

# Tolerance and effects on skin reactivity to latex of sublingual rush immunotherapy with a latex extract

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## SUMMARY

**Background.** Specific immunotherapy could be a therapeutic tool for the increasing problem of sensitisation to Natural Rubber Latex (NRL).

**Objective.** To investigate the tolerability of SLIT for Latex and its effects on skin reactivity.

**Methods.** Twenty-six patients (mean age 35.5 years) with an average history of 7.5 years of cutaneous symptoms plus respiratory symptoms (23/26) due to NRL were studied. All underwent rush sublingual therapy (4 days) with a standardized NRL extract followed by a 9-week maintenance treatment. Local and systemic adverse reactions were monitored throughout the treatment. Skin reactivity to NRL extract was evaluated before, during and at the end of the treatment by latex glove-use test, rubbing test and skin prick test.

**Results.** All patients reached the maintenance dose. Out of 1044 administered doses, 257 (24.6%) produced adverse reactions from which 21.4% were local. Only 10.1% of cases required treatment, mainly with antihistamines alone (5.8%), with 2-agonists alone (0.8%) or associated to antihistamines and/or corticosteroids (2.7%). One patient was precautionary treated twice with adrenaline but completed the treatment without further problems.

The glove-use test improved significantly after 5 days and 10 weeks of treatment ( $p=0.003$ ,  $p=0.0004$  respectively), whereas the rubbing test improved significantly only after 10 weeks of treatment. Doctor's assessments confirmed the results obtained with the glove-use test ( $p=0.003$  after 5 days, and  $p=0.004$  after 10 weeks) but not those obtained with the rubbing test. No change was detected for SPTs.

**Conclusion.** SLIT for NRL allergy is able to modify skin reactivity to NRL in days as assessed with methods reproducing HCWs normal exposure to the allergen. Tolerance of SLIT is better than tolerance reported for injective therapy with NRL, but the build up phase should be administered under medical surveillance until sufficient experience has been accumulated. The long-term effect of the treatment deserves further investigation.

**Keywords:** adverse reactions; allergy; natural rubber latex; skin reactivity; sublingual immunotherapy.

## Introduction

IgE-mediated sensitisation to natural rubber latex (NRL) is currently an important issue, with an estimated prevalence of 1% in the general population and 20% or higher in professionally exposed health care workers (HCWs).

Recent estimations indicate that NRL is used, alone or combined with other substances, in the manufacturing

of more than 40,000 different objects for technical, professional and everyday-life use such as tires, surgical gloves, rubber toys and condoms [1].

HCWs are highly and continuously exposed to latex allergens. Cornstarch powder, added to latex gloves to facilitate wearing, is airborne when gloves are put on and off, dispersing latex proteins that are easily inhaled [2].

Sensitisation can also occur during childhood as result of the repeated surgery in children with inborn

malformations such as *spina bifida*. Repeated surgical procedures have been shown to increase the probability of latex sensitisation by 13 times for any previous operation in children [3]. Allergy to NRL is also increased in adults after repeated operative procedures [4].

Latex allergens affecting HCWs are different than those involved in children sensitisation [5-12]. The clinical manifestations in these two groups also differ, consisting mainly of generalised urticaria in children as opposed to contact urticaria and respiratory symptoms in adults. These differences have been explained as the result of distinct routes of sensitisation [13]. NRL induces primarily type I rather than type IV sensitization [14].

Prevention is obviously the first step in the treatment of latex allergy but, since latex allergens are very common in both professional and private environments, strict avoidance measures can hardly be achieved and kept. Two anaphylactic shock episodes have been recently reported in a patient submitted to strict allergen avoidance upon accidental exposure to latex [15]. Moreover, currently used latex substitutes for gloves seldom allow for the same technical performance.

NRL shares allergens with some common fruits (banana, avocado, chestnut, kiwi, papaya, etc.) and with pollens from botanically-related species (*Ricinus communis*, *Mercurialis annua*). This of course leads to cross-reactions making both *in-vivo* and *in-vitro* specific diagnosis even more difficult [16-19].

