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Brief report

The safety of a novel sublingual rush induction phase for latex desensitization

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Key words

Natural rubber latex – Rush protocol – Safety –
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Abstract

Objectives:

In latex allergic individuals the avoidance of all exposure to natural rubber latex products is recommended. Sublingual immunotherapy against latex has recently been proposed. The aim of the study is to evaluate the tolerability of sublingual immunotherapy with latex extract, by a double-blind, placebo-controlled study, according to a three-day build-up phase rush protocol in a population of patients with latex-induced contact urticaria without a professional exposure to latex.

Methods:

Twenty-one patients with latex-induced urticaria were randomized to receive sublingual immunotherapy (SLIT) with latex extract or placebo. Rush (3-day) induction protocol of latex sublingual immunotherapy was performed with increasing doses of ALK-Abelló latex extract at three concentrations of latex proteins (5, 50 and 500 $\mu\text{g mL}^{-1}$). Any side-effects that might be related to immunotherapy, the corresponding dose and treatment were registered.

Results:

Among the 21 patients, 12 were treated with latex sublingual immunotherapy (9 women and 3 men) and 9 with placebo (8 women and one man). All patients ended the rush protocol. Four patients (19.0%) [one in the SLIT group (8.3%) and three in the placebo group (33.3%)] developed adverse reactions. One SLIT patient reported mouth itching and burning of the tongue. In the placebo group, one patient presented gastrointestinal complaints while two patients reported unspecific symptoms. All these side-effects regressed spontaneously. No statistically significant differences were found between the proportions of adverse events in the two examined groups.

Conclusion:

This study supports the safety of SLIT against latex conducted in adult patients with latex-induced contact urticaria according to a 3-day build-up phase rush protocol. The proposed 3-day induction phase for latex sublingual immunotherapy should be conducted under medical supervision, although in patients with only latex-induced contact urticaria the registered adverse reactions were so slight that it could be argued that patients could start safely our tested rush protocol at home.

Introduction

Natural rubber latex (NRL) allergy is recognized as a major occupational problem among healthcare workers^{1,2}, but the repeated contact with latex products and multiple operations³ represent a risk of sensitization also in the general population⁴. In sensitized/allergic individuals the avoidance of all exposure to NRL products is recommended, but always it is difficult to make due to the ubiquity of latex. Therefore sublingual immunotherapy (SLIT) against latex has recently been proposed^{5,6}. Latex SLIT should be performed in hospitalized

patients (day-hospital regimen) during the up-dosing phase just to assure all the facilities for a safe treatment.

This double-blind, placebo-controlled study was conducted to evaluate the tolerability of SLIT with latex extract according to a 3-day build-up phase rush protocol in a population of patients with latex-induced contact urticaria without a professional exposure to NRL.

Patients and methods

Twenty-one patients with latex allergy were enrolled. They were free from respiratory symptoms, had not received specific immunotherapy in the previous 3 years, and had no other significant disorders or chronic/severe asthma. We also excluded from our study patients who were taking drugs. In these patients, the allergological assessment confirmed the latex-induced contact urticaria diagnosis by: SPTs with ALK-Abelló latex extract (Lainate, Milan, Italy), undiluted and diluted 1:1000, 1:100, 1:10 in a glycerol-saline solution; SPT with latex extract⁷ using the incubation fluid obtained from 400 mg of latex rubber gloves incubated for 30 min in 5 ml of sterile physiological saline; serum-specific IgE to NRL (CAP System, Phadia, Uppsala, Sweden) (positive for a value >0.35 kUAL-1) (Table 1) and serum-specific IgE to recombinant allergens for *Hevea brasiliensis* (rHev b 1, 3, 5, 6.01, 6.02, 8, 9 and 11) that were dosed by ImmunoCap System (Phadia, Uppsala, Sweden). The most frequent recombinant latex proteins found in our study population were rHev b 6.01 (in 16 patients corresponding to 76.2% of cases) and rHev b 6.02 present in 10 subjects (data not shown). All patients showed positive results to glove use test as latex provocation test that was performed using same batch of NRL gloves (Le Petit; Grandate, Como, Italy) according to previous procedures⁷. Bronchial challenge test with latex⁵ gave negative results in all patients. All patients recruited at the Department of Allergy and Clinical Immunology of Bari Polyclinic, before the enrolment, gave written informed consent.

Patients 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 (Lainate, Milan, Italy).

