

BRIEF REPORT

Sublingual immunotherapy for latex allergy: tolerability and safety profile of rush build-up phase

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ABSTRACT

Objective: Sublingual immunotherapy represents an efficient therapeutic tool for the management of latex allergic patients. Local and systemic adverse reactions are reported, and risk factors for those reactions are poorly understood. The aim of this study is to compare two different rush induction protocols (2-day and 3-day) in terms of safety and tolerability and effectiveness in reaching the maintenance dose.

Methods: Twenty-three outpatients (F/M = 18:5; 5–64 years of age), with latex allergy were randomly assigned to: Group 1 (2-day) and Group 2 (3-day). Adverse reactions were classified by their type and severity.

Results: Twenty-one subjects, 10 from Group 1 and 11 from Group 2, reached the maintenance dose, 70% of them without side effects. Seven adverse events were reported in Group 1: three were local (oral itching) and spontaneously remitted; four were systemic (Grade-2: two reactions; Grade-3: two reactions) and were

effectively controlled with drugs. The protocol was interrupted in two cases because of recurrent reactions. No reactions were reported in Group 2. Age, gender, atopy, specific IgE, skin prick tests and sublingual challenge did not seem to influence the risk of side effects significantly. No significant modification of skin tests and specific IgE levels were reported in both groups. The cutaneous test turned negative in 16 patients, eight from Group 1 (80%) and eight from Group 2 (73%). The remaining patients (two from Group 1 and three from Group 2) showed a reduction of latex reactivity, in terms of symptom score (MIS: 2 vs. 0.5 in Group 1, 3 vs. 1 in Group 2).

Conclusions: This study confirms the safety of rush induction. The 3-day protocol was better tolerated than the 2-day. Significant risk factors for the occurrence of adverse reactions were not identified. Only the type of protocol but not patient-related parameters seemed predictive of side-effects.

Introduction

Allergen specific immunotherapy is the only specific and curative approach in the treatment of IgE-mediated allergic diseases. Sublingual immunotherapy (SLIT) is currently considered a valid option to subcutaneous immunotherapy (SCIT)¹⁻³.

It represents an efficient therapeutic tool for the management of patients allergic to latex proteins⁴⁻⁸. The prevalence of latex allergy is less than 1% in the general population, whereas it is significantly higher among healthcare workers, children with congenital malformations and atopic subjects. A high prevalence (25%) of latex-related adverse events was

found among the healthcare workers (HCW) of an Italian general hospital, although a true latex allergy was detected only in a minority of cases⁹. Despite some preventive measures having been shown to be effective in protecting healthcare workers and patients, allergic reactions can occur even in a presumably latex-free workplace^{10,11}. A complete latex avoidance is unfeasible, especially out of the healthcare setting, because latex-containing items are very common and some latex proteins cross-react with proteins from plant-derived foods (Latex-fruit Syndrome)¹². For these reasons specific immunotherapy is important for the therapeutic approach of latex allergic patients.

However, some local and systemic adverse reactions, especially during the incremental phase, are reported^{4-8,13}. Risk and pathogenic factors for those reactions are poorly understood and no reliable test is available which can predict higher risk for adverse reactions.

The aim of the present study was to compare two different rush induction protocols (2-day and 3-day) in terms of safety and tolerability and effectiveness in reaching the maintenance dose (10 drops of the pure latex solution, 200 µg/mL) and to identify possible risk factors for the occurrence of adverse events⁸.

Patients and methods

Study design

This randomized double-blind trial was conducted in parallel groups, in accordance with good clinical practice after being approved by our hospital's ethic Review Board.

Patients, or their parents, gave their written informed consent and were randomly assigned to one of the following:

- Group 1 (active, 2-day protocol);
- Group 2 (active, 3-day protocol).

The occurrence of adverse reactions was evaluated in both groups.

Patients

Twenty-three outpatients (female-male ratio = 18:5), aged 5-64 years, with immediate IgE-mediated allergy to latex, were recruited over 1 year (2006) in the Allergy Unit of the Policlinico A. Gemelli of Rome and randomized. Six of them were children (< 16 years old).

Inclusion criteria were:

- history of symptoms after latex exposure (urticaria-angioedema or itching erythema; rhinoconjunctivitis, bronchial asthma, anaphylactic shock);

- positive skin prick test and/or specific IgE (> 0.35 kU/L) to latex;
- positive latex provocation tests (cutaneous and/or sublingual).

Exclusion criteria were pregnancy or lactation, autoimmunity, asthma or urticaria-angioedema exacerbation 24 h before the treatment, β -blocking drugs, severe renal and cardiovascular diseases.

