

Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers

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Background: The prevalence of allergy to natural rubber latex proteins has increased over recent years among healthcare professionals but also in children undergoing multiple operations. Exposure to the antigen mainly occurs through the respiratory mucosa and the percutaneous route. Clinical manifestations range from urticaria to angioedema, rhinoconjunctivitis, bronchial asthma, or anaphylactic shock. Preventive measures have been proposed to reduce the risk of sensitization by using only powder-free or synthetic gloves and latex-free material in operating units, but this is not always possible. **Objective:** The aim of this study was to investigate the efficacy and safety of specific immunotherapy in sensitized workers. **Methods:** Seventeen patients with latex skin allergy and rhinitis (9 of whom also had asthma) were included in this randomized, double-blind, placebo-controlled trial (9 in the active group and 8 in the placebo group) for 1 year. Treatment started with a 2-day course of rush immunotherapy in hospital. Treatment efficacy was assessed after 6 and 12 months by means of symptom and medication scores recorded on diary cards. Conjunctival provocation tests were also performed. **Results:** Patients in the active treatment group had a significantly lower total rhinitis score after 6 ($P < .04$) and 12 months ($P < .05$), conjunctivitis score after 6 months ($P < .02$), and cutaneous score after 12 months ($P < .03$) than in the placebo group. Asthma symptoms after 6 or 12 months of treatment were not significantly different between the two groups after adjustment for baseline values. The global medication score was markedly decreased in the latex-treated group. A significant difference in conjunctival reactivity was observed in favor of the active group: the number of patients for whom the threshold dose was increased after 12 months of treatment was significantly greater in the active group than in the placebo group ($P < .02$). Most injections were well tolerated, but several adverse effects, including hypotension, urticaria, wheezing, and pharyngeal edema, were observed. **Conclusion:** The clinical benefits observed during the present study included a significant improvement of rhinitis, conjunctivitis, and cutaneous symptoms. Immunotherapy also decreased allergen-specific conjunctival reactivity. Latex-spe-

cific immunotherapy may allow sensitized personnel to remain at work, but further trials need to be conducted in a larger number of patients. (*J Allergy Clin Immunol* 2000;106:585-90.)

Key words: Latex, urticaria, rhinoconjunctivitis, asthma, anaphylactic shock, specific immunotherapy

Hevea brasiliensis sap was first used to manufacture gloves for medical use more than a century ago.¹ Since then, it has been used to manufacture thousands of industrial and medical products. However, immediate hypersensitivity reactions to natural rubber latex (NRL) proteins have been reported more recently.²⁻⁷ The number of possible contacts, starting at birth, with latex objects likely to induce type I allergic reactions or sensitize exposed subjects is incalculable. Apart from heavily exposed medical and paramedical personnel, children with spina bifida or urogenital malformations and children undergoing multiple operations also constitute another high-risk group as a result of multiple contacts with latex surgical gloves.⁸ Several other groups also present a certain risk: personnel working in the rubber industry, infants using dummies, children playing with rubber balls or toys, people using household gloves, and couples using condoms, for example. The problem of latex allergy is made even more complex by the presence of cross-reactions with a large number of foods (eg, avocado, banana, kiwi, papaya, and chestnut).⁹⁻¹¹

Sensitization in healthcare workers generally occurs through mucocutaneous contact or by inhalation, mainly caused by glove powder. Immediate reactions may be limited to cutaneous signs (contact urticaria) but usually consist of systemic reactions: rhinitis, conjunctivitis, asthma, and, more rarely, anaphylactic shock. It is now generally accepted that the diagnosis must be based on the clinical history and a positive in vivo test response, with the most reliable being the prick test. The specific IgE assay is useful but not sufficient to establish the diagnosis.^{12,13}

Latex allergy prevention protocols and legislation concerning the quality of surgical gloves have been proposed for medical and paramedical personnel. Avoidance of NRL is essential in sensitized subjects in addition to symptomatic treatments (antihistamines, bronchodilators, and corticosteroids). These personnel must work in an environment devoid of any latex protein allergens because very small quantities of NRL suspended in the air are sufficient to trigger an allergic reaction.^{14,15} This implies the use of nonpowdered and nonallergenic

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Abbreviations used

CPT: Conjunctival provocation test
 IR: Index of reactivity
 NRL: Natural rubber latex

gloves, as well as replacement of all material likely to contain NRL in examination or operating rooms; the list is long, including catheters, drains, tourniquets, dressings, and ventilation material. Latex-specific immunotherapy could constitute a new therapeutic approach and has already shown promising results in the one patient treated by Pereira et al.¹⁶

We therefore performed the first multicenter, double-blind, placebo-controlled trial evaluating the efficacy and safety of parenteral administration of a latex allergen extract in patients with rhinitis, conjunctivitis, and possible asthma who were exposed to latex as a result of their medical or paramedical occupation. The primary efficacy criterion was the course of symptoms and medication consumption after treatment.

