Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2006;141:369–376
DOI: 10.1159/000095463

Received: November 7, 2005
Accepted: May 8, 2006
Published online: August 30, 2006

Specific Immunotherapy with Standardized Latex Extract versus Placebo in Latex-Allergic Patients

Ana Isabel Tabar[a] Marta Anda[a] Floriano Bonifazi[b] Maria Beatrice Bilò[b] Francisque Leynadier[c] Thomas Fuchs[e] Johannes Ring[f] Sylvie Galvain[d] Claude André[d]

[a]Sección de Alergología, Hospital Virgen del Camino, Pamplona, Spain; [b]Department of Internal Medicine, Immunology, Allergy and Respiratory Diseases, Ospedale Regionale 'Umberto I', Ancona, Italy; [c]Service de Médecine Interne, Centre d'Allergie, Hôpital Tenon, Paris, and [d]Scientific and Medical Department, Stallergènes SA, Antony, France; [e]Hautklinik und Poliklinik, Georg-August-Universität Göttingen, Göttingen, and [f]Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, München, Germany

Key Words
Latex · Urticaria · Rhinoconjunctivitis · Asthma · Specific immunotherapy

Abstract
Background: Allergy to natural rubber latex proteins continues to be an important medical problem among health care professionals, but also in multioperated children. Clinical manifestations range from urticaria to angioedema, rhinoconjunctivitis, bronchial asthma and anaphylactic shock. ***Methods:*** The aim of this study was to investigate the efficacy and safety of a 12-month latex-specific immunotherapy in sensitized patients, most often health care workers. Twenty-three patients with latex rhinoconjunctivitis (20 of whom also had asthma) were included in this randomized, double-blind, placebo-controlled trial (11 in the active group, 12 in the placebo group). Treatment efficacy was assessed by means of symptom and medication scores. Conjunctival provocation tests and quantitative skin prick tests were also performed. ***Results:*** The clinical index (derived by combining changes from baseline of six efficacy variables during the treatment period) did not differ significantly between treatment groups. Change from baseline of rhinitis, conjunctivitis, skin symptoms, asthma symptoms, medication score and cutaneous reactivity were not significantly different between the two groups. A nonsignificant difference in conjunctival reactivity was observed in favor of the active group ($p = 0.09$). Systemic reactions were much higher in the specific immunotherapy than in the placebo group. ***Conclusions:*** The present study failed to show a significant improvement of symptoms and medication scores, probably because of the low level of symptoms at baseline and the low maintenance dose of therapy, even if allergen-specific conjunctival reactivity decreased in the active group. Moreover, the incidence of systemic reactions was very high in the active group.

Introduction

Raw latex is a milky sap drawn from the rubber tree *(Hevea brasiliensis)*. It is subsequently vulcanized into elastic rubber to manufacture thousands of products [1]. Immediate hypersensitivity reactions to natural rubber

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1018–2438/06/1414–0369$23.50/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Dr. Claude André
Stallergènes SA
6 rue Alexis de Tocqueville
FR–92183 Antony (France)
Tel. +33 1 55 59 21 87, Fax +33 1 55 59 20 68, E-Mail candre@stallergenes.fr

latex (NRL) proteins have been recognized as a significant health concern worldwide in the last 20 years [2–7]. Risk groups for NRL allergy are now well defined. They include health care workers and other workers using latex gloves, and employees working in NRL manufacturing plants. Children with spina bifida or urogenital malformations and patients who have undergone multiple surgical procedures also constitute another high-risk group due to multiple contacts with latex surgical gloves and urinary catheters [8]. Induction of latex allergy commonly occurs after exposure of skin or mucous membranes to NRL or by inhalation, mainly caused by glove starch powder. Latex hypersensitivity reactions can affect the skin, eyes and lungs and, more rarely, can induce anaphylactic shock. Latex allergy is related to atopic diseases [9]. Some patients develop allergic symptoms to a large number of foods (e.g. avocado, banana, kiwi, papaya and chestnut) [10, 11] because of cross-reactivity. The diagnosis of latex allergy is primarily based on clinical history and skin prick test (SPT), and secondarily on latex-specific IgE [12, 13].