Encouraging results have been obtained with specific immunotherapy for another life-threatening condition, sensitization to hymenoptera venom. Oral [20], injective [21-23], percutaneous [24] and sublingual routes [25-27] have been tested. The injective therapy, although effective, produced a high number of adverse reactions. Sublingual immunotherapy (SLIT) also returned promising results but the number of patients studied was too low to draw any conclusions.

We have therefore planned this evaluation to study on a larger experimental base the SLIT for the treatment of NRL allergy, considering that this route has already been documented and validated for the most common inhalant allergens [28,29].

## Methods

### Study design

As there is very poor documentation about SLIT in patients sensitised to latex, we have planned our study according to an open design using a commercially available preparation as treatment.

The assessment of treatment safety and changes, if any, in skin reactivity to latex are the primary goals of this trial. Two centers took part in the study.

### Patients

Patients were selected according to the following inclusion

criteria: clinical history of urticaria, rhinoconjunctivitis, asthma and/or anaphylaxis due to sensitisation to NRL; age > 18 years and positive skin-prick test and/or specific IgE to NRL. As exclusion criteria: standard contraindications for specific immunotherapy [30]; problems at oral level (infection, inflammation, etc.) not compatible with the correct, easy and safe administration of the treatment; and patients with problems to comply with the administration and/or follow up schedule, or not able to receive treatment under the specialist's direct surveillance.

Clinical sensitisation to other inhalant allergens was not considered as an exclusion criterion.

A total of 26 patients (5M/21F), with a mean age of  $35.5 \pm 7.5$  years were studied.

Patients had an average of  $7.5 \pm 5.7$  years history of cutaneous symptoms due to NRL. Twenty-three out of 26 (88.5%) had also respiratory symptoms and 3 a history of anaphylaxis due to NRL when beginning the treatment.

All patients underwent immunotherapy according to the criteria specified in the EAACI position paper [30] and following the normal clinical practice of the Allergy Department at their respective hospitals. SLIT was individually prescribed to all patients after being informed of the possible alternatives such as allergen avoidance or symptomatic medication by their regular physicians, and giving their consent to it.

### Allergy diagnosis

Specific diagnosis of NRL allergy was made *in-vivo* by a commercially available skin prick test (SPT) with a NRL extract standardised at 500 g/mL of total protein (ALK-Abelló, S.A. Madrid, Spain) prepared as previously described from ammoniated latex [31] and *in-vitro* specific IgE by CAP (Pharmacia, Peapack, USA).

### Assessment of skin reactivity to NRL

The assessment of skin reactivity to NRL was performed according to 3 different techniques, described below, immediately before the beginning of the SLIT treatment (T0).

Glove-use test and rubbing test were repeated after the build-up phase (T1, day 5) and again at the end of the 10-week treatment (T2, day 70). Gloves from the same batch of one identified supplier (Safeskin LPE Latex Low Powder) were used throughout the trial for both the use and rubbing tests.

Skin prick test (SPT) was repeated at T1 and T2.

### Glove-use test

This technique has been first described by Turjanmaa and co-workers [32]. Briefly, patients were asked to wet both hands with water and to put on a vinyl glove first (negative

control) on one hand and then a latex glove on the other for 15 minutes. Local symptoms (itching, erythema, wheals) and general symptoms were evaluated 15 and 60 minutes after the beginning of the test. Each symptom scored 1 point, being 8 points the maximum possible test score.

Doctors classified the responses at T1 and T2 as better, unchanged or worse compared to T0.

### Rubbing test

The forearm of the patient was wet with water and rubbed with a NRL glove for 30 seconds [33]. As in the glove-use test, local symptoms (itching, erythema, and wheals) as well as systemic symptoms were evaluated 15 and 60 minutes after the beginning. The scoring system was the same as for the glove-use test. Doctors classified the responses similarly to the Glove-use test.

