

Specific immunotherapy with a standardized latex extract in allergic workers: A double-blind, placebo-controlled study

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Background: Preventive measures have been proposed to reduce the risk of sensitization to natural rubber latex (NRL), but this is not always feasible.

Objective: The aim of this study was to determine the efficacy and safety of specific immunotherapy with a standardized latex extract in sensitized workers.

Methods: Twenty-four patients allergic to NRL with contact urticaria ($n = 8$) and rhinitis or asthma ($n = 16$) were included (16 in the active group and 8 in the placebo group). Treatment started in a cluster immunotherapy protocol, with injections every week for 3 months and then every other week for another 3 months.

Results: Patients in the active group had significantly lower values than patients in the placebo group in skin terms of reactivity to NRL ($P < .01$), rubbing test results ($P = .047$), and latex glove use test results ($P = .046$) after 6 months of treatment. There were no significant differences between the active and placebo groups in symptom scores, use of medication, self-assessment, or methacholine test results either before or after treatment. Differences in nasal and bronchial symptoms during specific inhalation challenges ($P =$ not significant and $P = .05$, respectively) were observed in favor of the active group. In the active group 32 systemic reactions were observed (8% of doses), mostly during the build-up period, being more frequent in patients with respiratory symptoms ($P = .004$). All reactions responded promptly to treatment.

Conclusion: Clinical efficacy was shown mainly on cutaneous symptoms, although an improvement in rhinitis and asthma symptoms was also observed during specific inhalation challenges. Latex-specific immunotherapy might be a useful approach for the treatment of latex allergy in sensitized workers. (*J Allergy Clin Immunol* 2003;111:985-94.)

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

IgE-mediated hypersensitivity to natural rubber latex (NRL) has been recognized as an important health problem during the last decade.^{1,2} This fact is due to an increase in

Abbreviations used

CTI:	Cutaneous tolerance index
EAACI:	European Academy of Allergy and Clinical Immunology
HEP:	Histamine equivalent prick
IQR:	Interquartile range
NRL:	Natural rubber latex
SIC:	Specific inhalation challenge
SIT:	Specific immunotherapy
SR:	Systemic reaction
SPT:	Skin prick test
VAS:	Visual analogue scale

the prevalence of latex allergy, to the potential severity of latex-induced reactions, and to its presentation as an occupational disease in workers using latex gloves. The prevalence of NRL allergy among the general population is probably less than 1%.³ Risk groups for NRL allergy include workers using latex gloves and other latex-containing products, workers involved in collecting and processing NRL from rubber trees, children with spina bifida, patients who have undergone multiple surgical procedures, and subjects with certain food allergies.⁴⁻⁶ Patients with atopy are more susceptible to latex allergy.⁷ Different proteins present in various NRL products have been implicated in causing allergy in distinct risk groups.¹⁻⁷

Treatment of latex allergy has been thus far limited to the prevention measure of avoiding latex-containing products and symptomatic medication. A report on latex specific immunotherapy (SIT) as a treatment for health care workers was first published by Pereira et al⁸ in a single patient with good results. The first double-blind, placebo-controlled study that evaluated the safety and efficacy of latex SIT was published by Leynadier et al.⁹ This study showed that rhinitis, conjunctivitis, and cutaneous total symptom scores, but not asthma scores, were significantly lower in patients treated with latex SIT after 12 months of treatment. Conjunctival provocation test results also improved in the active group. Several systemic reactions (SRs) were observed during treatment.

We performed a double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous SIT with a standardized NRL extract in a population of patients occupationally sensitized to latex who had cutaneous and, in some cases, respiratory symptoms.

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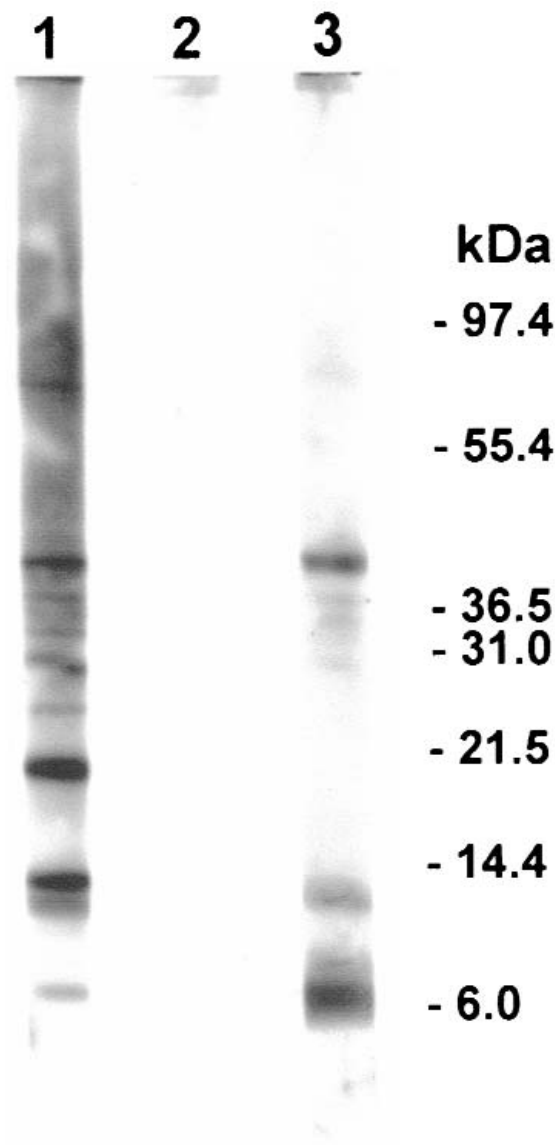


FIG 1. IgE immunoblot of the latex allergen extract: *lane 1*, extract used in the study incubated with a serum pool from patients allergic to latex; *lane 2*, latex glove extract incubated with control non-allergic sera; *lane 3*, latex glove extract incubated with a serum pool from patients allergic to latex.