Skin tests

Skin prick tests (SPTs) with a standard latex extract (500 µg/mL; ALK Abellò, Madrid, Spain) were performed with a Morrow-Brown needle (ALK Abellò) on the volar surface of the forearm. Glycerin solution and histamine (10 mg/mL) were used as negative and positive controls, respectively. A positive response was defined as one producing a wheal greater than 3 mm in diameter at 20 min after application, without reaction to negative control.

Laboratory tests

Serum levels of specific IgE to latex were measured by fluorescent enzyme immunoassay (UniCAP System; Pharmacia, Uppsala, Sweden). IgE concentration of > 0.35 kU/L was regarded as positive.

Challenge tests

These were performed in a day-hospital regimen. Anti-histamines were withheld for 10 days before each challenge. Expiratory peak flow, pulse rate, and blood pressure were monitored during each challenge and for 2 h after its end. Positivity was assigned if one or more immediate-type symptoms occurred (erythema, local or generalized cutaneous itching, mucous itching, urticaria, angioedema, conjunctivitis, rhinitis, cough, dyspnea, asthma, etc).

A cutaneous test was carried out asking the patients to wear a latex glove (Allegiance Triflex) until symptoms appeared. The maximum exposure time was 1 h. Before the challenge patients had to wash and perfectly dry their hands. As a control they had to wear a synthetic (vinyl) glove on the opposite hand. Then the gloves were taken off and their hands were washed again. A physician assessed possible clinical reactions. The test was considered positive if immediate-type symptoms occurred without reactions to the control glove. Patients with active hand dermatitis at the time of the challenge were excluded.

During the sublingual test, patients had to maintain one drop of latex solution under the tongue for 3 min and then spit, increasing the concentration (from the

smallest of 500×10^{-8} µg/mL to the largest of 500 µg/mL) every 20 min. The threshold dose was defined as the smallest allergen concentration able to induce the appearance of symptoms. A preliminary control test with placebo (physiologic saline) was performed. Patients with oral lesions at the time of the challenge and with a positive control test were excluded.

Reactivity scoring during provocation tests

Symptom scores

Ocular (tearing, itching, edema, conjunctival edema), respiratory (rhinorrhea, nasal itching, nasal blockage, sneezing, wheezing, cough, dyspnea, laryngospasm) and muco-cutaneous symptoms (generalized pruritus, erythematous-papular rash, urticaria-angioedema, oral and pharyngeal itching) were recorded during challenges and scored on a 4-point scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe).

Drug scores

If patients experienced a FEV₁ decrease of 20% or more from baseline level, they were treated with inhaled bronchodilator and corticoid. If symptoms occurred patients were administered antihistamines and corticoids. On the basis of drug consumption during challenges and within 2 h after they had finished, for each patient, a score was recorded on a 5-point scale: 0 (no drugs), 1 (nasal/ocular steroid), 2 (inhaled bronchodilator and corticoid, oral antihistamine), 3 (intramuscular antihistamines, intramuscular and/or intravenous corticoids), 4 (subcutaneous epinephrine).

Mean individual score (MIS)

This is the mean value of the total score (symptom + drug score), recorded for each patient.

Clinical protocols

The rush phase of the SLIT was performed according to two different protocols (Table 1), with increasing doses of latex extract (500 µg/mL, ALK-Abellø) under the patients' tongues for 3 min every 20 min, until reaching the maintenance dose (10 drops of the undiluted latex solution)⁵. After 3 min the latex solution was swallowed. The treatment was administered by the same doctor.

In order to administer the same number of doses in the two groups and assure double blinding of the trial, placebo (physiologic saline in identically labeled vials) was used.

Patients were hospitalized during such procedures and resuscitative equipment and personnel were

available. Antihistamines were withheld for 10 days before the rush phase.

Safety assessment during the trial was based on physical examination, vital signs (pulse rate and blood pressure), expiratory peak flow, oral examination, and recording of adverse events and concomitant medication.

After the rush phase patients underwent a second allergological evaluation (skin tests, specific IgE, cutaneous test).

Adverse events

These were recorded and classified by their type and severity. Adverse events were considered local if they occurred in the oropharynx (oral itching, swelling under the tongue and/or lower lip). Systemic reactions were divided into four grades, according to the EAACI Position Paper on Immunotherapy¹⁴; *grade 0*: no symptoms; *grade 1*: unspecific symptoms – reactions probably not IgE mediated (discomfort, headache or arthralgia); *grade 2*: mild systemic reactions – mild rhinitis or asthma responding adequately to antihistamines or β₂-agonist therapy; *grade 3*: non-life-threatening systemic reactions – urticaria, angioedema or severe asthma, responding well to treatment; and *grade 4*: anaphylactic shock – rapidly evoked reaction of itching, flushing, erythema or bronchial obstruction, requiring intensive treatment.