### Skin prick tests (SPT)

Each patient was skin-prick tested by duplicate on the volar surface of the forearm with four five-fold serial dilutions (500, 100, 20, and 4  $\mu\text{g}/\text{mL}$  of NRL proteins in 50% glycerol) of the same standardised NRL extract used for treatments. Positive (histamine hydrochloride 10 mg/mL) and negative (saline solution) controls were also included in each test.

Wheal areas were marked with a fine-tipped ball pen and transferred by means of transparent adhesive tape onto paper for the subsequent planimetric evaluation and statistical analysis.

### Treatment

SLIT-LATEX (ALK-Abelló, S.A., Madrid, Spain), a commercially available NRL extract for sublingual

Table 1. Concentration of vials and build-up treatment schedule.

Day	Vial concentration ( $\mu\text{g}/\text{mL}$ of NRL proteins)	Drops	Administered dose ( $\mu\text{g}$ of NRL proteins)	Cumulative dose ( $\mu\text{g}$ of NRL proteins)	Daily dose $\mu\text{g}$ of NRL proteins
1	$5 \times 10^{-8}$	1	$2 \times 10^{-9}$	$2 \times 10^{-9}$	$2 \times 10^{-5}$
		10	$2 \times 10^{-8}$	$2.2 \times 10^{-8}$	
	$5 \times 10^{-5}$	1	$2 \times 10^{-6}$	$2.02 \times 10^{-6}$	
		10	$2 \times 10^{-5}$	$2.2 \times 10^{-5}$	
2	$5 \times 10^{-2}$	1	0.002	0.002	2.2
		10	0.02	0.022	
	5	1	0.2	0.222	
		10	2	2.222	
3	500	1	20	22.2	400
		2	40	62.2	
		3	60	122.2	
		4	80	202.2	
10	500	10	200	402.2	500
		25	500	902.222	

administration was used. The extract was prepared by neutralization, semi-purification and concentration of an ammoniated latex suspension and biologically standardized, as described elsewhere [31].

The treatment was prepared in 5 vials containing dilutions of the NRL extract in glycerosaline solution, phenol (0.4% W/V) as a preservative and human serum albumin (0.04% W/V) in all vials except in the most concentrated. All doses of the build-up phase were administered in a hospital setting with the availability of complete resuscitation equipment and trained personnel, keeping the patient under constant observation after each administration and for at least 30 minutes after each day's last administration.

Patients were instructed to keep the allergen solution in the mouth for at least 3 minutes and then to swallow (sublingual-swallow technique). The protein concentration of each vial in  $\mu\text{g/mL}$  and the treatment schedule is detailed in Table 1. The build-up phase was completed in 4 days according to a rush schedule. During the first day, 4 doses of treatment were administered at 15 minutes intervals, from 1 drop of  $5 \times 10^{-8} \mu\text{g/mL}$  of NRL proteins up to 10 drops of  $5 \times 10^{-5} \mu\text{g/mL}$ . On the second day, four doses were administered every 15 minutes, from 1 drop of  $5 \times 10^{-2} \mu\text{g/mL}$  up to 10 drops of the  $5 \mu\text{g/mL}$  concentration. Five doses were administered on the third day with the same time interval, from 1 to 10 drops of the highest concentration,  $500 \mu\text{g/mL}$ . On the fourth day only one dose, 25 drops of the highest concentration, was administered.

After the build-up phase all patients followed the same maintenance schedule, consisting of 5 drops of the maximum concentration (resulting in  $100 \mu\text{g}$  of NRL per administration) 3 times a week for a total of 9 weeks. During the first week of the maintenance phase, doses were dispensed at the hospital, where patients remained under medical surveillance for at least 30 minutes after administration. The following maintenance administrations were performed at home by each patient, who had been instructed on how to proceed in case of adverse effects and specifically asked to immediately report any adverse reaction or discomfort to the allergists.