NRL allergy prevention protocols have been proposed for medical and paramedical personnel known to be latex-allergic. These personnel must work in reduced allergen environment: switch to low-allergen latex or nonlatex gloves reduced the concentration of allergen in the work site and allowed most of patients with latex allergy to remain in their current work area [14, 15]. Nonlatex gloves made of vinyl and nitrile are now available. However, some workers are compelled to change work because of NRL allergy [16]. Subcutaneous latex immunotherapy could constitute an alternative treatment and has already shown promising results in the case reports described by Pereira et al. [17, 18] and in the first double-blind, placebo-controlled studies published by Leynadier et al. [19] and by Sastre et al. [20]. We performed a double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous specific immunotherapy (SIT) in latex-allergic patients.

Methods

Trial Design

The clinical trial was an international multicenter study; it was conducted in accordance with good clinical practice, after being approved by each national ethics committee. All patients gave their written informed consent to participate in the trial.

This was a randomized, double-blind, placebo-controlled trial conducted in parallel groups by 5 centers. Patients preselected between October 2000 and January 2002 were randomized to two treatment groups, active or placebo.

Patients

Twenty-three patients (6 males and 17 females; mean age: 35 ± 8 years, range: 24–58 years) with latex hypersensitivity were included (table 2). All patients presented signs of latex conjunctivitis; all patients except 1 had latex allergic rhinitis, 22 out of 23 also presented cutaneous signs of latex allergy (isolated skin itching, urticaria or hand eczema) and 20 suffered from latex-related asthma (intermittent to chronic moderate) [21]. Three patients in each group had severe bronchospasm. Angioedema in the presence of latex was reported in 3 patients in the active group, and 4 in the placebo group. There was no history of anaphylactic shock.

The diagnosis of latex allergy was based on a clinical history of rhinoconjunctivitis and/or asthma for at least 2 years, a positive latex SPT (Stallergènes SA, Antony, France), a positive latex conjunctival provocation test (CPT) and a latex-specific IgE level of at least class 2 (Pharmacia, Sweden). One patient was also sensitized to grass pollen and house dust mite in the active group, another one to house dust mite in the placebo group.

Allergen Preparations

A standardized latex extract [22] (Stallergènes) was used throughout the study. Its biological activity had been controlled by RAST inhibition [23] and compared to an internal standard by in vivo and in vitro tests. It was expressed in IR (index of reactivity) according to the following definition: a 100 IR/ml extract induces a wheal with a geometrical mean diameter of 7 mm on a prick test in 30 patients sensitized to the allergen considered.

Treatment

Treatment comprised a dose progression phase (presented in table 1) during which the extract (Stallergènes) was administered in hospital according to a 2-day rush protocol. This phase was followed by a 12-month phase of maintenance treatment (table 1) at the maximum tolerated dose (0.5 ml of 10 IR/ml vial, depending on tolerance). The placebo preparations included histamine dihydrochloride 0.01, 0.1 and 0.5 mg/ml. The active and placebo vials presented an identical visual appearance.

Symptom Scores

Symptoms of rhinitis and conjunctivitis and cutaneous signs were recorded daily by the patients during a 2-month baseline period and weekly throughout treatment. Each symptom was scored on a scale from 0 (symptom absent) to 3 (symptom intolerable). Asthma symptoms were also recorded and scored on a scale from 0 (symptom absent) to 3 (asthma attack).

Based on these data, a mean rhinitis score (total, from 0 to 12, of four symptoms: rhinorrhea, nasal itching, nasal blockage, sneezing), a mean conjunctivitis score (total, from 0 to 12, of four symptoms: tearing, itching, edema and conjunctival erythema), a mean rhinoconjunctivitis score (from 0 to 24) and a mean cutaneous score (total, from 0 to 9, of three symptoms: pruritus, urticaria and eczema) were calculated each week. A daily average symptom score was calculated of the whole baseline period and of the whole treatment period for each symptom score and for each mean score previously described. The efficacy of treatment was evaluated by calculating changes from baseline and comparing these changes between treatment groups.