METHODS

Study design

This clinical trial was conducted in accordance with good clinical practice after approval by the hospital ethics committee and the Spanish Medicine Agency. All patients provided written consent to participate in the trial. This was a randomized, double-blind, placebo-controlled trial conducted in parallel groups. Fifty patients were screened, and 24 were randomized into 2 treatment groups (ie, active or placebo groups). Treatment lasted 6 months, and tolerance to SIT was monitored throughout the study. A complete laboratory analysis (blood count and serum biochemistry measurement) was performed before and after treatment.

During the full length of the study, the patients were allowed to use medication to control their symptoms (antihistamines, intranasal corticosteroids, and short-acting inhaled β_2 -agonists). Patients recorded symptoms and use of medication on diary cards during 2-week periods before treatment and after administration of the last maintenance dose. In addition, the patients performed a self-assessment of their symptoms on a visual analogue scale (VAS). Skin prick titration tests with NRL extract, rubbing tests, latex glove use tests, methacholine inhalation, and specific inhalation challenge (SIC) were performed at 2 control times (T_0 and T_F) set before SIT and after the last maintenance dose.

Patients

Twenty-four patients allergic to NRL, most of them health care workers, were recruited and randomized. All patients experienced cutaneous symptoms (contact urticaria), and some of them had rhinitis and asthma related to latex allergy. Patients were stratified into 2 groups on the basis of their symptoms (ie, either cutaneous or cutaneous and respiratory; Table I) and randomized according to an aleatory number list. Sixteen patients were assigned to the active group and 8 to the placebo group. No patients had any contraindication to SIT according to the European Academy of Allergy and Clinical Immunology (EAACI) position paper.¹⁰

The diagnosis of latex allergy was based on clinical history, positive skin prick test (SPT) responses to NRL or latex-specific IgE levels of at least CAP class 2 (Pharmacia), and positive cutaneous challenge test results, positive inhalation challenge test results, or both.

Latex extract

NRL extract was prepared from fresh latex obtained from *Hevea brasiliensis* trees. After successive steps of washing and concentration by means of ultrafiltration, the extract was sterilized and glycerinated. It yielded a protein and allergen profile similar to US Food and Drug Administration reference E8, as determined by means of SDS-PAGE and IgE immunoblotting. Among the 11 IgE-binding proteins visualized in the immunoblotting, prohevein (Hev b 6.01), rubber elongation factor (Hev b 1), acidic latex protein (Hev b 5), patatin (Hev b 7), β -1,3 glucanase (Hev b 2), and heveamine were identified on the basis of their electrophoretic mobilities (Fig 1).

The extract was standardized in vivo in histamine equivalent prick (HEP) units¹¹ and used to manufacture a standardized aluminum hydroxide-adsorbed vaccine (ALK-ABELLÓ). Five 10-fold dilutions were prepared from the maximum concentration vial of 5 HEP/mL, which is equivalent to 20 μ g of total protein per milliliter. Placebo extract was spiked with aluminum hydroxide buffer with 0.01 mg of histamine hydrochloride. Placebo was identical in appearance to active treatment. Fifty percent of the placebo vials were randomly substituted for identically labeled vials containing different concentrations of histamine ranging from 0.5 to 5 μ g/mL to ensure double blinding of the trial.

The same standardized extract in 50% glycerol was used for SPTs. Four 5-fold dilutions starting at 100 HEP/mL were prepared.

Immunotherapy

Immunotherapy consisted of a build-up phase of cluster administrations of the first 2 vials followed by weekly administrations up to the maximum tolerated dose or 20- μ g dose and 2-week administrations of the maintenance dose until an entire administration length of 6 months (Table II). SIT was always administered by the same doctor, and patients remained under observation for at least 1 hour after each injection. Before each injection, patients were asked about their health condition, reactions to the previous dose, intercurrent infection, or worsening of their disease. Peak expiratory flow values were recorded before and 60 minutes and 6 hours after SIT administration.

