

Analysis of Safety, Risk Factors and Pretreatment Methods during Rush Hymenoptera Venom Immunotherapy

Lucyna Gorska^a Marta Chelminska^a Krzysztof Kuziemski^a Marcin Skrzypski^a
Marek Niedoszytko^a Iwona Damps-Konstanska^a Amelia Szymanowska^a
Alicja Siemińska^a Beata Wajda^a Adrianna Drozdowska^a Marek Jutel^b
Ewa Jassem^a

^aDepartment of Allergology, Medical University of Gdańsk, Gdańsk, and ^bDepartment of Internal Medicine, Medical University of Wrocław, Wrocław, Poland

Key Words

Hymenoptera · Venom immunotherapy · H₁/H₂ receptor blockers

Abstract

Background: The safety profile of venom immunotherapy is a relevant issue. We evaluated the frequency of severe adverse events (SAE), associated risk factors, retrospective comparison of pretreatment protocols including solely H₁ receptor blockers and a combination of H₁ and H₂ receptor blockers during rush Hymenoptera venom immunotherapy.

Methods: The study group comprised 118 patients. The treatment was initiated according to a 5-day rush protocol with the use of standardized venom allergens of either wasp or honeybee. **Results:** During the rush induction, side effects occurred in 18 patients (15.2%), whereas SAE were present in 7 patients (5.9%). Twelve out of 18 (66.6%) developed anaphylactic reactions on the fourth day of the rush protocol, with the majority of cases at a dose of 40 or 60 µg of the venom extract ($p = 0.001$). The frequency of SAE was also significantly higher on the fourth day than thereafter ($p = 0.0001$) as well as in patients allergic to bee venom ($p = 0.049$). All systemic side effects were more frequent in wom-

en ($p = 0.0065$). However, this relation was not true when SAE were considered ($p = 0.11$). A higher percentage of SAE was observed in the subjects pretreated with both H₁ and H₂ receptor antagonists than in those pretreated with H₁ blocker only (8.8 vs. 4.1%); however, the difference was not significant.

Conclusions: Considerable severity of allergic adverse events requires particular attention to patients allergic to bee venom and during rush phase, especially when rapidly increasing doses are administered. Pretreatment with H₂ blockers is debatable and warrants further investigation.

Copyright © 2008 S. Karger AG, Basel

Introduction

Hymenoptera venom allergy poses a significant challenge to clinicians [1]. Following a sting, sensitized individuals, apart from extensive and persistent local reaction, occasionally develop severe systemic response including anaphylactic shock which may be fatal [2]. It is estimated that up to 5% of individuals stung by an insect may develop anaphylactic reactions [3, 4]. There are several professions imposing a higher risk of exposure: pastry cooks, forestry workers and beekeepers. Among the

latter group, the frequency of allergic reactions to bee stinging varies between 14 and 43% [5, 6]. In Poland, anaphylactic reactions most commonly develop after stings of the honeybee (*Apis mellifera*, family Apidae) or the wasp (*Vespula vulgaris* and *Vespula germanica*, family Vespidae, subfamily Vespinae). Less common is an allergy to other members of Vespinae: hornets (*Vespa crabro*) and other wasps (*Dolichovespula* species). Recently, an increase in the incidence of bumblebee (*Bombus*, Apidae family) stinging has been observed, as these insects are increasingly used for flower pollination in glasshouses [7].

Hymenoptera venom immunotherapy (VIT) induces a long-term tolerance to insect stings in patients with a history of severe systemic anaphylactic reactions and is considered an effective [8] and safe procedure [9]. In spite of the relatively low incidence of severe adverse events (SAE) demonstrated in a large multicenter study [9], life-threatening reactions during treatment were occasionally reported [10]. Smaller studies provided discordant data; in their results, III–IV grade reactions (according to Mueller's scale) during rush phase varied from 0 to 16% [11–13]. At least 4 different protocols of the initial phase of immunotherapy are used: conventional, rush, ultrarush and cluster, which differ according to cumulative dose of allergen and time of procedure [14, 15]. Rush [14, 16, 17] and ultrarush [18, 19] protocols are widely used and described as safe and efficacious, although no comparative studies were performed [15]. The ultrarush regimen is definitely cheaper and faster. Different pretreatment protocols are used [15]; however, recent data indicate that pretreatment with H₁ receptor blockers alone may increase the safety and effectiveness of VIT [20, 21].