METHODS

Study design

The clinical trial was conducted in accordance with good clinical practice after being approved by the Paris Saint Antoine Ethics Committee. All patients gave their written informed consent to participate in the trial.

This was a randomized, multicenter, double-blind, placebo-controlled trial conducted in parallel groups in 3 centers. Patients preselected between October 1995 and January 1997 were randomized to two treatment groups, either active or placebo. Treatment was started with a rush dose progression performed in the hospital on 2 days according to a similar protocol to those used in wasp or bee venom-specific immunotherapy. During the maintenance period, patients were reviewed in the hospital at the time of each of the injections, which were administered once a week, once a fortnight, and finally every 3 or 4 weeks. For safety reasons, the outpatient injections were followed by a period of observation of 1 hour each time. Patients were allowed to use symptomatic medication to control their symptoms (ie, antihistamines, cromones, short-acting β_2 -agonists, or inhaled corticosteroids).

Patients had to record the intensity of symptoms and the use of symptomatic treatment on diary cards once a week throughout the trial. A conjunctival provocation test (CPT) was performed before treatment and after 12 months of treatment.

Patients

Seventeen patients (1 man and 16 women; mean age, 30 ± 5 years; age range, 22-41 years) with latex hypersensitivity were included. All patients presented signs of rhinitis and cutaneous signs of latex allergy; 16 of 17 also presented conjunctivitis, and 9 had asthma (Aas score of 1-3).¹⁷ Six patients (4 in the active group and 2 in the placebo group) had angioedema in the presence of latex, and one patient (placebo group) presented this reaction after eating banana and avocado. Only one patient (active group) had a history of anaphylactic shock. No patients presented with unstable asthma, and there were no contraindications for specific immunotherapy according to position papers. In regard to anaphylactic shock, this indication is accepted for specific immunotherapy for venom allergy.

The diagnosis of latex allergy was based on clinical history, a positive latex prick test response (Stallergènes SA, Antony, France), a positive latex CPT response, and a latex-specific IgE level of at least class 2 (Pharmacia, Uppsala, Sweden). Latex prick tests were used because a standardized extract was considered safe.¹⁸

Exclusion criteria included clinically significant sensitization to house dust mites. Patients allergic to domestic animals (cats or dogs) were only excluded when the incriminated animal was present in the patient's home. Patients with severe asthma (Aas score 4 or 5) and patients receiving immunotherapy for another allergen were excluded. Latex avoidance was recommended, but it is a difficult procedure to follow for healthcare workers.

Allergen preparations

A standardized latex extract¹⁸ (Stallergènes SA) was used throughout the study. Its biologic activity had been controlled by RAST inhibition¹⁹ and compared with an internal standard by *in vivo* and *in vitro* tests. It was expressed in index of reactivity units (IR) according to the following definition: a 100 IR/mL extract induces a wheal with a geometric mean diameter of 7 mm on a prick test in 30 patients sensitized to the allergen considered.

Treatment

Treatment comprised a dose-progression phase (Table I), during which the extract (Stallergènes SA, Antony) was administered according to a 2-day rush protocol in the hospital. This phase was followed by a 12-month phase of maintenance treatment (Table I) at the maximum tolerated dose (10 IR/mL or 100 IR/mL vial, depending on tolerance for each patient). The placebo vials were identical in appearance to those used for immunotherapy. They did not contain histamine.

Symptom scores

Symptoms of rhinitis and conjunctivitis and cutaneous signs were recorded weekly by the patients throughout treatment. Each symptom was scored on a scale from 0 to 3: 0, symptom absent; 1, symptom present but not bothersome; 2, symptom present and bothersome; and 3, symptom intolerable. Patients also scored asthma symptoms on the following scale: 0, symptom absent; 1, wheezing, occasional cough, and nondisabling breathlessness; 2, wheezing, breathlessness, and irritant cough interfering with everyday activities; and 3, asthma attack making the patient unable to perform everyday activities.

