylaxis (6/28)	4 days	902.2 µg	210 µg/week (daily)	1 year + 1 year

Abbreviations: A, active; C, control; SPT, skin prick test.

in SPTs reactions. Systemic reactions occurred in 3.6% of total administered doses (36/1,044), mainly locally (84.3%), equally subdivided between buildup and maintenance. Systemic reactions required no treatment in approximately 50% of patients, and only 2.3% of local reactions required antihistamines. The possibility of systemic reactions during the buildup suggests that the induction is performed under medical supervision, as confirmed by a case report of a severe reaction during latex-SLIT.²⁷ A 36-year-old woman allergic to latex had anaphylactic shock at the end of a rush (4-day) induction phase, with the 25 drops of the highest concentration extract (500 µg/mL).

Nettis et al²⁸ enrolled 40 adults patients with urticaria or asthma. Of them, 20 received the active treatment (SLIT-LATEX, Alk-Abellò, Milan, Italy), and 20 a matched placebo. The buildup lasted 4 days, with 15-minute up-dosing, to reach 500 µg protein, and was performed in hospital setting. The maintenance was given at home with 100 µg extract 3 times per week for 12 months. All patients had to avoid exposure during the study period. Symptom/medication scores, specific bronchial reactivity, titrated SPT, glove test, and specific IgE were assessed. At 12 months, the improvement in symptoms and medication scores, glove use test, bronchial reactivity, and SPT reactivity became significantly different between the active and placebo group, whereas no change was seen in specific IgE. Three patients in the active group reported local side effects during the induction, and 1 placebo patient experienced asthma. This study confirmed the overall safety of latex SLIT but, once again, it confirmed the need to perform induction under medical supervision.

The interest in rush protocols is constantly growing, with the aim of reducing the time and costs of hospitalization. Nucera et al²⁹ compared 2 different rush induction protocols (2 or 3 days) in terms of safety and tolerability: 23 patients with both respiratory and cutaneous latex allergy were divided in 2 groups, each group received a cumulative dose of latex proteins amounting to 502 µg sublingually in 2 days or in 3 days. Those patients on the 3-day protocol showed better tolerability and no systemic or local reactions during the buildup phase, whereas some patients on the 2-day protocol developed adverse events during the dose increase: 25% experienced local reactions; 33%, systemic mild or moderate reactions. Recently, a 3-day buildup phase protocol in patients with latex-induced urticaria without professional exposure to latex was assessed.³⁰ This double-blind, placebo-controlled study involved 21 patients (12 active and 9 placebo). The rush protocol used the dilutions of the third and fourth vials of SLIT-LATEX, corresponding to 591.2 µg of latex proteins (7.2 µg on day 1, 18 µg on day 2, 566 µg on day 3), with no systemic reactions in the SLIT group, where only 1 patient had a mild and transient local reaction. Buyukozturk et al³¹ described a randomized placebo-controlled study involving 12 patients (all HCW) with skin or respiratory symptoms attributable to latex exposure. Eight patients received active SLIT and 4 matched placebo. There was a significant decrease in symptom/medication score and an improvement in the glove use test only in the active group at 12 months, but 3 patients from the active group dropped out because of severe systemic side effects. The more recent study with latex SLIT is a randomized, double-blind, placebo-controlled one, lasting 1 year, followed by an additional open-label year of follow-up.³² This study evidenced a very low rate of adverse effects during the 2 study phases but suggested that the dose of latex extract used (40 µg/day) during maintenance results in no appreciable efficacy. The authors also suggested that increasing the maintenance dose until 500 µg is well tolerated. However, some bias in the distribution of patients in active and placebo groups may have influenced the results. In fact, the authors reported a greater number of patients affected by latex-induced asthma in the active group as compared with the placebo group. Latex-specific IgE were higher in the active group, and in the placebo group the medians of

Table 5
Outcomes and results in the SLIT trials

Author, Year	Outcomes	Main results	Safety
Patriarca, 2002	PROVOCATION: Glove use, conjunctival challenge, sublingual challenge. SEROLOGICAL: specific IgE	PROVOCATION: In all active patients, glove use, sublingual challenge, and ocular challenge turned negative. SEROLOGICAL: No change in IgE	2 Spontaneously resolving local side effects during maintenance.
Cistero, 2004	PROVOCATION: Glove use, rubbing test CLINICAL: SPT	PROVOCATION: Significant improvement in glove use and rubbing test. CLINICAL: No change in SPT results	Systemic reaction in 3.6% (38/1,044) of doses, corresponding to 46.2% patients (12/26), no treatment required in 44.7% systemic reactions; 1 patient precautionary treated twice with epinephrine. Local reactions in 21.4% doses, corresponding to 88.5% patients (23/26).
Nettis, 2007	PROVOCATION: Glove use, specific bronchial provocation, CLINICAL: Symptom/med.score, SPT SEROLOGICAL: specific IgE	PROVOCATION: Significant improvement in glove use CLINICAL: Decrease in symptom/medication score and SPT results at 12 mo. SEROLOGICAL: No change in IgE	3/35 active had local side effects. 1/17 placebo patients had asthma. All side effects during build-up
Nucera, 2008	Only safety evaluation of 2-day vs 3-day induction	The 3-day protocol was better tolerated and safer than the 2-day protocol	No side effect in 16/22 patients. 3 local reactions and 4 systemic reactions in the 2-day protocol; no reactions in the 3-day protocol.
Nettis, 2010	Only safety evaluation of the induction phase	The 3-day build-up phase schedule was safe and well tolerated in adult patient with latex-induced contact urticaria	1 active patient had a local side effect; 2 placebo patients group had systemic reactions with nonspecific symptoms. In all patients side effects spontaneously resolved.
Bernardini, 2006	PROVOCATION: Glove use and rubbing test CLINICAL: SPT, prick by prick SEROLOGICAL: specific IgE	PROVOCATION: Decrease in symptoms at glove use and rubbing test. No change in placebo group. CLINICAL: No change in SPT both groups SEROLOGICAL: No change in IgE both groups.	No side effect was observed
Buyukozturk, 2011	PROVOCATION: Glove use test. CLINICAL: Symptom/med. score.	PROVOCATION: Improvement at glove use CLINICAL: Decrease in symptoms	3 severe systemic events (2 epinephrine) in SLIT group, who discontinued
Gastaminza, 2011	PROVOCATION: Glove use test, conjunctival challenge. SEROLOGICAL: IgE, basophil activation test. CLINICAL: SPT	No significant difference in all parameters after 12 months of therapy.	4 SLIT and 5 placebo patients had mild adverse events in the build-up phase. All but 1 patient reached the maximum dose. During maintenance 1 patient dropped-out due to systemic itch.