The onset time of any reaction was recorded. If the reaction developed 60 min after the last daily dose, it was accepted as delayed.

If a patient developed an adverse reaction during the dose increase, treatment was interrupted until complete recovery was obtained (by drugs), and then restarted with the last tolerated dose. In the case of reactions not requiring drugs, the protocol continued without dose reduction.

The patients received antihistamines, steroids, and adrenaline according to the reaction severity. If a patient experienced a recurrent reaction (despite the rescue medications) the treatment was stopped.

Statistical analysis

Analyses were performed using SPSS software package (release 13.0 for Windows, Chicago, USA). Odds Ratio (OR) was calculated by binary logistic regression. Prevalence of adverse events was evaluated by Pearson-χ². A *p* < 0.05 was considered as significant.

Results

All patients met all inclusion criteria and no exclusion criteria and were randomly assigned to:

Table 1. Protocol 1 (2 days build-up phase) versus Protocol 2 (3 days)

Days	Protocol 1 (2-day)		Protocol 2 (3-day)	
Day 1	Placebo*	1 drop	Latex solution†	1:10 ¹⁸ 1 drop
		1 drop		1:10 ¹⁷ 1 drop
		1 drop		1:10 ¹⁶ 1 drop
		1 drop		1:10 ¹⁵ 1 drop
		1 drop		1:10 ¹⁴ 1 drop
		1 drop		1:10 ¹³ 1 drop
		1 drop		1:10 ¹² 1 drop
		1 drop		1:10 ¹¹ 1 drop
		1 drop		1:10 ¹⁰ 1 drop
		1 drop		1:10 ⁹ 1 drop
Day 2	Latex solution†	1:10 ¹² 1 drop	Latex solution†	1:10 ⁹ 1 drop
		1:10 ¹¹ 1 drop		1:10 ⁸ 1 drop
		1:10 ¹⁰ 1 drop		1:10 ⁷ 1 drop
		1:10 ⁹ 1 drop		1:10 ⁶ 1 drop
		1:10 ⁸ 1 drop		1:10 ⁵ 1 drop
		1:10 ⁷ 1 drop		1:10 ⁴ 1 drop
		1:10 ⁶ 1 drop		1:10 ³ 1 drop
		1:10 ⁵ 1 drop		1:10 ² 1 drop
		1:10 ⁴ 1 drop		1:10 1 drop
		1 drop		1 drop
Day 3	Latex solution†	1:10 ³ 1 drop	Placebo*	1 drop
		1:10 ² 1 drop		1 drop
		1:10 1 drop		1 drop
		Pure 1 drop		Latex solution† Pure 1 drop
		Pure 2 drops		Pure 2 drops
		Pure 3 drops		Pure 3 drops
		Pure 4 drops		Pure 4 drops
		Pure 5 drops		Pure 5 drops
		Pure 10 drops		Pure 10 drops

*Placebo (physiologic saline in identically labeled vials) was used, in order to administer the same number of doses in the two groups and assure double blinding of the trial

†Latex solution (500 µg/mL, ALK-Abellö) diluted with saline

- Group 1 (2 days): 12 patients;
- Group 2 (3 days): 11 patients.

The baseline characteristics of all patients are described in Table 2: groups were well matched for demographics and symptoms.

Of 23 patients under rush SLIT, 21 subjects, 10 from Group 1 and 11 from Group 2, reached the maintenance dose (10 drops of pure solution).

In the remaining two patients (17% of Group 1; 9% of the whole population) induction had to be stopped due to persistent side-effects despite treatment with intravenous antihistamines and corticosteroids. Of patients reaching the maintenance dose, 16 (70%) did not experience side effects. Seven treatment-related adverse events were reported in Group 1. On the contrary, no reactions were observed in Group 2. No adverse reactions were related to the placebo doses.

Adverse events occurred within 20 min of administration of the latex. No late reactions have been reported. Side-effects showed no significant dose-dependency ($p > 0.05$).

Three reactions (43%) were local: oral itching. One of them occurred after the last dose (10 drops of the pure solution). Four systemic reactions were reported: two rhinitis (grade 2; threshold dilution: 10⁻⁸ and 10⁻¹ respectively), one generalized urticaria (grade 3; threshold dilution: 10⁻¹), one generalized urticaria-angioedema with bronchial asthma and rhinoconjunctivitis (grade 3; threshold dilution: 10⁻²).