TABLE I. Demographic and clinical characteristics of the patients at the beginning of the study

	Active (n = 16)	Placebo (n = 8)	Test result
Sex (M/F)	2/14	1/7	NS
Age (y)			NS
Mean $\pm$ SD	33 $\pm$ 8.7	35.3 $\pm$ 9.4	
Range	23-51	21-48	
Disease duration (y)			NS
Mean $\pm$ SD	5.5 $\pm$ 4.2	5.6 $\pm$ 4.6	
Range	1-15	4-15	
Occupation			NS
No. of health care workers	11/16	6/8	
No. of patients with:			
Cutaneous reactions	16/16	8/8	NS
Rhinitis	13/16	4/8	NS
Conjunctivitis	12/16	6/8	NS
Asthma	10/16	5/8	NS
No. of patients with NSBH	9/10	5/5	NS
Mean $\pm$ SD PC ₂₀	0.93 $\pm$ 0.53	2.39 $\pm$ 2.85	
No. of patients with:			
Positive food SPT response	13/16	6/8	NS
Positive food IgE level	13/16	6/8	NS
Food symptoms	7/16	4/8	NS
Positive pollen SPT response	16/16	8/8	NS
Positive pollen IgE level	16/16	8/8	NS
Pollen symptoms	16/16	8/8	NS
Other aeroallergens	3/16	1/8	NS
No. of patients with:			
SIC	11	5	NS
Positive SIC result	11/11	5/5	NS
No. of patients with:			
Positive rubbing test result	13/16	7/8	NS
Positive glove test result	10/16	5/8	NS
Latex SPT*			NS
Mean $\pm$ SD (mm ²)†	46.1 $\pm$ 2.3	50.1 $\pm$ 2.6	
Range (mm ²)	7-121	9.5-157.5	
No. of positive responses‡	16/16	8/8	
Latex IgE			NS
Median (IQR), kU/L	1.4 (0.4-5.2)	2.8 (1.5-6.9)	
Range, (kU/L)	<0.35-29.5	<0.35-8.7	
No. of positive results§	12/16	6/7	

NSBH, Nonspecific bronchial hyperresponsiveness; NS, not significant.

*SPT = 100 HEP/mL.

†Geometric mean and SD.

‡SPT response greater than 7 mm².

§CAP class greater than 1.

Every adverse event was recorded and classified according to the EAACI guidelines.¹⁰ The causal relationship with the treatment was established according to the method of Venn.¹²

Hematologic and serum biochemical analyses were also performed at the 2 control times (T₀ and T_F).

Diary cards

Patients recorded their daily bronchial (cough, wheezing, and shortness of breath), ocular (swelling, itching, and watery eyes), nasal (itching, sneezing, congestion, and rhinorrhea), and skin-related (itching, redness, and wheals) symptoms on a 0- (absent) to 3-point (severe) scale, as well as their daily medication consumption, during a 2-week period on a diary card before and after SIT (T₀ and T_F). Medication use was scored as 1 point for antihistamines, 1 point for inhaled β_2 -agonists, 2 points for topical corticosteroids (bronchial or nasal), and 3 points for oral corticosteroids. Patients

were allowed to take symptomatic medication during the study as needed, recording the medication used daily in accordance with the scoring system described.

Total symptom and medication scores were calculated for each affected organ. The efficacy of the treatment was evaluated by comparing the different parameters registered on the diary cards (symptom score, medication score, and combined score of symptoms and medication) before and after SIT in patients and control subjects. Patients' subjective evaluations of their disease was assessed by means of a VAS¹³ from 1 (no symptoms) to 10 (very severe symptoms).

Skin prick tests

SPTs were performed at T₀ and T_F with four 5-fold dilutions of latex extract (100, 20, 4, and 0.8 HEP/mL; Soluprick, ALK-ABELLÓ), 10 mg/mL histamine HCl, and glycerinated saline as

TABLE II. Immunotherapy schedule

Day	Dose			
	Vial (□g/mL total protein)	Injected volume (mL)	Injected protein (□g)	Accumulated dose (□g)
0	0 (0.002)	0.4 + 0.8	0.0024	0.0024
7	1 (0.02)	0.2 + 0.4 + 0.8	0.028	0.030
14		0.2	0.04	0.070
21	2 (0.2)	0.4	0.08	0.150
28		0.8	0.16	0.310
35		0.1	0.2	0.510
42	3 (2)	0.2	0.4	0.910
49		0.4	0.8	1.710
56		0.8	1.6	3.310
63		0.1	2	5.310
70		0.2	4	9.310
77	4 (20)	0.4	8	17.310
84		0.6	12	29.310
91		0.8	16	45.310
98		1	20	65.310

controls, all by duplicate on the volar side of the forearm. Prick-by-prick tests with avocado, chestnut, kiwi, and banana were also performed at T_0 . A wheal diameter of 3 mm or greater with erythema compared with that produced by the saline control was defined as a positive reaction. Any medication that could influence the skin reactivity was discontinued beforehand.¹⁴ Skin responses were registered after 15 minutes, and wheal areas were measured by means of planimetry. The difference in immediate skin reactivity was analyzed by means of parallel-line assay and expressed by means of the cutaneous tolerance index (CTI) as the ratio of the allergen extract concentrations provoking the same skin response.¹⁵

Methacholine inhalation test

Methacholine inhalation testing was performed according to the method of Cockcroft et al,¹⁶ with some modifications.¹⁷ Patients conducted 2-minute methacholine inhalations at concentrations ranging from 0.125 to 16 mg/mL. Results were expressed as PC_{20} values. This test was performed before and 24 hours after SIC at T_0 and T_F .

Specific inhalation challenge

SICs with NRL gloves were performed in a 7-m³ challenge room, according to a previously described protocol.¹⁸ Monitored parameters included symptoms, pulmonary function, exposure duration, and asthmatic reaction. This challenge chamber was equipped with vacuum exhaust and high-efficiency particle arrest filtration, which removed residual particles after each challenge. Spirometry was assessed before each challenge and thereafter at regular intervals for at least 9 hours.