Diary cards were handed out to all patients for the registration of each administration and of each adverse event related or not to the treatment. During the maintenance phase, patients regularly visited the clinic every 15 days.

## Adverse reactions

Systemic adverse reactions were classified according to the EAACI Position Paper on Immunotherapy [30]. Because local reactions after SLIT have not been officially classified up to now, symptoms affecting the tongue, lips and/or mouth as well as itching and reddening of the eyes and gastrointestinal complaints were classified as local reactions.

The allergists classified the causal relationship of the reactions as related, of uncertain relationship or unrelated based on the clinical characteristics of the patients, the time of appearance of the adverse event and its manifestation. Adverse reactions unrelated to the treatment have not been considered.

## Statistical methods

Changes in use and rubbing test scores were analysed by the Wilcoxon test. Doctor's evaluation of the change in these tests was performed by comparing the frequencies of every possible situation (better, no change, or worse) by Chi-square test.

Changes in skin reactivity to the SPT with the NRL extract were evaluated by means of a specific software developed for the analysis of the parallel line biological assay. The features of this software have been described in a previous paper [34]. All other analyses have been performed with SPSS statistical software (SPSS Inc., Chicago, USA). P values  $<0.05$  have been considered as statistically significant.

## Results

### Tolerance and adverse reactions

All patients reached the planned maximum dose of 25 drops from the most concentrated vial, corresponding to  $500 \mu\text{g}$  of latex proteins, but one patient decided for personal reasons not related with the treatment to interrupt it during the first week of maintenance performed in hospital.

A total of 1044 doses were administered, 366 during the build-up phase and 678 during maintenance. A cumulative dose of  $902 \pm 0.4 \mu\text{g}$  and of  $2608 \pm 493.9 \mu\text{g}$  NRL proteins was administered during the build-up phase and at the end of the treatment, respectively.

Systemic reactions (SR) were observed in 3.6% (38/1044) of the administrations. A LR accompanied four of these cases. Local reactions (LR), mainly represented by an immediate lip itching, 84.3% (188/223), were observed in 21.4% (223/1044) of the administrations. With reference to patients, at least one SR was observed in 12 patients (46.2%), whereas at least one LR was observed in 23 patients (88.5%). Adverse reactions are summarized in Table 2.

The rate of total adverse reactions during the build-up, 24.59% (90/366), and maintenance phase, 24.63% (167/678), was almost identical. With reference to the dose of NRL allergen administered, both immediate and delayed SRs have been observed with almost all dosages, and are apparently unrelated to the amount of allergen administered. Immediate local reactions (ILR) have been observed already with the lowest dosages, but the rate increased with the most concentrated vial. Six out of seven delayed local reactions (DLR) were observed with

Table 2. Side effects reported during treatment

Adverse Reaction	Grade	During Build-up	During Maintenance	Total	% of total administrations
ISR	1	1	2	3	0.3
	2	9	9	18	1.7
	3	1	0	1	0.1
DSR	2	5	7	12	1.1
	3	2	2	4	0.4
Total Systemic Reactions		18	20	38	3.3
ILR		69	141	210	20.1
DLR		7	27	34	3.3
Total Local Reactions		74*	149*	223*	21.4*
Total Reactions		90*	167*	257*	24.6*

ISR: Immediate Systemic Reactions, DSR: Delayed Systemic Reactions, ILR: Immediate Local Reactions, DLR: Delayed Local Reactions

\*Because in some patients more than one reaction was reported after a single administration, the sum of side effects is higher than the total number of administrations leading to at least one adverse event.

dosages of at least 200 µg of NRL proteins. Side effects observed after the administration of different dosages are shown in Table 3.

SRs required no treatment in about half of the cases (44.7 %), or were treated with antihistamines alone (26.3%), or β<sub>2</sub>-agonists alone (5.3%) or associated to antihistamines and/or corticosteroids (18.4%). One patient was precautionary treated twice with adrenaline because of immediate dyspnoea in one case and abdominal pain, headache, cough, dyspnoea, rhinitis and chest tightness in the other. LRs were treated in only 2.3% of cases with antihistamines.