Table 1. Immunotherapy protocol

Concentration	Doses injected ml	Frequency
Dose progression: first day		
0.1 IR/ml vial	0.10	30-min interval between two injections
	0.20	
	0.30	
	0.40	
1 IR/ml vial	0.10	25-min interval between two injections
	0.20	
	0.30	
	0.40	
	0.50	
Dose progression: second day		
10 IR/ml vial	0.10	1-hour interval between two injections
	0.20	
	0.30	
	0.40	
	0.50	
Maintenance therapy: first month		
10 IR/ml vial	0.50	1 injection once a week
Maintenance therapy: second month		
10 IR/ml vial	0.50	1 injection once a fortnight
Then: 10 IR/ml vial	0.50	1 injection once a month for 10 months

Table 2. Demographic data

	Active	Placebo	Test
Patients	11	12	
Gender, M/F	2/9	4/8	NS
Age, years			
Mean ± SD	35 ± 9	35 ± 8	NS
Range	24–58	25–54	
History of latex allergy (mean), years			
Rhinitis	6.3	6.6	NS
Conjunctivitis	6.3	6.4	NS
Asthma	5.1	5.2	NS
Skin reactions	6.3	6.8	NS
Clinical features of latex allergy			
Rhinitis	11	11	NS
Conjunctivitis	11	12	NS
Asthma	9	11	NS
Severe bronchospasm	3	3	NS
Skin reactions	10	12	NS
Isolated skin itching	8	10	NS
Urticaria	8	10	NS
Hand eczema	1	3	NS
Angioedema	3	4	NS
Food allergy by cross-reactivity	8	10	NS
Household exposure	2	5	NS
Occupational exposure	10	10	NS
Patients with another sensitization	1	1	NS
Grass pollen	1	0	NS
House dust mite	1	1	NS

NS = Not significant.

Medication Scores

The patients were allowed to take symptomatic medication during the study whenever necessary. They recorded the quantities consumed each week. Based on these data, a total medication score was calculated according to each therapeutic category (0.5 point for topical antiallergic treatment, 1 point for each puff of rapid-acting β_2-agonist, 1 point for each dose of nasal corticosteroids equivalent to 50 μg of beclomethasone, 1.5 point for each dose of inhaled corticosteroids equivalent to 200 μg of budesonide and for each dose of long-acting β_2-agonist equivalent to 25 μg of salmeterol, 2 points for an antihistamine tablet, and 18 points for a corticosteroid tablet equivalent to 20 mg of prednisolone). The change from baseline of daily average medication score during the treatment period was calculated.

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, 1.2 IR/ml) of an aqueous latex extract obtained from a 100-IR lyophilisate (Stallergènes) were used for the CPT. Tests were performed by instilling one drop of the extract into the lower conjunctival fornix of the right eye, starting with the lowest concentration. A control test was performed on the left eye by instilling physiological 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 al. [24] (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 7.

Quantitative Skin Prick Tests

Quantitative skin prick tests (QSPT) were performed on inclusion and at treatment completion with the Stallerpoint® device (Stallergènes) using a latex extract at concentrations of 300, 100, 33 and 11 IR/ml (Stallergènes), a positive control (9% codeine phosphate) and a negative control (phenolated glycerol-saline diluent).

For each patient, the least squares method was used to calculate the following regression line equation: $\log3(Y) = a \times \log3(X) + b$, where Y was the diameter of the wheal produced by each concentration and X the concentration in IR/ml of each solution. This regression line was used to calculate the theoretical wheal diameter obtained in response to a concentration of 100 IR/ml in each patient before and after treatment.

Laboratory Tests

Latex-specific IgE and IgG4 titers in serum collected before and after treatment were determined using the CAP System and the RIA CAP System (Pharmacia Diagnostics, Uppsala, Sweden), respectively.

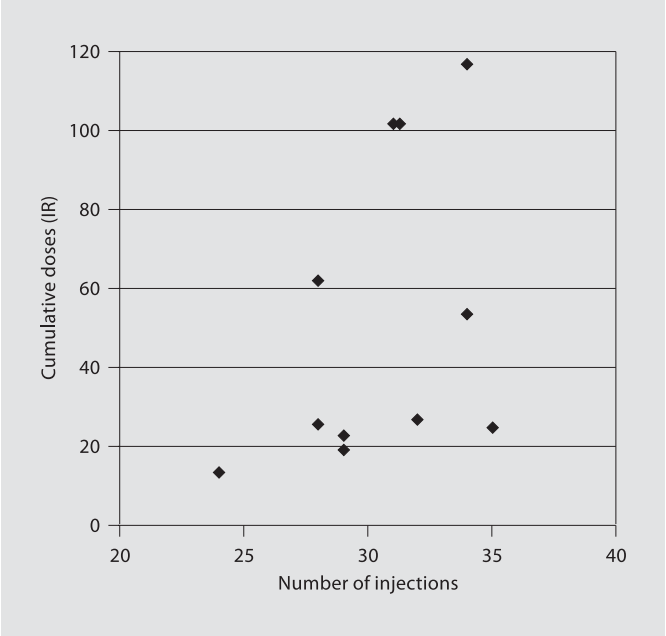

Fig. 1. Number of injections and cumulative doses for each patient in the active group.