Rescue medicines were administered in 57% of side effect cases. Local reactions spontaneously remitted and the protocol was continued without dose reduction. Both the grade-2 reactions responded well to treatment (oral antihistamine) and the protocol was restarted

Table 2. Demographic and clinical data of participants at the beginning of the study

	Group 1	Group 2	Test result*
Build-up phase	2 days	3 days	
Patient numbers	12	11	NS
Sex (M/F)	3/9	2/9	NS
Age (years)	7–48	5–64	NS
(Mean $\pm$ SD)	29 ($\pm$ 13)	32 ($\pm$ 16)	
Number of patients with personal history of			
Atopy	5	8	NS
Asthma	4	2	NS
Atopy + asthma	2	2	NS
Clinical features of latex allergy			NS
Mucous-skin reactions	12	9	NS
Urticaria-angioedema	8	6	NS
Eczema	1	–	NS
Itching erythema	3	3	NS
Respiratory symptoms	4	9	NS
Asthma	2	8	NS
Rhinoconjunctivitis	3	5	NS
Mucous-skin + respiratory symptoms	4	7	NS
Latex-specific IgE (kU/L)			NS
Mean $\pm$ SD	9 ($\pm$ 16)	9 ($\pm$ 13)	
Number of positive responses (> 0.35 kU/L)	9	11	
Wheal diameter (mm)			NS
Mean $\pm$ SD	7.8 ($\pm$ 4)	8 ($\pm$ 5)	
Number of positive responses (> 3 mm)	12	11	
Number of patients with positive			
Cutaneous challenge	12	11	NS
Sublingual challenge	12	11	NS

*Pearson- χ^2

NS = no statistically significant difference ($p > 0.05$) between the two groups

SD = Standard deviation

with the last dose tolerated. Both grade-3 reactions were effectively controlled with drugs (intravenous antihistamine and steroid, inhaled bronchodilator in one case) but the protocol was interrupted due to recurrent reactions. None of them required intramuscular adrenaline and intensive treatment. No life-threatening or fatal reactions were reported.

Only one patient among the six children enrolled in the study experienced mild side effects (rhinoconjunctivitis).

The 3-day protocol was better tolerated mainly owing to the lower frequency of adverse effects (0% vs. 58%, on a *per patient* basis; $p = 0.002$).

In Table 3 possible risk factors for the occurrence of side effects are considered. There was no significant effect of age and gender and personal history of asthma and atopy upon the occurrence and severity of adverse reactions ($p > 0.05$). The level of specific IgE and results of SPT did not show any correlation with the

risk of developing side effects, independently of the protocol used ($p > 0.05$).

Furthermore, as shown in Tables 3 and 4, if we consider the results of sublingual challenge, frequency of side effects did not increase with higher reactivity (in terms of both symptom score and threshold dose).

Moreover, significant correlation between grade of side effects during rush treatment and the severity of allergic reactions after latex exposure could not be found.

No significant modification of skin prick tests and latex specific IgE levels were reported after the rush phase in both groups. The cutaneous challenge test turned negative after the induction phase in 16 patients, eight from Group 1 (80%) and eight from Group 2 (73%). Patients (two from Group 1 and 3 from Group 2) with a positive cutaneous test presented a reduction of latex reactivity, in terms of symptom score (MIS: 2 vs. 0.5 in Group 1, 3 vs. 1 in Group 2).

Table 3. Possible risk factors for the occurrence of adverse events during the rush phase

Variable		Estimated OR	95% confidence interval for OR	p value*
Personal history	Asthma	1.2	[0.164; 8.799]	> 0.05
	Atopy	1.037	[0.137; 6.233]	> 0.05
Symptoms on exposure to latex	Asthma	0.4	[0.059; 2.701]	> 0.05
	Urticaria-angioedema	6	[0.582; 61.842]	> 0.05
Allergy testing	Specific IgE > 0.35 kU/L	0.167	[0.012; 2.255]	> 0.05
	SPT results (diameter > 10 mm)	1.650	[0.264; 10.313]	> 0.05
Reactivity during sublingual test	MIS > 2	1.750	[0.125; 4.488]	> 0.05
	Threshold dose† (dilution) > 10 ⁻²	2.22	[0.365; 13.65]	> 0.05

*Pearson- χ^2

†Largest dilution of latex able to induce symptoms

OR = odds ratio; SPT = skin prick test with latex extract; MIS = mean individual symptom score recorded during sublingual challenge

Table 4. Comparison between reactivity during sublingual test and side effects during desensitization