### Skin reactivity

Twenty-one (80.8%) and eighteen (69.2%) patients presented reactions in the use and rubbing tests, respectively. Mean scores at T0 were 2.69 and 2.54, respectively. In the glove-use test, a very significant decrease could be already detected at T1 (average score 1.11,  $p=0.0028$ ), and it became even more pronounced after 10 weeks of treatment (average score 0.81,  $p=0.0004$ ), as shown in Fig. 1. A statistically significant difference was reached for the rubbing test at T2 (average score 1.85,  $P=0.0366$ ) but not at T1 (average score 1.81,  $P=0.077$ ) (Fig. 1). The objective improvement at T1 was confirmed by the doctor's evaluations for both in use ( $p=0.003$ ) and rubbing ( $p=0.041$ ) tests. At T2 the doctor's evaluations confirmed a significant improvement for the glove-use test ( $P=0.004$ ) but not for the rubbing test ( $P=0.131$ ).

No change was on the contrary detected by the parallel line assay for SPTs at T1 and T2 as compared to T0.

### Discussion

Specific immunotherapy is a relatively new approach to NRL allergy, the first report on this subject having been published in 1998 [20]. Three patients with severe allergic symptoms due to work-related exposure to NRL were treated with progressively increasing oral dosages of NRL extract until a daily maintenance dose of 1 mg NRL was reached. The three of them showed a reduction of skin reactivity and could return to work, which involved heavy NRL exposure, without symptoms. One of the subjects discontinued therapy after 6 weeks because of gastrointestinal symptoms.

A further experience was conducted on a HCW suffering cutaneous and respiratory symptoms upon exposure to latex. This patient received subcutaneous administrations of an aqueous NRL extract prepared and standardised by the same producer and according to the same technique used in our trial [21]. Immunotherapy was administered at the hospital, keeping the patient under observation for 4 hours. Treatment began with a 0.003 µg NRL protein dose, reaching a 0.4 µg dose in 20 administrations. The 0.4 µg dose was established as the maintenance dose because the next increment (to 0.5 µg of NRL proteins) led to a SR requiring treatment with adrenaline, methylprednisolone, and clemastine. After 5 months of treatment the patient had received a cumulative dose of 3.2 µg of NRL proteins. SPTs with NRL showed a relevant reactivity decrease after treatment. A parallel decrease of skin reactivity was also found for food allergens cross-reactive with latex, such as banana, kiwi, and chestnut. No change was on the contrary detected for NRL specific IgE and IgG<sub>4</sub>. Clinical symptoms

Table 3. Side effects in relationship with the administered dose

Day	Dose in mg of NRL proteins	Number of Doses	ISR	DSR	ILR	DLR
<b>Build-up phase</b>						
1	$2 \times 10^{-9}$	26	1	0	1	0
	$2 \times 10^{-8}$	26	2	0	6	0
	$2 \times 10^{-6}$	26	0	0	1	0
	$2 \times 10^{-5}$	26	0	2	1	1
2	0.002	26	1	0	0	0
	0.02	26	0	0	2	0
	0.2	27	2	0	1	0
	2	27	2	1	4	0
3	20	26	0	0	5	0
	40	26	1	0	10	0
	60	26	0	0	10	0
	80	26	0	0	6	0
	200	26	0	2	11	5
4	500	26	2	2	11	1
<b>Maintenance phase</b>						
	100	678	11	9	141	27

ISR: Immediate Systemic Reactions, DSR: Delayed Systemic Reactions  
 ILR: Immediate Local Reactions, DLR: Delayed Local Reactions

improved, with an evident reduction in nasal obstruction and eye manifestations. Moreover, the patient showed no cutaneous, eye, nasal, or bronchial symptoms upon re-exposure to latex.