Immunotherapy protocol

SLIT with latex extract is usually performed with four different vials. Rush (3-day) induction protocol of SLIT consisted of three concentrations of ALK-Abelló latex: 5, 50 and 500 µgmL⁻¹ using only the third and fourth vials. Treatment contemplated: on Day (D) 1 the administering of six doses of the undiluted third vial (at 5 µgmL⁻¹ concentration of latex proteins) and three doses of the fourth vial diluted 1:10 corresponding to 50 µgmL⁻¹ of protein concentration; on D2 nine doses of fourth vial diluted 1:10; on D3 the first three doses of fourth vial diluted 1:10 and the last six doses of fourth vial undiluted corresponding to 500 µgmL⁻¹ protein titre (Table 2). Interval time between successive doses was 15 minutes⁵. The placebo preparation was identical to the active treatment in terms of presentation, taste and colour. The protocol was performed in hospital under strict medical supervision and the SLIT administration to the patient was made by the same doctor. The drops were always held under the tongue for 3 min before being swallowed. In case of adverse reactions requiring drug administration, the protocol was discontinued, while if slight adverse events occurred, the protocol was continued according to the schedule.

Adverse events

Physicians recorded any side-effects or suspected adverse events that might be related to SLIT, the corresponding dose and treatment (if any). Reactions were classified as systemic according to the EAACI Position Paper on Immunotherapy⁸: Grade 0: no symptoms, Grade 1: unspecific symptoms presumable not IgE-mediated like

Table 1. Patient demographics.

	SLIT latex group	Placebo group
Patients, n (%)	12 (57.1%)	9 (42.9%)
Sex, M (%) / F (%)	3 (25.0%) / 9 (75.0%)	1 (11.1%) / 8 (88.9%)
Mean age (yrs)	34.3 (range, 20–46)	36.8 (range, 22–49)
Profession		
Housewife, n (%)	6 (50.0%)	4 (44.5%)
Student, n (%)	3 (25.0%)	2 (22.2%)
Employer, n (%)	2 (16.7%)	1 (11.1%)
Teacher, n (%)	1 (8.3%)	1 (11.1%)
Countryman, n (%)	–	1 (11.1%)
Latex-specific IgE (kUAL-1)	1.40–45.65	1.25–50.04
Positive cutaneous challenge test, n (%)	12 (100.0%)	9 (100.0%)

SLIT = sublingual immunotherapy.

headache or general malaise, Grade 2: mild systemic reactions as rhinitis or asthma well responding to drugs, Grade 3: non-life-threatening systemic reactions as urticaria, angioedema or severe asthma responding to drugs, Grade 4: anaphylactic shock⁸. Since up to now no official classification is disposable, the local reactions were considered: oral itching/swelling, oedema of the tongue, gastrointestinal complaints. During the rush SLIT protocol and before the beginning of immunotherapy, all patients were informed by physicians of the risks of NRL allergy and given instructions on preventive measures (avoidance of exposure to latex-containing products also used in daily life) providing them latex-free alternatives.

Statistics

The differences between proportions of adverse events observed in the two groups (SLIT and placebo) were compared using the Fisher test. A *p* value <0.05 was considered statistically significant.

Results

Twenty-one patients with demonstrated latex-induced contact urticaria (4 men and 17 women) aged 20–49

years had a history of urticaria and/or angioedema handling latex products (gloves, dummies, sports equipments, balloons, etc.). All subjects (10 housewife, 5 students, 3 employers, 2 teachers and 1 countryman) were not professionally exposed. Among the 21 randomized patients, 12 (57.1%) were treated with SLIT (9 women and 3 men) and 9 (42.9%) with placebo (8 women and one man) (Table 1). All patients completed the rush protocol. Four patients (19.0%) [one in the SLIT group (8.3%) and three in the placebo group (33.3%)] developed adverse reactions. No differences statistically significant were found between the proportions of adverse events in the two examined groups.

One female SLIT patient (8.3%, not statistically significant in comparison to placebo group, *p*>0.05) reported mouth itching and burning of the tongue rose ten minutes after the fourth dose of the D1. In the placebo group, one subject (11.1%, not statistically significant in comparison to treated group, *p*>0.05) presented gastrointestinal complaints after the fifth dose of D1 while two patients (22.2%, not statistically significant in comparison to treated group, *p*>0.05) reported a Grade 1 reaction with unspecific symptoms after the second dose of D1 and the fifth dose of D2, respectively. In all four patients, these side-effects regressed spontaneously without needing drugs administration and the

Table 2. Rush protocol of sublingual immunotherapy for latex.