Adverse Events

The clinician evaluated the safety of the treatment at each visit. Any local (pruritus, wheal, or edema) or systemic reactions (SRs; e.g., rhinitis, conjunctivitis, asthma attack, urticaria, or eczema) considered to be related to the trial treatment had to be recorded on the case report form.

Statistical Methods

The primary efficacy variable was the clinical index, corresponding to a parameter derived by combining several changes from baseline of the following six individual efficacy variables after treatment: mean rhinitis score, mean conjunctivitis score, medication score, fold change from baseline of threshold dose after treatment during CPT, fold change from baseline of latex-specific IgG4 after treatment and change from baseline of theoretical wheal diameter for 100 IR/ml after treatment. A lower clinical index corresponded to more effective treatment: for each criterion, rank 1 was assigned to the greatest improvement and the last rank to the worst result.

The χ^2 test or Fisher exact test were used for intergroup comparison of qualitative variables. Quantitative variables were compared between groups using the parametric Student t test for specific IgG4 and QSPT as these data were normally distributed and the nonparametric Wilcoxon 2-sample test for the other data. No intragroup statistical test was performed. Intention-to-treat (ITT) statistical analysis was performed on all randomized patients who started immunotherapy including those who finished treatment but also those who did not complete treatment. In the patients who did not complete treatment, the clinical index was calculated from the three available variables: rhinitis, conjunctivitis and medication scores; the three other variables (threshold dose during CPT, specific IgG4 and theoretical wheal diameter for 100 IR/ml during QSPT) were quoted as missing values. Owing to the limited number of patients a per-protocol analysis was not performed. A sensitivity analysis was carried out on patients who finished treatment allowing confirmation of the results obtained in the ITT analysis. All tests were bilateral and performed at the limit of $\alpha = 0.05$.

Results

Twenty-three patients were randomized: 11 to the active treatment group and 12 to the placebo group. Two patients in the placebo group dropped out of the trial for the following reasons: personal reasons and lack of efficacy. Three patients in the active group dropped out of the trial for the following reasons: intercurrent disease, noncompliance, personal reasons and intercurrent disease. The 8 other patients in the active group completed the study. However, only 3/8 patients reached the planned maintenance dose (0.50 ml of 10 IR/ml) or cumulative dose (101.60 IR). For the other patients, the maintenance dose was very low (0.05, 0.10 or 0.20 ml of 10 IR/ml), so the cumulative dose was also very low (fig. 1).

The demographic characteristics of the 23 patients are presented in table 2. No significant difference was demonstrated between the groups regarding age and gender, personal history, clinical manifestations of the disease, symptom scores and medication scores, ocular and cutaneous reactivity and latex-specific IgE (tables 3, 4). In the active group, 10 patients were occupationally exposed to latex (7 health care workers, 1 laboratory technician, 1 patient working in a flooring factory and 1 cleaner) by using latex gloves, masks, or moss whereas 1 patient was exposed only domestically (latex gloves). In the placebo group, 10 patients were occupationally exposed to latex (8 health care workers, 1 biologist and 1 car painter) whereas 2 patients were exposed only domestically (latex gloves, cars, hospital). All the participants remained exposed to the same quality of latex gloves during the course of the trial. No patient changed their occupation.

Clinical Index

The clinical index did not differ significantly between the treatment groups during the treatment period, although the median value in the active treatment group (median: 9.17, 95% CI: 6.75–12.83) was lower than that in the placebo group (median: 11.79, 95% CI: 8.25–12.67), but 95% confidence intervals for the two treatment groups were very large and overlapped.