The aims of this study were (1) the evaluation of the frequency of SAE, (2) associated risk factors, and (3) retrospective comparison of pretreatment protocols including H₁ receptor blockers alone and a combination of H₁ and H₂ receptor blockers during rush Hymenoptera VIT.

Materials and Methods

The study group comprised a consecutive series of 118 patients from 1 institution, treated with immunotherapy due to Hymenoptera allergy in the years 2002–2006. There were 65 women and 53 men; the mean age at the time of treatment initiation was 41.5 years (range 16–73). None of the patients were treated with either angiotensin-converting enzyme inhibitors or β -blockers.

The diagnostic work-up included a history of anaphylactic reaction (grade III or IV according to Mueller's scale) following insect sting, positive intracutaneous allergen serial dilution tests and detection of specific antibodies (sIgE) in serum.

Ninety and 28 patients were treated with the standardized allergen of wasp venom (Venomenhal Wespe) or bee venom (Venomenhal Biene; HAL-Allergy, Düsseldorf, Germany), respectively. Twenty-five patients presented with allergy to both bee and wasp allergens. In this group, the decision regarding VIT was based on the patients' history, the risk of exposure, the extent of the skin reaction in the intracutaneous test and the level of sIgE antibodies. In total, 18 patients who primarily received wasp immunotherapy were also hypersensitive to bee allergens, whereas 7 patients who were administered honey bee allergen extracts had concomitant wasp venom allergy.

Patients treated in the years 2002–2005 ($n = 45$) were pretreated with oral H₁ receptor blockers (20 mg of either cetirizine or loratadine, orally) and additionally received H₂ receptor blockers (300 mg of ranitidine, orally). Therapy of the patients cured in the years 2005–2006 ($n = 73$) was reduced to H₁ receptor blockers according to data on higher efficacy and safety [15].

The initiation phase was administered according to a 5-day protocol. The cumulative dose of allergen during the initiation phase of immunotherapy was 486.46 μ g. Subsequently, allergen injections (100 μ g, i.e. $2 \times 50 \mu$ g s.c.) were given every 4–6 weeks as a 5-year maintenance therapy.

Side effects of VIT stage III or IV according to Mueller's scale were defined as SAE [13]. The safety of the 5-day rush protocol and maintenance phase was assessed.

Statistical Analysis

Statistical analysis included the following variables: age, sex, grade of anaphylactic reaction following a field insect sting, comorbidities, side effects of immunotherapy and concomitant chronic treatment. The data were analyzed with the use of a χ^2 test (Statistica 7.0). A p value ≥ 0.05 was considered significant.

Results

Adverse Reactions during Rush Phase

During the rush induction, 18 patients (15.2%) developed adverse events. Eight patients (6.8%) developed a grade I anaphylactic reaction, 3 (2.5%) a grade II reaction, 4 (3.4%) a grade III reaction and 3 (2.5%) a grade IV anaphylactic reaction (table 1).

In total, 7 patients had SAE during rush. In 1 patient with a grade IV anaphylactic reaction, the signs of urticaria pigmentosa occurred in the short time thereafter; subsequently, mastocytosis was diagnosed. Patients who developed severe systemic reactions were treated with dexamethasone intravenously and with antihistamines (antazoline hydrochloride) intramuscularly. In cases of associated bronchospasm, patients were given β_2 -mimetics (salbutamol sulfate) in nebulization. Additionally, grade IV reactions were managed with intramuscular

adrenaline. In no case did the side effects result in discontinuation of immunotherapy.