Day	Vial (dilution)	Protein concentration ($\mu\text{g mL}^{-1}$)	Drops	Dose (number)	Cumulative dose (μg)	Interval between doses		
1	3	5	1	I	7.2	15 min		
			1	II		15 min		
			1	III		15 min		
	4 (1:10)	50	1	IV	15 min			
			1	V	15 min			
			1	VI	15 min			
			1	VII	15 min			
			1	VIII	15 min			
			1	IX	15 min			
2	4 (1:10)	50	1	I	18	15 min		
			1	II		15 min		
			1	III		15 min		
			1	IV		15 min		
			1	V		15 min		
			1	VI		15 min		
			1	VII		15 min		
			1	VIII		15 min		
			1	IX		15 min		
3	4 (1:10)	50	1	I	566	15 min		
			1	II		15 min		
			1	III		15 min		
	4	500	1	IV		15 min		
			2	V		15 min		
			3	VI		15 min		
			5	VII		15 min		
			7	VIII		15 min		
			10	IX		15 min		
			Total Dosage			591.2		

regular assumption of successive doses was continued without other discomforts.

Discussion

On the basis of several studies that have already demonstrated the safety of rush SLIT induction in patients afflicted from IgE-mediated rhinitis and/or asthma both in adults and in paediatric age^{9,10}, we have decided to study the safety and the tolerability of a 3-day rush build-up phase of latex SLIT. This is the first double-blind, placebo-controlled evaluation on the safety and the tolerability of a rush induction phase of latex SLIT conducted in adult patients allergic to NRL suffered from cutaneous manifestations (contact urticaria) only.

Nucera *et al.*¹¹, in a previous study that compared the safety of two different rush induction protocols performed on 2 and 3 days, showed, in patients with both respiratory and cutaneous latex allergy, a better tolerability in patients treated with the 3-day protocol, without any systemic and local reactions during the build-up phase. In these protocols the total amounts of latex proteins administered were 524 µg and 536 µg in 2-day and 3-day protocols, respectively. Instead, our protocol provided for the administration of a total cumulative dose higher than those of Nucera *et al.*¹¹, corresponding to 591.2 µg of latex proteins (7.2 µg on D1, 18 µg on D2 and finally 566 µg on D3).

Despite the high dose reached during the third day, our results show that no systemic reactions occurred in the SLIT group, while non-specific symptoms appeared in 22.2% of cases in placebo group subjects ($p > 0.05$); in addition, only one patient (8.3%) in the SLIT group presented a slight local reaction as well as one subject (11.1%) belonging to placebo group ($p > 0.05$). Side effects in this study are reported as mild and temporary, and did not differ between the treatment and placebo groups, although the high allergen dose administered in the SLIT group. Our results are in accordance with previous publications in which it is demonstrated that the comparison of studies respectively performed administering high and low allergen doses shows a better tolerability of SLIT at high allergen doses in both adults and children^{12,13}.

Finally, in our population we have found a high frequency of Hev b 6.01 and Hev b 6.02 at a low dosage (< 0.60 KUA/L). These results agree with those of authors on the presence and the levels of specific IgE to Hev b 6.01 that might represent a predictive value for the maximum tolerated dose of allergen during immunotherapy¹⁴. So, in subjects afflicted from latex-induced contact urticaria syndrome the finding of low dosage of Hev b 6.01 and Hev b

6.02 may be a protective factor against adverse reactions during a rush build-up phase of latex SLIT.

Conclusion

This double-blind, placebo-controlled study, supports the safety of SLIT with latex extract according to a 3-day build-up phase rush protocol in a population of patients with latex-induced contact urticaria without a professional exposure to NRL.

The proposed 3-day induction phase for latex SLIT should be conducted under medical supervision, although in patients with only latex-induced contact urticaria the registered adverse reactions were so slight that it could be argued that patients could safely start our tested rush protocol of latex SLIT at home.

Transparency

Declaration of funding

ALK-ABELLÓ S.p.a., Milan, Italy provided the placebo vials, but provided no financial support.

Declaration of financial/other relationships

E.N. has declared that he has consultancy arrangements with Phadia, Allergy Therapeutics, Anallergo, Stallergenes and served on the speakers bureau for Schering-Plough, Almirall, GSK, Astellas, MSD. E.L., G.C., P.D.D. and A.F. have declared no relevant financial relationships. M.M. has declared that he is a member of the Medical Department of ALK. A.V. has declared that he has received grants/research support from Almirall, Schering-Plough and served on the speakers bureau for Phadia, Novartis, GSK, MSD.

Peer reviewers may receive honoraria from CMRO for their review work. Peer Reviewer 1 has declared that he/she has no relevant financial relationships. Peer Reviewer 2 has declared that he/she has received grant/research support from Glaxo SmithKline and Medpointe Pharmaceuticals.

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