On a control day, the subjects were asked to handle vinyl gloves up to 15 minutes to ensure that fluctuations of FEV_1 were less than 10%. On the next day, the subjects were challenged by handling powdered NRL gloves. Aerosols of NRL allergenic proteins were generated by agitating a pair of inside-out powdered NRL gloves every 3 minutes during the exposure period. Patients wore vinyl gloves to prevent direct skin contact with NRL. SICs were performed with the same batch (2V9J003) of nonsterile medical examination gloves commonly used in the hospital (Flexam powdered, Allegiance Healthcare Corp). Exposure times were progressively increased (ie, 3, 6, 15, 30, and 60 minutes) until FEV_1 decreased by 15% or greater or until a cumulative exposure of 114 minutes was

completed. Methacholine PC_{20} values were assessed again 24 hours after NRL exposure to detect changes in nonspecific bronchial hyperresponsiveness.⁵ A greater than 2-fold variation in postchallenge PC_{20} value compared with the control value was considered a significant change. During SIC, bronchial (cough, wheezing, and shortness of breath) and nasal (itching, sneezing, congestion, and rhinorrhea) symptoms were scored on a 0- (absent) to 3-point (severe) scale and registered.

Rubbing and latex glove use tests

Rubbing tests were performed at T_0 and T_F by wetting patient's forearm with water and rubbing a latex glove (same batch as in SIC) for 30 seconds on the skin. Fifteen and 60 minutes after the challenge, the patient was examined for local skin reactions, such as itching, redness, or wheals, or SRs.

The use test was performed according to the method of Turjanmaa.¹⁹ After wetting both hands with water, a latex glove was placed on one hand, and a vinyl glove was placed on the other hand as a control (Triflex). Gloves were kept on for 15 minutes and taken off for skin examination. At 15 and 60 minutes, the presence of itching, redness, wheals, or SRs was assessed. Latex glove use tests were carried out both at T_0 and T_F . Five control subjects were also challenged in the same way. None of the control subjects reacted to these tests.

Symptoms were scored as 1 for local itching without any other manifestations, 2 for redness, 3 when wheals became apparent, and 4 if any SRs appeared.

In vitro parameters

Blood samples were collected from every patient at T_0 and T_F . Serum samples were stored at -20°C and processed together at the end of the study to avoid interassay variations.

NRL-specific IgE levels in sera were determined by using the Pharmacia CAP system according to manufacturer's instructions at T_0 and T_F . CAP system assays were carried out by using NRL enriched with recombinant Hev b 5 (Pharmacia).

Statistical analysis

The comparison of categorical variables was performed by using the χ^2 test or the Fisher exact test (2-tailed). The results of SPTs were analyzed by means of parallel-line assay¹⁵ after logarithmic

transformation of wheal areas and extract concentrations. The scores from the rubbing and latex glove use tests and diary cards (symptom and medication), VAS results, methacholine PC₂₀ values, and latex-specific IgE levels were analyzed by means of nonparametric tests, the Mann-Whitman test for group comparison, and the Wilcoxon test for intragroup evolution. The exposure time in SIC to obtain a 15% decrease in FEV₁ value was analyzed also by using nonparametric, Mann-Whitney, and Wilcoxon tests. Median values and interquartile ranges (IQRs) are given as descriptive statistics. The change in symptoms after SIC was compared between groups by using the Fisher exact test. Two-sided tests were used, and *P* values of less than .05 were considered to be significant.

RESULTS

The baseline characteristics of subjects are shown in Table I. Both treatment groups were similar in their demographic and clinical characteristics at baseline.

Safety and adverse events

There were no significant changes in the analytic and hematologic screening with the SIT treatment.

The average maximum tolerated dose was 11.1 ± 9.3 μ g of latex protein. Five patients tolerated less than 1 μ g of latex protein, with a cumulative dose of 5.1 ± 3.2 μ g; 3 patients tolerated between 1 and 10 μ g, with a cumulative dose of 58.2 ± 25.3 μ g; and 8 patients received the maximum dose of 20 μ g repeated 6 or 7 times, with a cumulative dose of 186.3 ± 14.5 μ g.

Thirty-one SRs were observed in 387 doses, and 11 patients in the active group experienced SRs (8% of doses and 68.7% of patients). Five patients had 1 SR, 2 had 2 SRs, 1 had 3 SRs, 1 had 5 SRs, and 2 had 7 SRs. No patients dropped out of the study as a result of SRs or other causes.

According to the phase of treatment, the SRs occurred in 8.9% and 5.3% of doses during the build-up and maintenance phases, respectively (*P* = .3831, Fisher exact test). Twenty-two SRs were immediate, and 10 were delayed (in one case a delayed SR followed an immediate SR). Immediate SRs were classified as grade 1 in 3 cases, grade 2 in 17 cases, and grade 3 in 2 cases according to the EAACI position paper.¹⁰ No grade 4 reactions were observed, with all reactions responding promptly to treatment, and no episodes of anaphylactic shock were observed.

Patients with respiratory symptoms had a significantly higher rate of immediate SRs than patients with only cutaneous symptoms (8.0% vs 2.7%, respectively; *P* = .004, Fisher exact test). The rate of delayed SR was similar for the active and placebo groups and in patients with respiratory or cutaneous symptoms.