Leynadier and co-workers ran a larger DBPC trial with latex injective therapy on hospitalised HCWs [22]. Seventeen patients suffering from both cutaneous and respiratory symptoms were enrolled. Nine patients were treated with an aqueous NRL extract standardised in reactivity units (IR), reaching a maintenance dose between 2 and 10 IR which continued for 12 months after a 2-day rush build-up phase. Actively treated patients showed, compared to placebo, a significant improvement in rhinitis, conjunctivitis, cutaneous symptoms, and drug consumption. Furthermore, the conjunctival provocation test showed a significant threshold increase in the active as compared to the placebo group.

The administration of the active treatment led unfortunately to a significantly higher frequency of SRs (rhinitis, conjunctivitis, asthma attack, pharyngeal oedema, giant urticaria, angioedema, hypotension, and others) as well as LR (pruritus, urticaria, oedema) than placebo treatment. Several adverse effects were reported not only during the build-up, but during the maintenance phase too. In total, 21 immediate systemic reactions (5.7% of doses) and 10 delayed systemic reactions (2.6% of

doses) were reported, mainly affecting those patients with underlying respiratory diseases. For these reasons, the authors state that "...this modality of treatment appears to be delicate to perform in view of the risk of systemic reactions".

A further trial with injective therapy, run with the same extract used by Pereira and co-workers [21] but adsorbed to aluminum hydroxide, has been recently reported by Sastre and co-workers [23] and reviewed by Tabar and co-workers [35]. Twenty four HCWs with a diagnosis of latex allergy after inhalation challenge in a closed 7m<sup>3</sup> chamber in case of respiratory symptoms, or after glove-use and rubbing tests in case of contact urticaria, were treated following a DBPC trial design (16 active, 8 placebo). The 14 weeks build-up phase, included the administration of 18 doses and was followed by a 6 months maintenance phase with a maintenance dose of 20 µg of NRL proteins. After six months of active treatment patients showed a clear improvement in their cutaneous response in the rubbing and glove-use test, as well as reduction of the bronchial symptoms in the challenge chamber.

Three reports on a non-injective approach in NRL allergy have been recently published. In one case, five patients with a clinical history of latex sensitisation were treated by means of an exposure protocol, i.e. putting on