IgE to Hev b 5 and Hev b 6 were 0 and 0.4, respectively. Two patients were sensitized to Hev b 1, but their allocation in the 2 groups was not specified. Finally, the authors underlined that Hev b 1 was not present in the composition of the extract used.

Bernardini et al³³ assessed the efficacy and safety of latex SLIT in children (4–15 years) with latex allergy. The study was randomized, double-blind, and placebo-controlled. Twenty patients were enrolled (2 patients had spina bifida). Twelve patients received SLIT and 8 placebo. SLIT was administered according to a 4-day buildup. The maintenance dose consisted of 2 drops of the higher concentration (40 µg of extract per administration) daily for 12 months. All children completed the 12-month treatment with no local/systemic side effects. In the active group, a significant decrease in symptom score at the glove use and at the rubbing test was observed at the end of the trial. Conversely, significant changes were not seen in serum latex-specific IgE nor in skin reactivity to latex. After the first year of treatment, the study was unblinded and the 12 active SLIT subjects prosecuted the maintenance schedule.⁶ Every 3 months, parents and patients were interviewed during a control visit to check the safety of SLIT through a clinical evaluation. The significant reduction of the glove use score was further reduced in the second year, and after 3 years all patients had a negative glove use test. Baseline wheal areas of skin prick test were significantly reduced after 2 and 3 years of SLIT, and specific IgE were significantly reduced after 3 years. Therefore, 3 years of latex SLIT is safe and consolidates the efficacy previously observed after 1 year³³ of treatment. Finally, a case report concerns a boy treated with SLIT for 7 years without adverse reactions, and maintaining the clinical benefits 1 year after discontinuation.³⁴ Efficacy and safety of latex SLIT in children was documented also in another case-report,³⁵ whereas SLIT given to an allergic boy allowed the administration of a latex-containing hepatitis B vaccine without side effects.

Discussion

Allergy-specific immunotherapy represents the only antigen-specific, disease-modifying treatment for IgE-mediated allergy. Latex is a relatively common allergenic source, often unavoidable, and responsible for severe IgE-mediated reactions, especially in HCW.³⁶ Several attempts have been made with SCIT for latex allergy, but the results were variable (2 positive and 1 negative trial), and side effects were quite frequent.^{19–21} The introduction of SLIT allowed the achievement of a better safety profile, with overall favorable results, although some concerns remain. For instance, a maintenance dose of 40 µg/day proved effective in children³³ but not in adults.³² According to the literature, the commercially available latex-SLIT products seem to represent a viable therapeutic option for carefully selected patients. Nonetheless, the evidence available relies on small studies (approximately 200 patients in total), with a moderate methodological quality. In addition, also with SLIT, patients should receive the up-dosing under medical supervision. This is acceptable because usually the up-dosing lasts 3 to 4 days only.

New and safer approaches to immunotherapy, such as recombinant allergens and peptide immunotherapy, are currently under investigation.² Peptide-based SIT was developed thanks to improved understanding of the mechanisms of immunotherapy. It involves treatment with short synthetic peptides capable of inducing T-cell reactivity but unable to induce an IgE binding.³⁷ This treatment has been used in cat and insect venom allergy with encouraging results, but side effects are possible. Because recent studies have indicated that the most clinically relevant allergens among HCW are Hev b 5, 6, and 7, Sutherland et al³⁶ suggested these molecules as suitable candidates for a peptide immunotherapy. Another attractive approach is the use of recombinant allergens. Extracts for immunotherapy produced with this technique

contain allergens that are well known in composition and amount and are not contaminated by other allergens or undesirable materials. In addition, recombinant techniques also allow production of modified allergens with lower IgE affinity. Trials conducted with recombinant/modified inhalant allergens provided positive results.³⁸ Thus, the use of recombinants in latex allergy could be reasonable, as well as planning the use of mixtures of single molecules, specifically adapted to patients' sensitization profiles.

Conclusion

In conclusion, although official guidelines do not indicate SIT in latex allergy,^{16,39,40} and the experimental evidence is far from being robust, at least SLIT may represent a valuable option to be used in selected patients, with severe symptoms, and who cannot avoid latex. The optimal maintenance dose (balancing reasonably side effects and efficacy) should be between 300 and 500 µg extract per week, and the efficacy has been documented with 9- to 12-month courses, although no data are available on the optimal duration of the treatment to achieve long-term effects. Also in those cases, strict medical supervision is recommended.

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