Table 3. Comparison of total symptom scores and medication scores between the two groups

	Active	Placebo	Test
Rhinitis			
Baseline	0.25 (0.00; 0.94)	0.15 (0.02; 0.61)	NS (p = 0.73)
Treatment period	0.06 (0.00; 1.57)	0.07 (0.00; 0.81)	NS (p = 0.97)
Change from baseline	0.00 (–0.38; 1.16)	–0.02 (–0.24; 0.60)	NS (p = 0.87)
Conjunctivitis			
Baseline	0.02 (0.00; 0.74)	0.18 (0.00; 0.85)	NS (p = 0.51)
Treatment period	0.01 (0.00; 1.51)	0.15 (0.00; 1.04)	NS (p = 0.20)
Change from baseline	0.00 (–0.60; 1.17)	0.06 (–0.15; 0.63)	NS (p = 0.60)
Skin symptoms			
Baseline	0.01 (0.00; 0.45)	0.06 (0.00; 0.29)	NS (p = 0.53)
Treatment period	0.09 (0.00; 1.31)	0.08 (0.00; 0.70)	NS (p = 1.00)
Change from baseline	0.08 (–0.32; 0.94)	0.01 (–0.04; 0.45)	NS (p = 0.60)
Asthma			
Baseline	0.02 (0.00; 0.98)	0.06 (0.00; 0.36)	NS (p = 0.90)
Treatment period	0.02 (0.00; 2.00)	0.06 (0.00; 0.93)	NS (p = 0.42)
Change from baseline	–0.01 (–0.40; 1.02)	0.03 (–0.08; 0.77)	NS (p = 0.24)
Medication score			
Baseline	0.08 (0.00; 11.73)	0.03 (0.00; 14.12)	NS (p = 0.68)
Treatment period	0.26 (0.00; 14.03)	0.05 (0.00; 13.65)	NS (p = 0.43)
Change from baseline	0.00 (–3.03; 2.30)	0.00 (–1.99; 0.53)	NS (p = 0.57)

Values represent median with the range given in parentheses. NS = Not significant.

Table 4. Comparison of theoretical wheal diameter, threshold dose in CPT and specific antibodies between the two groups

	Active	Placebo	Test
Threshold dose in CPT, IR/ml			
Baseline	11 (3.7; 100)	3.7 (1.2; 33)	NS (p = 0.10)
Following treatment period	33 (3.7; 100)	3.7 (1.2; 100)	
Fold change from baseline	3 (0.33; 9)	1 (0.33; 27)	NS (p = 0.09)
Theoretical wheal diameter for 100 IR, mm			
Baseline	6.58 (0.10; 9.88)	8.35 (3.36; 16.96)	NS (p = 0.07)
Following treatment period	3.76 (1.78; 5.19)	6.85 (2.05; 11.11)	p = 0.02
Change from baseline	–2.38 (–7.79; 4.64)	–1.28 (–9.63; 2.82)	NS (p = 0.90)
Latex-specific IgE, kIU/l			
Baseline	18.3 (5.15; 100.00)	4.06 (1.06; 71.30)	NS (p = 0.06)
Following treatment period	19.60 (6.50; 100.00)	4.47 (0.71; 62.50)	
Fold change from baseline	0.98 (0.56; 5.46)	0.88 (0.51; 2.51)	NS (p = 0.41)
Latex-specific IgG4, μg/l			
Baseline	576.0 (153; 7,301)	176.5 (150; 1,200)	p = 0.03
Following treatment period	1,212.5 (254; 12,287)	159.5 (150; 839)	
Fold change from baseline	1.70 (0.61; 5.59)	1.00 (0.69; 1.26)	p = 0.04

Values represent median with the range given in parentheses. NS = Not significant.

Symptom and Medication Scores

Changes from baseline of daily average symptom during treatment (table 3) did not differ significantly between treatment groups in terms of rhinitis, conjunctivitis, skin symptoms and asthma. As the symptom scores were very low at baseline, absolute values of changes were close to zero.

The analysis of change from baseline of medication scores during the treatment period did not reveal any significant difference between the two groups.

Conjunctival Provocation Tests

Before treatment, median values of the threshold dose were 11 IR/ml in the active group versus 3.7 IR/ml in the placebo group (not significantly different, table 4). After treatment, median values of the threshold dose were 33 IR/ml in the active group versus 3.7 IR/ml in the placebo group (table 4). Median values of fold change (which is the coefficient of multiplication of the threshold dose before treatment to obtain the result after treatment) were 3 in the active treatment group and 1 in the placebo group. Subjects in the active immunotherapy group had a 3-fold increase in the threshold dose of latex required to produce a reaction in the CPT but fold change was not significantly different between the groups ($p = 0.09$).