Three SRs (1 immediate grade 3 and 2 delayed) were recorded in 3 patients in the placebo group (1.6% of doses). Only 2 doses provoked large local reactions, one in the active group and another in the placebo group.

Skin prick tests

Patients in the active treatment group had a significant decrease in skin reactivity to the latex extract during treatment. The CTI was 12.0 (95% CI, 4.1-54.8; *P* < .01),

meaning that, after treatment, patients in the active group required a concentration of latex extract 12 times higher than that before to induce the same wheal area by means of skin prick testing. Patients in the placebo group, however, did not show changes in their cutaneous response on the basis of SPTs. As a consequence, significant differences between the 2 groups (CTI, 8.9; 95% CI, 2.2-69.7; *P* < .01) were shown after treatment (Fig 2).

Rubbing and latex glove use tests

The scores for the rubbing and glove use tests were similar in patients from the active and placebo groups before treatment. Median (IQR) scores were as follows: 3.0 (2.0-3.0) for both the active and placebo groups in the rubbing test (*P* = .273); 2.0 (0-2.7) and 2.0 (0-3.0) for the active and placebo groups, respectively, in the glove use test (*P* = .745, Mann-Whitney test). After immunotherapy, patients in the active group scored significantly lower than patients in the placebo group: 0 (0-4.0) vs 4.0 (1.0-4.0) for the rubbing test (*P* = .047); 0 (0-0) vs 2.0 (0-2.0) for the glove use test (*P* = .046). In the active group, a significant reduction was observed in the score for the latex glove use test (*P* = .026, Wilcoxon test) and, to a lesser extent, in the rubbing test (*P* = .072, Wilcoxon test; Figs 3 and 4).

Specific IgE levels

Five patients, 1 in the placebo group and 4 in the active group, had negative specific IgE levels to latex, as determined by means of the CAP assay. Median and IQR values were 1.4 kU/L and 2.8 kU/L at T₀ without differences between groups (*P* = .460, Mann-Whitney test). Median values after treatment were similar to values before treatment for both groups (*P* = .8613 and *P* = .437, Wilcoxon test, for the active and placebo groups, respectively; Table I).

Symptom and medication scores

Symptom and medication scores were similar for both groups before treatment (median of 4.7 [IQR, 2.0-10.4] and 4.4 [IQR, 3.1-8.9], *P* = .687, in the active and placebo groups, respectively; *P* = not significant for the combined symptom and medication score) and after SIT (6.5 [IQR, 3.2-10.1] and 3.6 [IQR, 0.8-7.4], respectively; *P* = .145). Neither the active nor the placebo group showed changes in their symptom scores, medication scores, or both (*P* = not significant, Wilcoxon test, for the combined symptom and medication scores, respectively).

The subjective evaluation of the disease, as measured with a VAS, was similar for both groups before (2.6 cm [IQR, 1.2-3.4 cm] and 1.7 cm [IQR, 1.0-3.8]; *P* = .515) and after the treatment (1.8 cm [IQR, 1.3-3.8 cm] and 2.5 cm [IQR, 0.4-3.9 cm]; *P* = .940, Mann-Whitney test).

Methacholine inhalation test

Fifteen of 16 patients tested for methacholine provocation showed nonspecific bronchial hyperresponsiveness. PC₂₀ methacholine values were similar in both groups before immunotherapy (median of 0.9 mg/mL

