
Specific ultrarush desensitization in Hymenoptera venom-allergic patients

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Background: Hymenoptera venom hypersensitivity is an epidemiologically important problem. The only effective treatment in the management of venom-allergic patients with a history of generalized reactions to insect sting is specific immunotherapy.

Objective: To demonstrate safety and effectiveness of a modified ultrarush desensitization protocol in venom-allergic patients.

Methods: Fifty-seven patients with Hymenoptera venom allergy underwent a specific 1-day ultrarush desensitization by the subcutaneous route, reaching the cumulative dose of 101.1 μg in 2.5 hours. The maintenance dose (100 μg) was administered after 15 days and thereafter once a month. Patients were followed up for a year. Antihistamines were withheld for 15 days before and during desensitization to not underestimate the incidence of adverse effects.

Results: All patients but 1 completed the ultrarush desensitization. (This patient discontinued the treatment because of a hypertensive crisis not related to the desensitization.) The treatment caused a rapid variation of immunological parameters (IgE, IgG4) since the 15th day. After the desensitization, skin prick test results became negative in 15 patients (27%, decrease of 3.5 log), whereas they decreased in 14 patients (25%, decrease of 1 log). Sixty-four percent showed no adverse effects. Only 7% had a mild systemic reaction.

Conclusions: Ultrarush desensitization is an effective and safe therapy in the management of patients with Hymenoptera venom allergy. In fact, it provides a faster tolerance, without significant differences regarding incidence of severe adverse effects, compared with traditional and rush protocols. It can be adopted for all patients, even children and teenagers.

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INTRODUCTION

The occurrence of severe, even fatal, allergic reactions after Hymenoptera sting has been known for some time. Despite the use of purified venoms and the improvement of diagnostic and therapeutic means, Hymenoptera venom allergy still is epidemiologically significant: 0.15% to 3% of the general population has a personal history of systemic reactions caused by Hymenoptera stings.¹ Clinical manifestations range from local (edema, erythema, lymphadenitis, lymphangitis) to systemic reactions (urticaria-angioedema syndrome, severe generalized reactions involving the respiratory tract and the cardiovascular apparatus), ending with anaphylactic shock. Systemic reactions are divided into 4 groups of severity according to Müller classification²: degree 1, generalized urticaria, itching, and anxiety; degree 2, any of these plus 2 of the following: angioneurotic edema, dizziness, constriction of chest, abdominal pain, nausea, vomiting, and/or diarrhea; degree 3, any of these plus 2 of the following: dyspnea, dysphagia, hoarseness or thickened speech, confusion, and/or feeling of impending disaster; and degree 4, any of these plus collapse, cyanosis, incontinence, and unconsciousness.

Specific immunotherapy, extensively used in the treatment of IgE-mediated allergic diseases, has been shown to be the

only effective way to reduce the risk of life-threatening re-sting systemic reactions from 27% to 61% (same or worse grade of reaction compared with the previous sting) to 2% to 3%.³ Specific immunotherapy is administered by subcutaneous injections of progressively increasing doses of pure venom extract to reach the maintenance dose of 100 μg , generally considered adequate.⁴

Since 1974, when the first attempt of immunotherapy was performed, many protocols of different duration have been devised.^{5,6} Apart from traditional regimens, which require several weeks, rush protocols are available to achieve the target maintenance dose in 3 to 7 days and to induce a faster tolerance before the onset of the flying season of insects.^{7–12} There are also cluster, modified rush schedules, with initial administrations every 15 to 30 minutes, that reach the maintenance dose in 6 weeks. Both traditional and rush desensitizing treatments have been used for many years and have been shown to be effective and safe. In the past few years, some ultrarush protocols have achieved the dose of 100 μg in a few hours. Their safety is controversial because of a potentially higher frequency of severe systemic reactions.¹³ Some authors¹⁴ have more recently used an ultrarush (210 minutes) protocol, which resulted in fewer systemic reactions compared with traditional and rush ones. Its efficacy and safety have been well established. The purpose of our study is to demonstrate the safety and effectiveness of a modified ultrarush (150 minutes) desensitizing protocol in venom-allergic patients.

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METHODS

We studied 57 patients (40 males and 17 females) aged 11 to 68 years (among them two 11-year-olds, two 12-year-olds, two 15-year-olds, and a 16-year-old patient; 6 males and 1 female). They all had a personal history of systemic reactions to Hymenoptera sting. Forty-eight were allergic to Vespidae venom and 9 to bee venom (Table 1). The diagnosis was made on the basis of an accurate allergological evaluation (skin tests, specific IgE).