On the basis of these data, a total rhinitis score (total, from 0 to 12, of 4 symptoms: rhinorrhea, nasal itching, nasal blockage, and sneezing), a total conjunctivitis score (total, from 0-12, of 4 symptoms: tearing, itching, edema, and conjunctival erythema), and a total cutaneous score (total, from 0-9, of 3 symptoms: pruritus, urticaria, and eczema) were calculated each week. The efficacy of treatment was evaluated after 6 and 12 months by calculating the mean asthma score and the mean total score in terms of rhinitis, conjunctivitis, and cutaneous signs for weeks 23 to 26 and weeks 49 to 52, respectively.

Medication scores

The patients were allowed to take symptomatic medication during the study whenever necessary. They recorded the quantities consumed each week. On the basis of these data, as described for the symptom scores, a total medication score assessing consumption of symptomatic medications was calculated according to each therapeutic category: 1 point for local antiallergic treatment and for each puff of β_2 -agonist, 2 points for an antihistamine tablet, 2.5 points for a dose of inhaled corticosteroids equivalent to 250 μ g of beclomethasone, and 18 points for a corticosteroid tablet equivalent to 20 mg of prednisolone.

TABLE I. Immunotherapy protocol

Concentration	Doses injected	Frequency
Dose progression: First day		
0.01 IR/mL vial	0.10 mL	25-min interval between two injections
	0.20 mL	
	0.40 mL	
0.1 IR/mL vial	0.05 mL	25-min interval between two injections
	0.10 mL	
	0.20 mL	
	0.40 mL	
1 IR/mL vial	0.05 mL	25-min interval between two injections
	0.10 mL	
	0.20 mL	
	0.40 mL	
Dose progression: Second day		
10 IR/mL vial	0.05 mL	1-h interval between two injections
	0.10 mL	
	0.15 mL	
	0.20 mL	
Maintenance therapy: First month		
10 IR/mL vial	0.20 mL	1 injection once a week
	0.30 mL	
	0.30 mL	
	0.40 mL	
Maintenance therapy: Second month		
100 IR/mL vial	0.05 mL	1 injection once a fortnight
then		
100 IR/mL vial	0.05 mL (possibly 0.10 mL)	1 injection once a month for 10 months

Conjunctival provocation test

A CPT was performed before treatment and after 12 months of treatment. Five extemporaneous dilutions (100, 33.3, 11.1, 3.7, and 1.2 IR/mL) of an aqueous latex extract obtained from a 100-IR lyophilisate (Stallergènes SA) were used. Patients had to be asymptomatic and must have observed a treatment washout period for antihistamines, anti-inflammatory drugs, corticosteroids, and eye drops. Tests were performed by instilling one drop of the extract into the lower conjunctival fornix of the right eye, starting with the lowest concentration. When the test result remained negative after 15 minutes, the higher concentration was used. A control test was performed on the left eye by instilling physiologic saline. The threshold dose was defined as the lowest allergen concentration able to induce the appearance of symptoms scored according to the scale of Abelson et al²⁰ (hyperemia, chemosis, and tearing on a scale of 0-3; itching scored by the patient on a scale of 0-4) inducing a total symptom score of at least 5.

Adverse events

The clinician evaluated the safety of treatment at each visit. Any local (eg, pruritus, wheal, and edema) or systemic reactions (eg, rhinitis, conjunctivitis, asthma attack, pharyngeal edema, giant urticaria, and angioedema) considered to be related to the trial treatment had to be recorded on the case report form. The clinician also recorded any unexpected events.

Statistical methods

The Mann-Whitney *U* test, χ^2 test, or Fisher test were used for intergroup comparison of qualitative variables. Quantitative variables were compared between groups by using nonparametric Mann-Whitney *U* tests because of the small sample sizes. Intent-to-treat statistical analysis was performed on all randomized patients

TABLE II. Demographic data

	Active	Placebo	Test
No. of patients	9	8	
Sex (M/F)	1/8	0/8	NS
Age (y)			
Mean $\pm$ SD	28.8 $\pm$ 5.07	32.4 $\pm$ 5.85	NS
Distribution	22-36	26-41	
History of disease (y), mean $\pm$ SD	2.8 $\pm$ 1.8	5.8 $\pm$ 4.5	NS
Household exposure	6	4	NS
Occupational exposure	9	8	NS
Clinical features of the disease			
Rhinitis	9	8	NS
Conjunctivitis	8	8	NS
Asthma	3	6	NS
Dermatologic reactions	9	8	NS
Angioedema	4	2	NS

NS, Not significant.

who started immunotherapy. All tests were bilateral and performed at an α limit of .05.