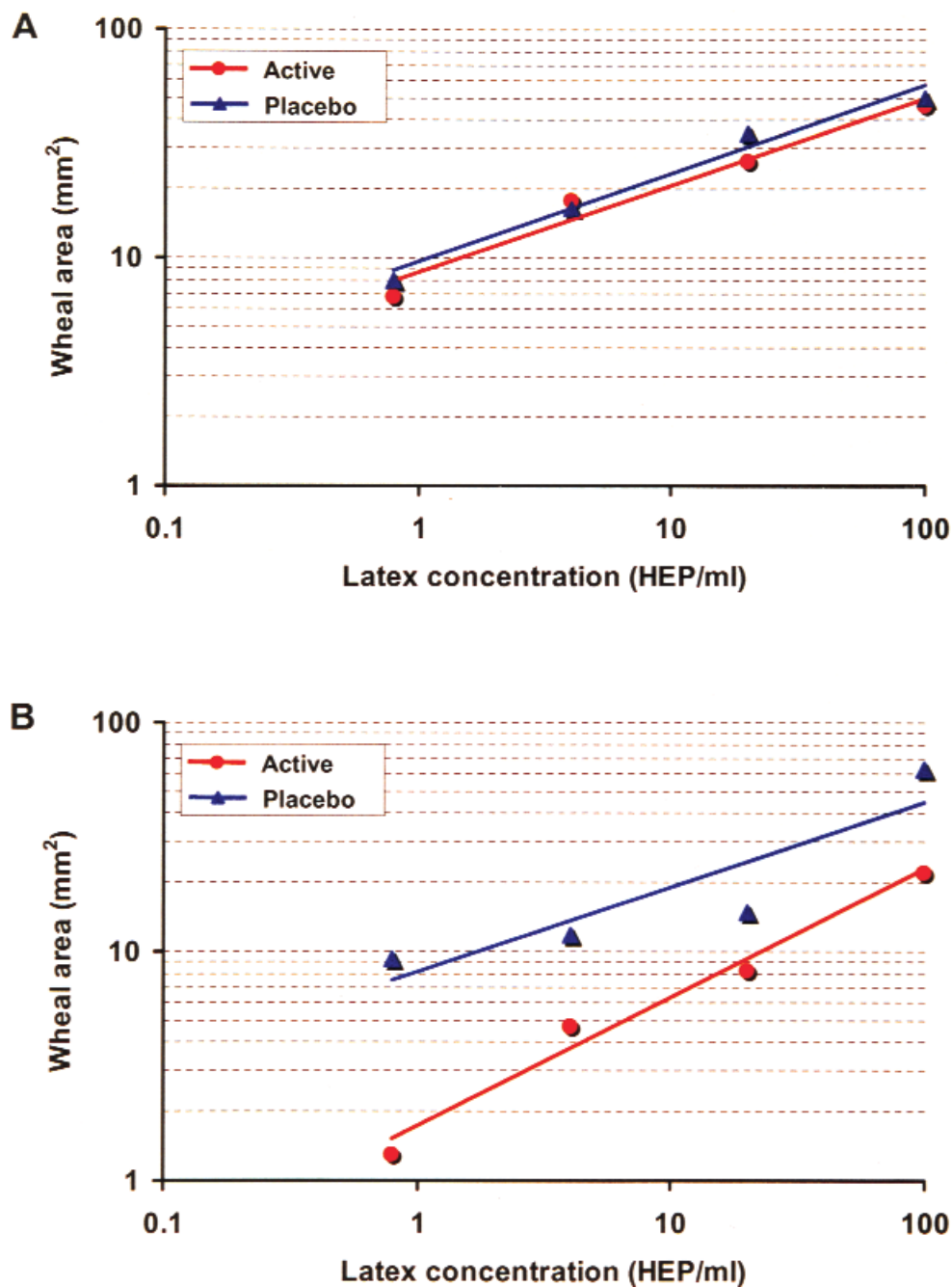


FIG 2. Results of immediate cutaneous response to latex extract: **A**, before immunotherapy; **B**, after immunotherapy. *P* values correspond to parallel-line assay test. See text for details. *NS*, not significant.

[IQR, 0.4-1.6] and 1.5 mg/mL [IQR, 0.4-3-7] for the active and placebo groups, respectively, $P = .624$) and neither varied with the treatment nor was a variation evidenced before and after SIC.

Specific inhalation challenge

Sixteen patients were challenged before the beginning of the treatment. Thirteen showed a decrease in FEV_1 val-

ues of greater than 15% (range, 16.2%-42.5%), and in 3 patients the appearance of symptoms impelled the test to be stopped before a significant decrease in FEV_1 was observed. One patient responded after an exposure time of 3 minutes, 6 after 6 minutes, 5 after 15 minutes, 3 after 30 minutes, and 1 after 1 hour. Bronchial and nasal symptom scores during the SIC were reduced in 88.9% and 77.8% of patients in the active compared with the placebo group

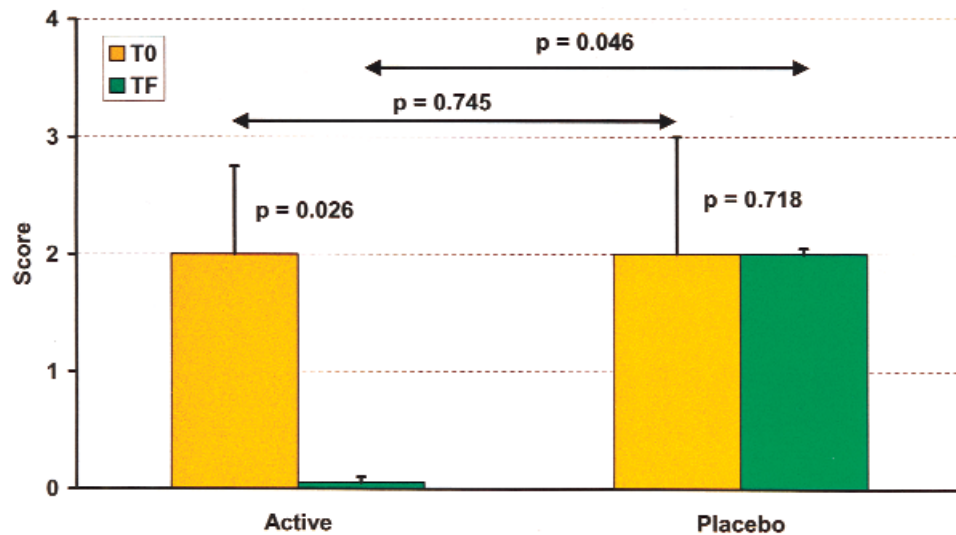


FIG 3. Results of latex glove use tests. *P* values in arrows show Mann-Whitney results for group comparisons. *P* values in bars show Wilcoxon results for evolution.