Prick and intradermal tests with Hymenoptera venom purified extracts (Pharmalgen, 100 µg/mL; ALK-Abello, Hørsholm, Denmark), diluted 1:10,000, 1:1,000, 1:100 (0.01, 0.1, and 1 µg/mL, respectively), were performed on the volar surface of the forearm.¹⁵ Negative (glycerin solution) and positive (0.1% histamine) controls were performed too. Skin test results were read after 20 minutes; a wheal diameter larger than 4 mm was considered a positive response.

Total and specific IgE levels for honeybee, *Vespa* wasp, *Polistes* wasp, and *Vespa crabro* venoms and eosinophilic cationic protein (ECP) levels were determined in the serum by means of fluorescent enzyme immunoassay (UniCAP System; Pharmacia, Uppsala, Sweden). In vitro detection of specific IgG4 antibodies was obtained by commercially available fluorescent enzyme immunoassay (CAP-FEIA; Pharmacia). Results below 0.35 kU/L were considered negative. Total IgE, specific IgG, and ECP levels, even though not necessary for the diagnosis, were measured to study patients' basal conditions and changes after 1 year of desensitization.

The clinical trial was conducted in the Department of Allergology of Policlinic A. Gemelli, Rome, Italy, in accordance with good clinical practice, after being approved by our hospital's ethic review board. All patients gave a fully informed, written consent to the desensitizing treatment. Parental consent was obtained for children included in the study.

Table 1. Clinical Data of Patients Receiving Ultrarush Venom Immunotherapy

Variable	Bee venom	Vespidae venom
No. of patients	9	48
Age range, y	11–62	11–68
Sex, F/M	2/7	15/33
Grade of field sting reactions, No. (%) [*]		
I		
II	2 (22)	10 (21)
III	5 (56)	13 (27)
IV	2 (22)	25 (52)
Adverse effects, No. (%)		
Mild local reactions	2 (22)	8 (17)
More severe local reactions	2 (22)	4 (9)
Mild systemic reactions	1 (11)	3 (6)
Field sting reactions after desensitization, No. (%)		
Local reactions	3 (33)	20 (42)
Systemic reactions		

^{*} According to Müller classification.²

We used an ultrarush (1-day hospitalization) modified protocol^{13,14}: increasing doses of Hymenoptera venom (Pharmalgen; ALK-Abello) were administered subcutaneously every 30 minutes, starting with an initial dose of 0.1 µg, to a cumulative dose of 101.1 µg administered in 2.5 hours (Table 2). The maintenance dose (100 µg) was administered after 15 days and thereafter once a month. Pulse rate, blood pressure, and peak expiratory flow rate (PEFR) were recorded during the desensitization. Full emergency resuscitation equipment was readily available.

The ECP, total IgE, specific IgE, and IgG4 levels of venom insect allergic patients were measured 24 hours, 15 days, and 1 year after the desensitization. Antihistamines were withheld for 15 days before and during desensitization to not underestimate the incidence of adverse effects.

The Shapiro-Francia test was used to evaluate normal distribution of raw data. Values of IgG4 and IgE did not fit with normal distribution. The Wilcoxon test for paired data was used to evaluate variations of IgG4 and IgE at different times (basal and 24 hours, 15 days, and 1 year after the desensitization). The Bonferroni correction for multiple comparisons was used, with the *P* value set at .01. Stata statistical software version 6.0 (Stata Corp, College Station, TX) was used to perform statistical analysis. Skin tests were performed again 1 year after the desensitization.

RESULTS

All patients were diagnosed as having IgE-mediated allergy to Hymenoptera venom. A personal history of atopy (allergic rhinoconjunctivitis and/or asthma) was found in 7 patients (12%). Fifty patients had positive skin test results to the insect venom, which had caused clinical manifestations. Seven patients had negative skin test results (5 Vespidae- and 2 bee venom-allergic patients) with high serum levels of specific IgE. They all underwent the ultrarush desensitizing treatment. The treatment was successfully completed by all patients but 1, who was allergic to Vespidae venom and had to discontinue treatment because of occurrence of a hypertensive crisis not related to the desensitizing treatment (he had hypertension and was taking calcium antagonists). The other patients did not manifest any modification of pulse rate, blood pressure, and PEFR during desensitization. The interval between the last allergic reaction and the initiation of desensitization was 6 to 36 months.

Table 2. Ultrarush Desensitizing Protocol^{*}

Dose administered, µg	Time, min
0.1	0
1	30
10	60
20	90
30	120
40	150

^{*} The cumulative dose was 101.1 µg. The maintenance dose was 100 µg administered on the 15th day and thereafter once a month.