RESULTS

Seventeen patients were randomized, with 9 randomized to the active treatment group and 8 to the placebo group. Three patients (in the placebo group) dropped out of the trial for the following reasons: surgical operation, withdrawal of consent, and loss to follow-up. All other patients completed the study. The demographic characteristics of the 17 patients are presented in Table II. No

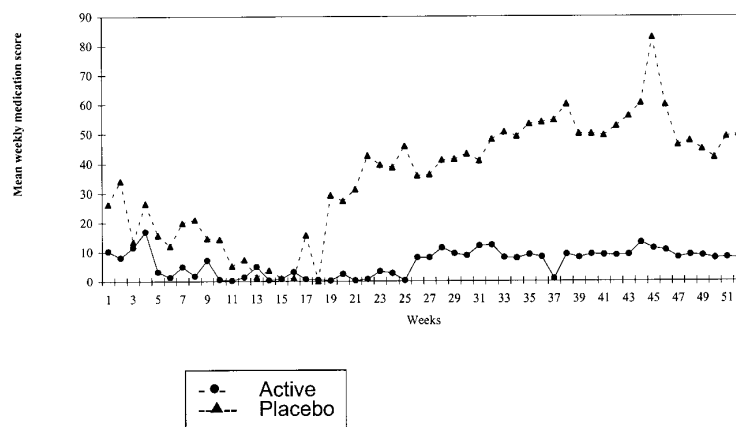


FIG 1. Mean weekly medication score in each group.

TABLE III. Comparison of the symptom scores between the two groups

	Active	Placebo	Test
Rhinitis (mean total score $\pm$ SD)			
Baseline	2.8 $\pm$ 2.15	4.8 $\pm$ 1.85	NS
6 mo	1.6 $\pm$ 2.00	4.0 $\pm$ 2.11	$P < .04$
12 mo	0.9 $\pm$ 1.22	2.9 $\pm$ 2.26	$P < .05$
Conjunctivitis (mean total score $\pm$ SD)			
Baseline	2.4 $\pm$ 2.30	3.6 $\pm$ 2.31	NS
6 mo	0.9 $\pm$ 0.94	3.0 $\pm$ 1.81	$P < .02$
12 mo	0.4 $\pm$ 0.78	1.8 $\pm$ 1.95	$P = .05$
Cutaneous signs (mean total score $\pm$ SD)			
Baseline	1.3 $\pm$ 1.31	1.2 $\pm$ 1.45	NS
6 mo	0.4 $\pm$ 0.56	1.7 $\pm$ 2.06	NS
12 mo	0 $\pm$ 0.08	1.2 $\pm$ 1.36	$P < .03$
Asthma (mean score $\pm$ SD)			
Baseline	0.1 $\pm$ 0.18	0.8 $\pm$ 0.59	$P < .05$
6 mo	0.1 $\pm$ 0.33	0.6 $\pm$ 0.77	$P < .05$
12 mo	0 $\pm$ 0	0.4 $\pm$ 0.76	NS

NS, Not significant.

significant difference was demonstrated between the groups on inclusion for age, sex, personal history, or clinical manifestations of the disease, but the mean asthma score on inclusion was significantly higher in the placebo group than in the active group ($P < .05$, Mann-Whitney U test; Table III), which required adjustment to baseline values for analysis of the asthma criterion.

Symptom and medication scores

Analysis of total symptom scores (Table III) showed a significant improvement in the treated group compared with the placebo group in terms of rhinitis ($P < .05$ at 6 and 12 months), conjunctivitis ($P < .02$ at 6 months), and cutaneous signs ($P < .03$ at 12 months).

The difference in asthma score observed between the two groups on inclusion required adjustment of the values observed at 6 and 12 months of treatment for baseline values. This adjustment was performed by comparing the groups in terms of the absolute variations of the scores at 6 months compared with inclusion and then at 12 months compared with inclusion. Analysis of asthma

signs did not reveal any significant difference between the two groups after adjustment for baseline values.

The course of the mean medication score in each group is represented graphically in Fig 1. It was clearly lower in the active group than in the placebo group: the active/placebo ratio of areas under the curve was 21%, which, according to Malling's criteria,²¹ indicates high efficacy with 79% improvement.