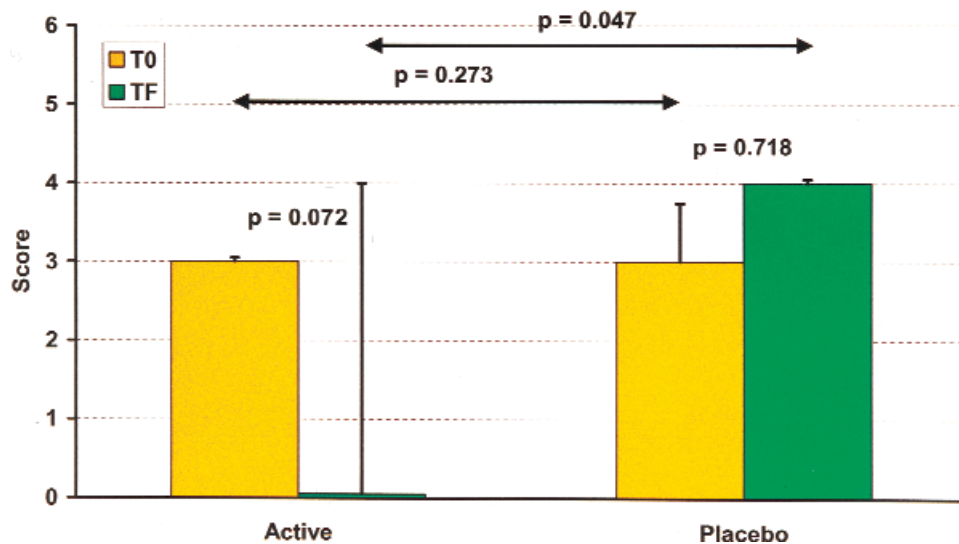


FIG 4. Results of latex rubbing tests. *P* values in arrows show Mann-Whitney results for group comparisons. *P* values in bars show Wilcoxon results for evolution.

(25.0% and 20.0% of patients; $P = .052$ and $P = .091$, Fisher 2-tail exact test; Fig 5). However, there were not statistically significant differences between groups either in the exposure time to elicit a 15% decrease in FEV_1 or in the magnitude of FEV_1 decrease. Patients in both treatment groups experienced a nonsignificant increase in the challenge exposure time after treatment, from 15 minutes (IQR, 6-30 minutes) to 21.2 minutes (IQR 15-60 minutes)

in the active group ($P = .168$) and from 6 minutes (IQR, 4.2-19 minutes) to 15 minutes (IQR, 6.7-30 minutes) in the placebo group ($P = .250$, Wilcoxon test).

DISCUSSION

This study compares the results of latex SIT with placebo in sensitized workers in terms of safety and