Quantitative Skin Prick Tests

Mean wheal diameter in response to a concentration of 100 IR/ml predicted by the dose-response curve (table 4) was not significantly different between the two groups at baseline and no significant difference was observed for the variations from baseline on treatment completion. The significant difference between the groups after treatment completion is related to a higher skin reactivity in the placebo group before treatment.

Serological Assays

Median values of fold change for latex-specific IgE were close to 1 in both groups, indicating that IgE generally remained unchanged after treatment (table 4). Median (mean) values of fold change for latex-specific IgG4 were 1.70 (2.32, range: 0.61–5.59) in the active group and 1.00 (0.96, range: 0.69–1.26) in the placebo group ($p = 0.04$) indicating that IgG4 increased in the active group but remained unchanged in the placebo group (table 4).

Physician and Patient Global Evaluation of Immunotherapy

At treatment completion, the physician and patient rated overall treatment efficacy using a four-point scale (much better, better, unchanged, worse). Median values of physician and patient global evaluation were both 'better' in the active group and 'unchanged' in the placebo group. The percentage improvement (54.5% in the active group and 16.7% in the placebo group according to the physician, $p = 0.09$) was not statistically significant.

Safety

The frequency of SRs in relation to the total number of injections (335 injections in the active group and 354 injections in the placebo group) was clearly higher in the active group. One hundred and two SRs were observed in 335 doses and 9 patients in the active group experienced SRs (81.8% of patients). Nine SRs were observed in 354 doses and 2 patients experienced SRs in the placebo group (16.7% of patients). Most reactions were grade 2 according to the EAACI position paper [25]. SR such as rhinitis, conjunctivitis, mild asthma or mild urticaria which rapidly resolved with or without treatment were observed with the 1 IR/ml vial. Ten cases of grade 3 SR were observed in the active group, such as urticaria (6 reactions, 5 reactions in the same patient, 4 during the maintenance dose), asthma (3 reactions with 1 during the maintenance therapy), angioedema (1 reaction), cough associated with sneezing, palm itching, nausea and abdominal pain (1 reaction during maintenance phase) and throat itching associated with hand itching and cough (1 reaction during maintenance phase). All grade 3 reactions were successfully treated, half of them with adrenaline, the other half with oral steroids. There were no withdrawals due to grade 3 reactions and no grade 4 reactions were observed.

Nine out of 11 patients receiving active treatment experienced a local reaction such as pruritus and/or urticarial papule with the 0.1, 1 or 10 IR/ml vial.

Discussion

This multicenter study compared latex SIT versus placebo in terms of safety and efficacy in sensitized workers and in some patients with household exposure. To our knowledge, this is the third double-blind placebo-controlled study to be published on latex SIT. In the first trial, carried out by Leynadier et al. [19], 17 patients were randomized to receive SIT or placebo for 12 months. The maximum dose was 5 or 10 IR, corresponding to 1 or 2 μg of latex proteins. The active group was significantly improved in terms of rhinoconjunctivitis and cutaneous signs. Symptomatic medication was used much less fre-

quently in the active group than in the placebo group. In this study, comparison of the clinical index between groups did not reveal any significant differences. Changes from baseline of symptoms and medication scores also failed to demonstrate a significant difference between the groups. The lack of efficacy on these parameters could be explained by the very low level of severity of symptoms at baseline leaving little room for improvement with absolute values of changes close to zero. The selection of patients may be considered to be wrong, lacking a threshold limit under which patients were to be excluded. On the other hand, immunotherapy of severe patients, using a dangerous allergen, seems also questionable from an ethical point of view. Another reason could be the marked variability of medication scores at baseline (table 3). The cumulative dose was also much lower in the active group (median: 26.90 IR) than in the placebo group (median: 101.60 IR). In fact only 8 patients completed the trial in the active group (fig. 1), 3 of whom reached the planned maintenance dose (5 IR corresponding to about 1 μg of latex proteins) as they had a much lower number of adverse events (only one face erythema) after injection compared to the 5 other patients. For the 5 other patients, the maintenance dose was 0.1 μg (1 patient), 0.2 μg (3 patients) or 0.4 μg (1 patient) because of many SRs occurring after injection. It should be noted that the total cumulative dose in the study of Leynadier et al. [19] was 96 IR in the active group and 112 IR in the placebo group, using the same latex extract as that used in this study (Stallergènes). This indicates that the lack of efficacy on symptoms in the present study could be due to the low cumulative dose received. However, even if IgG4 is not a surrogate marker of the efficacy of immunotherapy, this antibody concentration, as is the case in the present study, generally increases during immunotherapy, indicating some immunological effect. The levels correlated neither with clinical efficacy nor with cumulative dose.