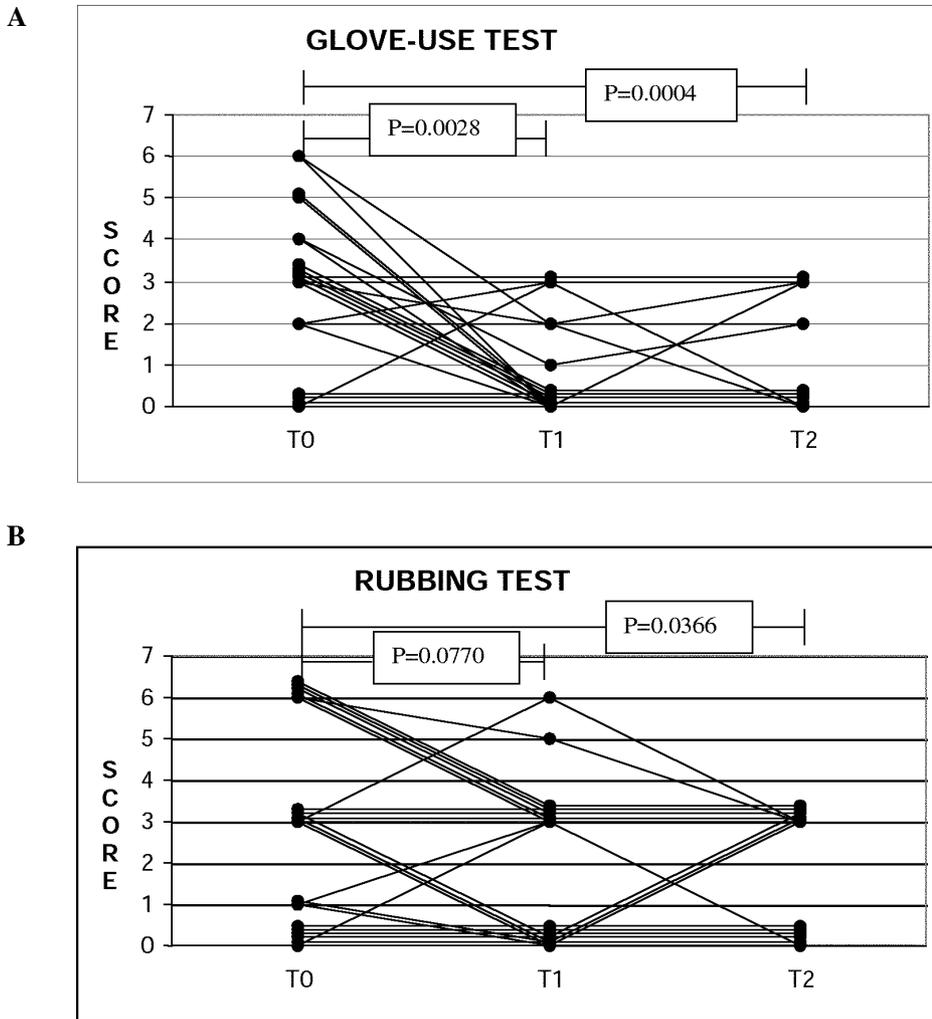


Figure 1: Score values for the glove-use test (A) and the rubbing test (B) in individual patients before (T0), after the build up phase (T1), and at the end of the treatment (T2).

latex gloves daily, progressively increasing the time of exposure up to 60 minutes. The desensitisation protocol was completely successful in all patients after 12 months of treatment, as they were able to wear latex gloves daily without any clinical manifestation [24]. In the other two trials, run by the same clinical group, 1 patient first [25], and 12 patients later [26,27], were treated accordingly to the same rush sublingual protocol after an accurate diagnosis. The NRL extract was similar to the one used by Pereira and co-workers [21], but obviously in a glycerosaline solution for sublingual administration. In the first study [25] the rush schedule was completed in 3 days with administrations every 20 minutes, starting from a very low cumulative dosage on day 1 ( $2.8 \times 10^{-9}$   $\mu\text{g}$  of NRL proteins) up to  $2.8 \mu\text{g}$  on day 2, and  $500 \mu\text{g}$  on day 3. The maintenance therapy started on day 4 with  $100 \mu\text{g}$  of NRL proteins following the sublingual-spit technique.

The treatment was very well tolerated without any side effect and turned mucosal challenges as well as glove-use test with latex gloves from positive to negative.

The same investigators repeated this pilot experience on a larger sample of patients, confirming both excellent tolerance and successful desensitisation [26,27].

The commercial treatment used by us recommends a schedule based on these last experiences, with 4 dilution vials and a higher initial dosage. This initial dosage is nonetheless 100-fold lower than used in the other two sublingual trials [25-27] for conjunctival and sublingual challenge.

These changes in the schedule, and perhaps the use of the sublingual-swallow technique instead of the sublingual-spit technique, may account for the reported local side effects, including gastrointestinal complaints, and some SRs, whereas no side effect was reported with the previous sublingual trials. Around half of the SRs did not require treatment, and the others were easily and well controlled with antihistamines and/or beta-2 agonists. For precautionary reasons and considering the very limited experience with SLIT for NRL allergy, one patient was treated twice with adrenaline to quickly control the systemic symptoms observed after the administration. The allergist watching over the treatment decided not to interrupt the treatment in this patient, because symptoms were promptly and very well controlled and because the patient asked to continue the immunotherapy. After these two episodes in the build-up phase, the patient reached

and continued the maintenance as planned without any further problems.