Conjunctival provocation tests

After 12 months of treatment, the threshold dose (for which the total symptom score was at least 5 on the CPT) increased for 7 of 9 patients in the active group versus 1 of 8 patients in the placebo group ($P < .02$). Conjunctival reactivity therefore tended to decrease during active treatment.

Safety

The frequency of reactions in relation to the total number of injections (336 injections in the active group and 251 injections in the placebo group) is shown in Table IV and

TABLE IV. Frequency of local and systemic reactions in relation to the number of injections

	Active (336 injections)		Placebo (251 injections)	
	No.	%	No.	%
Local reactions				
Pruritus	145	43.2	40	15.9
Urticarial wheal	135	40.2	24	9.6
Edema	34	10.1	2	0.8
Systemic reactions				
Rhinitis	51	15.2	14	5.6
Conjunctivitis	35	10.4	5	2.0
Asthma attack	9	2.7	2	0.8
Pharyngeal edema	4	1.2	0	0.0
Giant urticaria	4	1.2	0	0.0
Angioedema	2	0.6	0	0.0
Hypotension	1	0.3	1	0.4
Others	50	14.9	11	4.4

was clearly higher in the active group. Almost one half of patients receiving active treatment presented a local reaction, such as pruritus, urticarial wheal, or both, by the first injection of 0.01 or 0.1 IR/mL. Systemic reactions, such as rhinitis or conjunctivitis, which rapidly resolved with or without treatment, were observed in the two groups from the 1 IR/mL vial. Four of the 9 patients in the active group experienced more severe systemic reactions, such as angioedema (two reactions, with one during the maintenance therapy), pharyngeal edema (4 reactions, with one during the maintenance therapy), bronchospasm or asthma attack (9 reactions, with 6 during the maintenance therapy), hypotension (1 reaction during the maintenance phase), and giant urticaria (4 reactions, with 3 during the maintenance therapy). The clinical picture at inclusion in the study did not correlate with the type of adverse event.

Only one unexpected event was observed: thyroid surgery in a patient receiving placebo, which led to drop out.

DISCUSSION

This multicenter study compared latex immunotherapy with placebo in patients presenting with occupational exposure to latex. Patient selection was based on rigorous inclusion criteria. The cumulative dose was similar in the two groups (96 IR for active treatment and 112 IR for placebo).

The primary efficacy criterion was the course of symptom and medication scores after treatment because the patients were able to take symptomatic medication whenever necessary. Comparison of the groups after 6 months of treatment demonstrated a significant difference in favor of active treatment for signs of rhinitis and conjunctivitis. After 12 months of treatment, the active group was significantly improved in terms of rhinitis and cutaneous signs. After adjustment for baseline values, comparison of the two groups after 6 or 12 months of treatment did not reveal any significant difference for asthma. Symptomatic medication was used much less frequently in the active group than in the placebo group.

The reduction of the threshold dose on CPTs, which

was observed significantly more frequently in the active group, confirms the efficacy of treatment.

The decreases in rhinitis and conjunctivitis symptoms achieved during the present study corroborates results obtained by Pereira et al¹⁶ in a 31-year-old female patient who has been employed as a radiology technician since the age of 24 years. Nasal obstruction and eye symptoms steadily decreased during specific immunotherapy, mainly once the maintenance period was started, and gradually, the patient was able to return to work.

Although further clinical trials are required, this preliminary trial demonstrates the clinical benefit of latex immunotherapy. In a subsequent study patients will need to be randomized after a run-in period to define two groups of patients comparable in terms of their symptoms and medication consumption. Latex immunotherapy appears to be particularly useful in that it may allow the individuals concerned to continue their occupation as a result of its preventive effect on clinical signs of rhinitis, conjunctivitis, and cutaneous signs. However, like venom immunotherapy, this treatment modality appears to be delicate to perform in view of the risk of systemic reactions. In the present study several systemic reactions occurred during the maintenance phase. However, Pereira et al¹⁶ did not observe any systemic reaction once the maintenance period was started. This difference could be related to their prudent approach, consisting of choosing a maintenance dose on the basis of the appearance of a systemic reaction. We probably reached a higher maintenance dose in our study.

In conclusion, in contrast to common aeroallergens, immunotherapy with latex allergen has an increased prevalence of systemic reactions, as already reported.²² The present protocol cannot be used by a family physician. It has to be tested in a hospital center with full resuscitation facilities.

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