In the second study on latex SIT conducted by Sastre et al. [20], no difference was observed in terms of symptom scores and medication scores between the groups despite the high maximum dose of 20 μg used for maintenance phase. In the present study, patients in the active group had a reduction in conjunctival reactivity to latex extract as measured by the CPT: they required a 3-fold higher concentration of extract to induce a positive reaction after SIT whereas the threshold dose did not change in the placebo group. These results corroborate the results obtained in the study of Leynadier et al. [19], in which the reduction of the threshold dose on CPTs was observed significantly more frequently in the active group than in the placebo group. In the study of Sastre et al. [20], clinical efficacy was mainly demonstrated on cutaneous reactivity by means of SPT, rubbing and glove use tests. In the study of Leynadier et al. [19], a decrease in cutaneous symptoms was also observed after 12 months of treatment. However, in the present study, neither cutaneous signs nor skin reactivity assessed by SPT were improved.

Oral [26] and sublingual [27, 28] SIT with latex allergen have both been reported to be effective in patients with latex allergy. A second case report [27] described sublingual immunotherapy in a medical student; a cumulative dose of 500 μg of latex was reached after a 3-day rush with no side effects, and induced a reduction of symptoms and latex reactivity. However, these claims under open conditions need to be confirmed by double-blind trials.

This trial failed to demonstrate the clinical benefit of latex SIT, probably because of the inadequate population and the low maintenance dose and showed a high frequency of adverse events. Another alternative for latex SIT in the future could be to use modified heveins with a markedly decreased IgE-binding ability but retained T cell reactivity [29, 30]; such modified heveins should have a lower risk of SRs during the treatment.

Acknowledgments

This study was supported be Stallergènes SA, France. Claude André and Sylvie Galvain (Stallergènes) were responsible for the writing of the protocol and of the paper. The authors thank Mrs Armelle Montagut (Delta Consultants from Meylan, France) for the statistical analysis. They thank the staff of the Hospital Virgen del Camino in Pamplona (Dr. M. Jose Alvarez, Susana Echechipia, Blanca E. García, Jose M. Olaguibel and M.T. Lizaso), of the Hopital Tenon in Paris (Dr. Hafida Gaouar, Ouafia Doudou, Semia Graba and Claudia Duarte-Risselin), Dr. Carsten Gutgesell in Göttingen and Prof. Jürgen Rakoski in München for their patience and support while participating in this investigation.