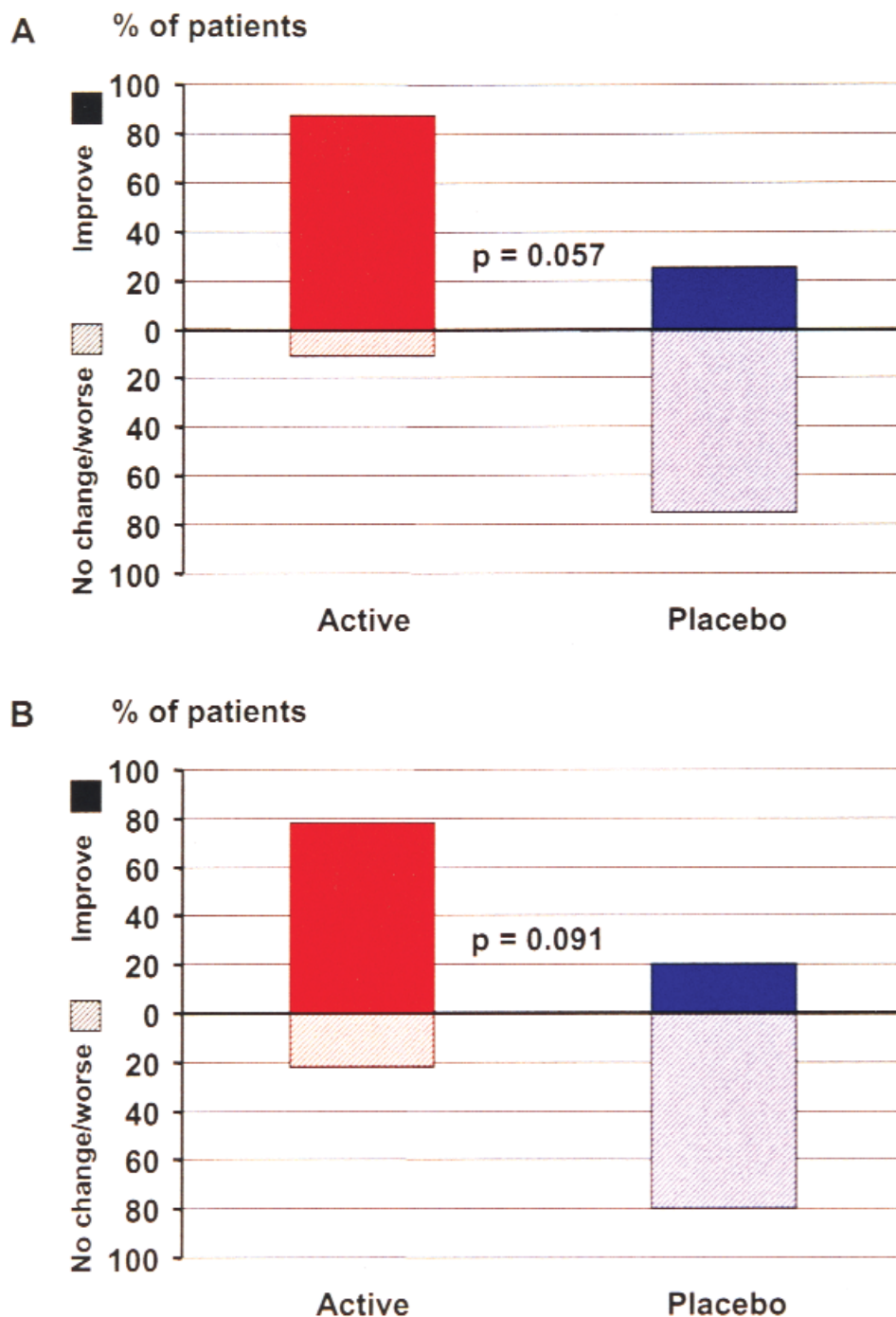


FIG 5. Evolution symptoms during SIC: **A**, bronchial symptoms; **B**, nasal symptoms. *P* values correspond to 2-tailed Fisher exact tests.

efficacy end points. To our knowledge, this is the second double-blind, placebo-controlled study published on latex SIT. The first was carried out by Leynadier et al⁹ at the end of 2000. In this trial a similar crude extract of latex was used for SIT. These authors used a

maximum dose of 5 to 10 reactivity units, which corresponds to 1 to 2 μ g of total protein, in contrast to the maximum dose of 20 μ g used in our study. A total of 17 patients were randomized to receive SIT or placebo for a total of 12 months. The active group showed a statis-

tically significant decrease in rhinoconjunctivitis and urticaria symptoms but not in asthma symptoms. The decrease in medication used in comparison with placebo started at week 20. Side effects were noted in the study by Leynadier et al. In the active group more than 40% of the doses administered produced local reactions, 15% induced rhinitis, 10% induced conjunctivitis, 2.7% induced asthma, 0.6% induced angioedema, and 0.3% induced anaphylaxis.

In our study 31 SRs (8% of doses) were observed in the active group, and 26 (84%) SRs were observed during the build-up period. No anaphylaxis was observed. Immediate SRs were more frequent in patients with respiratory symptoms, and because of the fact that these kind of reactions usually prevent the build-up phase from progressing, patients with respiratory symptoms tolerated lower doses of latex extract (median maximum tolerated dose of 4 μ g latex protein) than patients with only cutaneous symptoms (median maximum tolerated dose of 20 μ g). Thus we find a lower rate of SRs compared with that seen by Leynadier et al.⁹ The rate of immediate SRs increased with the dose, being quite low up to doses lower than 1 μ g and increasing steeply for higher doses. Thus a 1- μ g dose could be considered safe, but the efficacy of a latex SIT treatment on the basis of this dose has not yet been determined.

At present, SIT with crude latex extract can only be considered experimental and must be administered by experienced allergists in a hospital setting, as with venom SIT. Nevertheless, this fact should not deter allergists from their use or discourage further clinical trials because all SRs responded well to treatment, and no patients withdrew from the study. The use of other types of latex extracts (particularly extracts from ammoniated latex) or the use of peptides or DNA conjugation of latex allergens for SIT might reduce the risk of severe reactions and might be an alternative to crude extracts.²⁰ The potential of other means of administration, such as sublingual SIT, must also be explored.

As expected and as a result of the duration of treatment, levels of specific IgE to latex extract did not vary between groups. It is worth mentioning that in spite of using a solid phase enriched with Hev b 5, one of the most clinically important latex allergen among health care workers, 5 (20%) patients had negative results according to the CAP system. This rate of false-negative results is too high compared with the results obtained with the latex extract used for skin testing. Thus SPTs with a standardized crude extract should be recommended for diagnostic purposes.

Patients in the active group had a statistically significant reduction in skin reactivity to latex extract by means of SPT. In fact, patients in the active group required a concentration of extract 8.9 times higher to induce the same wheal by means of SPT than patients in the placebo group after SIT. Likewise, SIT also induced a significant improvement in rubbing and glove use test results, which confirms the efficacy of treatment on cutaneous symptoms. In the study by Leynadier et al,⁹ a decrease in

cutaneous symptoms was also observed, although after an SIT period of twice as long.

Comparison of the groups after 6 months of treatment showed that patients in the active group had a significant reduction in nasal and bronchial symptoms during the controlled SIC. However, there was no difference concerning methacholine reactivity, VAS results, symptom scores, or medication use between groups before and after treatment. The lack of efficacy on these parameters could be explained by the fact that all patients were also allergic to pollens, and part of the study was carried out during the pollen season. The inclusion of monosensitized patients could have eliminated this bias, but this would have been impractical from the clinical point of view. Another reason could be the length of the treatment (6 months); however, in the study of Leynadier et al,⁹ an improvement in symptom and medication scores was seen after 6 and 12 months of treatment.

In conclusion, the clinical efficacy observed during this 6-month trial was shown mainly on cutaneous symptoms, although a significant improvement of rhinitis and asthma symptoms was observed during controlled SIC. Because of the higher rate of SRs in comparison with those after conventional SIT, this treatment can only be considered experimental and must be administered by experienced allergists in a hospital setting. Latex SIT might be a useful approach to the treatment of latex allergy in more severely affected health care workers because no other causative treatment can be offered, and allergen avoidance is not always possible. Further trials are needed to confirm these results.

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