Among the 56 treated patients, 36 (64%) did not show any reaction during and immediately after the desensitization, 10 (18%) had a slight local reaction, and 6 (11%) manifested a more severe local reaction. Only 4 patients (7%) presented a mild systemic reaction (malaise, generalized itching, dizziness, pain in the side of injection) that required oral and intramuscular administration of antihistamines and intravenous administration of corticoids. In these 4 patients, the previous sting had caused second-degree (2 patients) and fourth-degree reactions (the other 2 patients). Three of these patients had high levels of specific IgE before the desensitization: 100 (class 4), 15.7 (class 3), and 14.4 kU/L (class 3). One patient had low levels of serum IgE (2.4 kU/L, class 2). No statistically significant correlation was found between adverse reactions during the desensitization and the field sting reactions, the degree of positive skin test results, and specific IgE levels. No one experienced life-threatening reactions. Also, young patients perfectly tolerated the desensitizing treatment: only one of them presented a mild local reaction that did not require therapy.

The mean value of venom-specific IgE had an increase after 24 hours ($P = .06$, not statistically significant) and a further increase after 15 days ($P < .01$) and showed a slight

decrease after a year ($P = .06$, not significant), remaining higher than initial levels. The mean value of venom-specific IgG showed an increase after 15 days ($P < .01$), which remained statistically significant ($P < .01$) after a year (Fig 1). The mean value of total IgE had an increase after 24 hours that became sharper after 15 days and showed a slight decrease after a year, remaining higher than initial levels (data are not statistically significant). The mean ECP value, which was higher than normal before the treatment, showed a slight decrease and became normal ($<20 \mu\text{g/L}$) after a year (not statistically significant).

One year after the desensitization, skin prick test results turned negative in 15 patients (27%, decrease of 3.5 log of threshold dilution), whereas they decreased in 14 patients (25%, decrease of 1 log), did not vary in 14 patients (25%), and increased in 6 patients (11%, increase of 1 log). In the remaining 7 patients (12%), skin prick tests were not performed again.

During the 1-year follow-up period, 3 honeybee venom- and 20 Vespidae venom-allergic patients (including a 12-year-old, a 15-year-old, and a 16-year-old) were re-stung by the insect they had been allergic to and presented only mild

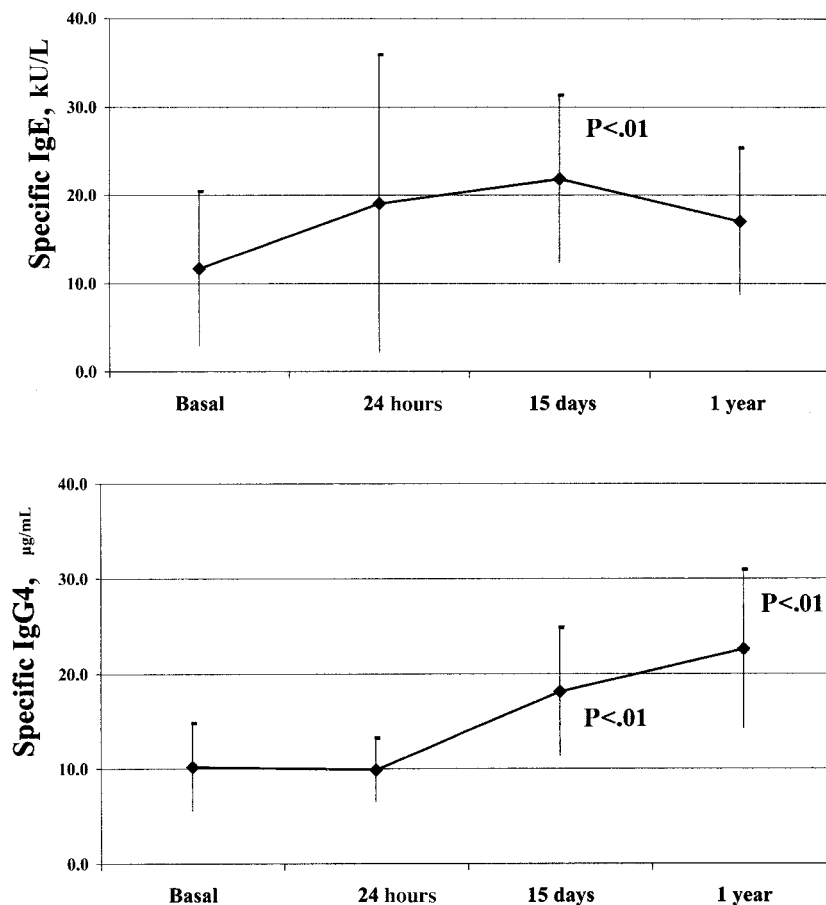


Figure 1. Variation of mean specific IgE and IgG4 levels during the 1-year follow-up period. Error bars indicate confidence intervals.

local reactions. Only a Vespidae venom-allergic patient was re-stung twice (the first time after a year) without problems.