Patients	Sublingual challenge		Side effects		
	Threshold dose†	Symptoms	Threshold dose†	Symptoms	Withdrawal*
1	Pure	RC, U, E	1:10 ⁸	RC	
2	1:10 ⁵	U	–	–	
3	1:10 ⁸	A, U, E	–	–	
4	Pure	U	–	–	
5	1:10 ⁸	RC, U	–	–	
6	Pure	U	–	–	
7	Pure	U	1:10	RC	
8	Pure	U	1:10 ¹¹	L	
9	1:10 ²	U	Pure (10 drops)	L	
10	1:10 ⁴	U	1:10 ¹	L	
11	1:10 ⁴	U, E	1:10 ¹	U, E	+
12	1:10 ⁵	U	1:10 ²	U, E, A, RC	+
13	1:10 ²	A, U, E	–	–	
14	Pure	U	–	–	
15	1:10 ⁵	A	–	–	
16	1:10 ⁸	A	–	–	
17	1:10 ⁸	U	–	–	
18	Pure	U	–	–	
19	Pure	U, E	–	–	
20	1:10 ⁵	U, E	–	–	
21	1:10 ⁸	RC	–	–	
22	1:10 ⁵	RC	–	–	
23	1:10 ⁵	U, E	–	–	

RC = rhinoconjunctivitis; A = asthma; U = urticaria; E = angioedema; L = local reactions

*Treatment was discontinued for the recurrence of symptoms, despite the rescue medication

†Smallest dose inducing symptoms

Discussion

Sublingual desensitization seems to be effective in patients with latex allergy and safer if compared with injective protocols^{4-8,15}. Rush protocols are particularly

interesting because they reduce the patient's stay in the hospital and provide an earlier tolerance to latex exposure⁴⁻⁸.

The present study evaluates the safety profile of the rush build-up phase, comparing two different protocols

(2-day and 3-day schedule). Secondly it aims to define risk factors for side effects to rush induction in order to adapt the future regimens to the individual patient's risk profile.

Previous studies reported on 4-day regimens, which have been shown to be safe and effective⁴⁻⁸. Considering the completion of up-dosing as an indicator of effects, our protocols have been shown to be effective: with both of them the maintenance dose was reached rapidly (48 and 72 h, respectively). Despite the lack of considerable modifications of immunological parameters (both serum parameters and skin tests) both treatments were rapidly effective. In fact all patients showed a significant improvement of latex allergy, in terms of reduced reactivity to latex and symptom onset time, during challenge tests.

Some authors reported no side effects during the build-up phase^{4,6-7}. Nettis *et al.* report the occurrence of side effects (17% of treated patients) during the dose build-up phase⁵: they were mild and all regressed spontaneously. The present study confirms the safety of rush induction. The 3-day regimen was well tolerated: no side effects (both local and systemic reactions) occurred and all the patients completed the protocol. These results are in accordance with data from the literature^{4,6-7}.

While the 3-day protocol was tolerated by all patients, 66% of patients completed the 2-day regimen without systemic reactions. In this group 25% patients experienced only local reactions, spontaneously remitted. The remaining four patients (33%) presented systemic mild or moderate reactions, rapidly controlled by rescue medications. The incidence is quite a bit higher if compared with previous studies⁴⁻⁸, but only in two cases the treatment was interrupted, because symptoms appeared again, despite the drugs.

Only one case of anaphylactic shock is reported in the literature following the administration of the final dose of 500 µg¹². Considering the whole study population, no one experienced anaphylactic shock and 21 patients (91%) reached the cumulative daily dose of 500 µg in the last day of induction.

In order to reduce the risk of side effects, differently from previous reports, in both our protocols the dose of 500 µg was not given in one administration in the last day. In fact we think there is not a rationale strong enough to give such a high dose after the maintenance dose was reached, because it is burdened from high risks and its impact on the effectiveness of the whole treatment is unknown.

No data are available in the literature about the impact of risk factors upon the occurrence and severity of adverse reactions during latex desensitization. According to Sastre *et al.* there is a negative correlation

between the basal levels of specific IgE to Hev b 6.01 and the maximum tolerated dose of allergen during immunotherapy¹⁶. Nevertheless these findings do not seem to be associated with clinical outcomes of immunotherapy in terms of efficacy or safety.

Also our study did not identify significant risk factors for the occurrence of adverse reactions. Only the type of protocol but not patient-related parameters seemed predictive of side-effects.

Conclusions

Our experience suggests that rapid induction is safe and should be considered in every case, even in patients with positive sublingual challenge, especially when a rapid protection is required.

According to the present findings the 2-day shortened build-up phase was less safe than the 3-day protocol.

Since no possible risk factors have been found for the occurrence of adverse events, all patients should be carefully monitored during the build-up phase. Further studies are needed to confirm our results.

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