In our trial, use and rubbing test scores at T0 and T2 showed that SLIT with high dosages of NRL extract is able to significantly decrease skin reactivity. These results are consistent with the results of both injective and non-injective therapy trials run before. Our data shows that the improvement in skin reactivity was already significant after 4 days of treatment for the glove-use test but not for the rubbing test. For the glove-use test, both objective and subjective evaluations coincided in showing an improvement at T1 and T2 over T0. Differently, rubbing test scores showed a significant improvement at T2 but not at T1, whereas objective assessments showed a significant improvement at T1 but no at T2. In our opinion, the very simple and easily reproducible technique used for the glove-use test allows for a good consistency between objective and subjective evaluations obtained with this test. The same considerations cannot be made for the rubbing test that is, for the technique used by us, more prone to uncontrolled variations.

In contrast with the results reported by Sastre [23], we were unable to detect differences in skin reactivity by SPT. However, it must be underlined that these reported results were obtained after 6 months of injective treatment, whereas in our trial the use and rubbing tests were performed after 4 days and 10 weeks of treatment and the SPTs were run after 5 days and after 10 weeks of treatment. These differences in timing may account for the different final outcome, but do not explain the divergence between the results obtained with the use and rubbing tests and the SPT. To what extent these differences are relevant from the practical and clinical point of view, and what are the mechanisms underlying such differences, are questions that deserve further study.

The rate of side effects and the highest dose tolerated or used for maintenance are clearly different when comparing injective to non-injective therapies. Rates as high as 46.4% of SR per dose and LR 93.45% per dose, have been reported for aqueous injective therapy by Leynadier and co-workers [22], whereas Sastre [23] reported a rate of 8.3 % SR per dose for depot injective therapy. In our trial we have observed a rate of 3.3 % SR per dose. Regarding the rate of SR per patient, although not explicitly reported by Leynadier et al, 44.4% of participating patients suffered several severe systemic reactions. Sastre and co-workers described the occurrence of SRs in 68.7% of the patients receiving active treatment and 37.5% of the placebo group. We observed a lower percentage of SR per patient, 46.2%. Nevertheless we have to remark that, leaving aside the absolute rates per dose and per patients, the severity of side effects was lower in our study than in studies run with injective therapy.

Comparing extracts with a known content of NRL proteins, after a build-up phase of 7 to 14 weeks the maximum tolerated dose was as low as 0.4 µg of NRL proteins in a trial with aqueous injective extract [21] and around 11 µg of NRL proteins in a trial with injective

depot treatment [23]. In our study, as well as in two previous experiences with sublingual therapy [25-27], all patients reached the maximum dose of 500 µg of NRL proteins in only 4 days. Cumulative doses reached were also greatly different, ascending to 2608 µg of NRL proteins in 10 weeks in our study, but not getting higher than 7.19 µg in 5 months or 105 µg in 6 months with injective therapy [21, 23].

According to the available data, injective therapy for NRL allergy with either aqueous or depot extracts should be regarded as an effective but high-risk treatment [35]. The approach with SLIT seems to be much more feasible, since local and systemic side-effects are either absent or of low grade and easily controlled. The sublingual-spit technique seems to lead to a better tolerance than the sublingual-swallow technique, mainly on regard to the gastrointestinal symptoms. A relatively high rate of gastrointestinal symptoms in children has been reported also with high-doses of sublingual-swallow administrations of *Parietaria* extract [36].

As already discussed in the introduction, latex avoidance measures or reduction of the exposure can obviously be useful but do not represent a definitive solution. Accordingly, immunotherapy has been admitted as an appropriate approach for this condition in a recent publication [37] although the rate of adverse reactions caused by the administration forms tested up to now were inadmissible.

In the present study we have observed a better tolerance with SLIT Latex than any other reported trial with the same allergen administered subcutaneously. Although this study was designed to evaluate tolerance, promising preliminary data on efficacy have been collected, showing a swift reduction of cutaneous symptoms and a positive clinical evaluation after just ten weeks of treatment.

We believe that, if the available data is confirmed and better defined on regard to the administration schedule, sublingual therapy for NRL allergy could play an important role in the desensitisation of allergic HCWs.

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