DISCUSSION

Hymenoptera venom allergy is still an epidemiologically significant problem. Male predominance (male-female ratio, 40:17) is probably due to men's greater exposure to insect stings at work (beekeepers, farmers) or during spare-time activities. Some studies show how approximately 50% of those allergic to insect venom are atopic.⁹ It has been demonstrated that an atopic background may influence the natural history and severity of clinical manifestation in venom-allergic patients.^{16,17} In our group of patients, atopy does not represent an important risk factor. Only 12% were atopic, and the incidence of anaphylactic symptoms was not significantly higher among them.

Specific immunotherapy is the only effective therapeutic tool for the management of Hymenoptera venom-allergic patients who experience generalized reactions to insect sting. Our data show how specific IgE and IgG4 levels rapidly vary since the 15th day of treatment. They confirm the results of another study on ultrarush immunotherapy, showing no change in specific IgG levels during the first hours of treatment and a significant increase by day 15.¹⁸ During traditional and rush treatments, such immunological modifications require a longer period to occur.

In samples collected after 1 year, specific IgE levels remained higher than normal. Some studies show a decrease of specific IgE serum levels with both traditional and rush methods.⁷⁻¹² On the contrary, the specific IgG4 mean value in this study showed a further increase. Such increases have been previously documented in other studies of traditional and rush desensitizations but happened later compared with our results.

Our patients also had high basal levels of ECP due to an eosinophilic activation probably related to Hymenoptera venom allergy. Such an increase has never been previously documented in works dealing with Hymenoptera venom allergy. After the desensitization, the ECP mean value decreased, especially in the bee venom-allergic group.

Our protocol has been shown to be effective: 23 of our patients (3 honey bee-, 20 Vespidae venom-allergic patients) were re-stung during the 1-year follow-up period, manifesting only local reactions. The treatment provided a faster tolerance. Rapid immunological modifications corresponded to an earlier occurrence of clinical tolerance to Hymenoptera sting: 2 patients were re-stung 7 to 15 days after the desensitization, showing only local erythema (second- and fourth-degree reactions, respectively, after the previous sting). During traditional and rush treatments, such protective effects occur later.

The only hypothetical risk related to an ultrarush protocol is the occurrence of adverse effects due to the administration of increasing doses of venom within a very short period (2.5 hours). These adverse effects do not seem to happen fre-

quently. The incidence of systemic reactions during the traditional desensitization is 17%.⁸

In a new study dealing with ultrarush desensitizing treatment performed in 210 minutes, 12.79% of patients manifested systemic reactions on day 1, with a significant difference in honeybee (30%) vs yellow jacket (3.2%) and wasp (6.1%) venom-allergic patients.¹⁴ Our study confirms that the safety of the ultrarush regimen is higher than the traditional one: only 4 (7%) of our patients presented with mild systemic reactions (malaise, generalized itching, pain in the side of injection, dizziness) that required antihistamines and corticoids. None of them manifested life-threatening reactions. Adrenaline has never been used. The honeybee venom was perfectly tolerated by 89% of patients. Among our patients with a history of grade III (18 patients) and IV (27 patients) field sting reactions, only 2 patients (4.4%) manifested adverse effects (mild systemic reactions not requiring adrenaline). In their study, the frequency of systemic reactions in children was 10.8%, not significantly different if compared with adults (11.2%). Three children experienced severe symptoms (grade III and IV). Our protocol has been shown to be effective and safe also in young patients. In fact, it was successfully performed in 4 children (aged 11–12 years) and 2 teenagers (aged 15–16 years). They all perfectly tolerated the desensitization without adverse effects except for 1, who presented with slight erythema in the side of injection. Three of them were re-stung without experiencing important allergic reactions.

In conclusion, our protocol of ultrarush (150 minutes) specific desensitization represents an important tool in the management of Hymenoptera venom-allergic patients, because it more rapidly induces a variation of immunological parameters and the occurrence of a clinical tolerance, if compared with traditional protocols, without important adverse effects. Even though we did not use any preventive medication during the performing of desensitization, administration of antihistamines should be recommended to improve treatment tolerance by further reducing the occurrence of adverse effects. Some authors¹⁹ even attribute an improved effectiveness of immunotherapy to this pretreatment.

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