References

1 Cantani A: Latex allergy in children. Invest Allergol Clin Immunol 1999;9:14–20.
2 Frankland AW: Latex allergy. Clin Exp Allergy 1995;25:199–201.
3 Spaner D, Dolovich J, Tarlo S, Sussman G, Buttoo K: Hypersensitivity to natural latex. J Allergy Clin Immunol 1989;83:1135–1137.
4 Gritter M: Latex Allergy. Lippincott Primary Care Pract 1997;1:142–151.
5 Levy DA, Charpin D, Pecquet C, Leynadier F, Vervloet D: Allergy to latex. Allergy 1992; 47:579–587.
6 Slater JE, Chhabra SK: Latex antigens. J Allergy Clin Immunol 1992;89:673–678.
7 Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Alenius H, Palosuo T: Natural rubber latex allergy – the European experience. Immunol Allergy Clin North Am 1995;15:71–88.
8 Kwittken PL, Sweinberg SK, Campbell DE, Pawlowski NA: Latex hypersensitivity in children: clinical presentation and detection of latex-specific immunoglobulin E. Pediatrics 1995;95:693–699.
9 Fuchs T, Spitzauer S, Vente C, Hevier J, Kapiotis S, Rumpold H, et al: Natural latex, grass pollen, and weed pollen share IgE epitopes. J Allergy Clin Immunol 1997;100:1–16.
10 Mäkinen-Kiljunen S: Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens. J Allergy Clin Immunol 1994;93:990–996.
11 Nel A, Gujuluva C: Latex antigens: identification and use in clinical and experimental studies, including crossreactivity with food and pollen allergens. Ann Allergy Asthma Immunol 1998;81:388–398.
12 Mathew SN, Melton AL, Wagner WO: Latex hypersensitivity: a case study. Ann Allergy 1993;70:483–486.
13 Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M: Latex allergy: clinical features and cross-reactivity with fruits. Ann Allergy 1994;73:309–314.
14 Hunt LW, Kelkar P, Reed CE, Yunginger JW: Management of occupational allergy to natural rubber latex in a medical center: the importance of quantitative latex allergen measurement and objective follow-up. J Allergy Clin Immunol 2002;110:S96–S106.
15 Turjanmaa K, Kanto M, Kautiainen H, Reunala T, Palosuo T: Long-term outcome of 160 adult patients with natural rubber latex allergy. J Allergy Clin Immunol 2002;110: S70–S74.
16 Bernstein DI, Karnani R, Biagini RE, Bernstein CK, Murphy K, Berendts B, Bernstein JA: Clinical and occupational outcomes in health care workers with natural rubber latex allergy. Ann Allergy Asthma Immunol 2003;90:209–213.
17 Pereira C, Rico P, Lourenço M, Lombardero M, Pinto-Mendes J, Chieira C: Specific immunotherapy for occupational latex allergy. Allergy 1999;54:287–296.
18 Pereira C, Pedro E, Tavares B, Ferreira MB, Carrapatoso I, Rico P, et al: Specific immunotherapy for severe latex allergy. Eur Ann Allergy Clin Immunol 2003;35:217–225.
19 Leynadier F, Herman D, Verloet D, Andre C: Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol 2000;106:585–590.
20 Sastre J, Fernandez-Nieto M, Rico P, Martin S, Barber D, Cuesta J, et al: Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. J Allergy Clin Immunol 2003;111:985–994.
21 Aas K: Heterogeneity of bronchial asthma. Sub-populations or different stages of the disease. Allergy 1981;36:3–14.
22 Turjanmaa K, Palosuo T, Alenius H, Leynadier F, Autegarden JE, André C, et al: Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. Allergy 1997;52:41–50.
23 Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB: Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. III. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989;83: 797–802.
24 Abelson MB, Chambers WA, Smith LM: Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. Arch Ophthalmol 1990;108:84–88.
25 Malling H-J, Weeke B: Immunotherapy. Position paper of the European Academy of Allergology and Clinical Immunology. Allergy 1993;48(suppl 14):9–35.
26 Toci G, Shah S, Al-Faqih A, Beezhold D, McGeady SJ: Oral latex desensitization of healthcare workers (abstract). J Allergy Clin Immunol 1998;101:S161.
27 Patriarca G, Nucera E, Pollastrini E, Roncallo C, Buonomo A, Bartolozzi F, et al: Sublingual desensitization: a new approach to latex allergy problem. Anesth Analg 2002;95: 956–960.
28 Cistero Bahima A, Sastre J, Enrique E, Fernandez M, Alonso R, Quirce S, et al: Tolerance and effects on skin reactivity to latex of sublingual rush immunotherapy with a latex extract. J Investig Allergol Clin Immunol 2004;14:17–25.
29 Drew AC, Eusebius NP, Kenins L, de Silva HD, Suphioglu C, Rolland JM, O'Hehir RE: Hypoallergenic variants of the major latex allergen Hev b 6.01 retaining human T lymphocyte reactivity. J Immunol 2004;173: 5872–5879.
30 Karisola P, Mikkola J, Kalkkinen N, Airenne KJ, Laitinen OH, Repo S, Pentikäinen OT, Reunala T, Turjanmaa K, Johnson MS, Palosuo T, Kulomaa MS, Alenius H: Construction of hevein (Hev b 6.02) with reduced allergenicity for immunotherapy of latex allergy by comutation of six amino acid residues on the conformational IgE epitopes. J Immunol 2004;172:2621–2628.