Twelve out of 18 (66.6%) systemic reactions occurred on the fourth day of the rush protocol after a dose of 40 or 60 µg of the venom extract (fig. 1). The frequency of all anaphylactic events on the fourth day was significantly higher than during the remaining days ($p = 0.001$; table 1). Similarly, SAE were also more frequent at this time of therapy ($p = 0.0001$).

Eight out of 28 patients (28.6%) treated with honeybee and 10 out of 90 patients (11.1%) treated with wasp VIT developed adverse events. The frequency of all systemic side effects in the group treated with honeybee allergen was higher, but not significant ($p = 0.06$). Bee vaccinations also carried a higher risk of SAE ($p = 0.049$). Systemic anaphylactic reactions occurred in 16 of 65 women (24.6%) and in 2 of 53 men (3.8%; $p = 0.0065$). However, gender was not related to a higher number of SAE ($p = 0.11$).

Eleven of 45 patients (24.4%) pretreated with H_1 and H_2 receptor inhibitors compared with 7 of 73 patients (9.6%) pretreated with H_1 blockers alone developed systemic side effects ($p = 0.065$). SAE occurred in 4 (8.8%) and 3 (4.1%) patients ($p = 0.3$).

A trend ($p = 0.084$) towards higher frequency of SAE in the group of patients with an sIgE level >0.7 was observed.

Adverse Reactions during the Maintenance Treatment

A total of 1,740 injections were given during the maintenance phase. Eight patients (7 women and 1 man) experienced side effects (0.46% of all maintenance injections) – 3 had a grade I and 4 had a grade III anaphylactic reaction. The signs observed in these patients included urticaria, pruritus, anxiety and dyspnea. These reactions always resolved following treatment and never recurred. One patient had a grade IV anaphylactic reaction including tachycardia, hypotension and syncope. Treatment with adrenaline was effective, and the systemic anaphylactic reaction did not return. Two patients experienced adverse reactions both during rush protocol and the maintenance phase of treatment.

At the beginning of the maintenance phase, intense local side effects (erythema, swelling and pain) were commonly observed. In 8 of the 9 cases, side effects occurred after administration of the first dose of the allergen (50 µg; $p = 0.02$). These signs tended to diminish in the course of treatment. No significant correlations were found (during both rush and maintenance phase) between the occurrence of systemic anaphylactic reactions and co-

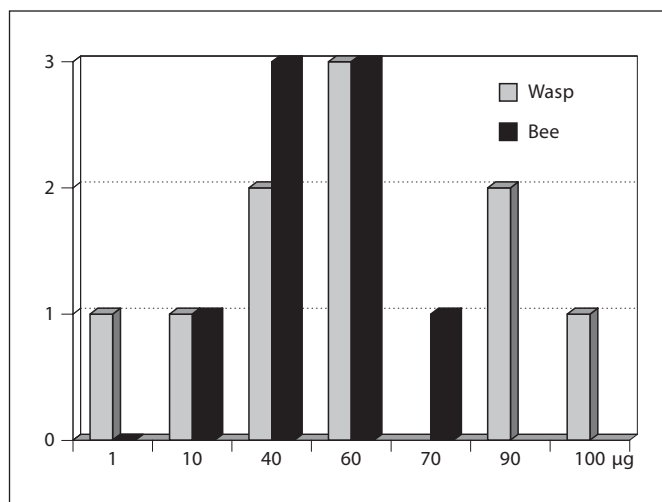


Fig. 1. All systemic reactions during the rush phase in relation to a particular allergen dose.

Table 1. SAE during the rush phase

Characteristic	Wasp allergy	Bee allergy	Total
Gender			
Male	0	1	1
Female	3	3	6
Grade of reaction			
III	1	3	4
IV	2	1	3
Fourth day of rush	2	3	5
Positive sIgE			
Class I–II	1	1	2
Class III–IV	2	3	5
H_2 blocker premedication	2	2	4

morbidities, the extent of skin reactivity in intradermal testing with venom allergens and the sIgE level (both performed prior to immunotherapy).

Discussion

The incidence of adverse events in the present study was 15.2%, including 2.5% severe anaphylactic reactions. These results are in line with other reports on similar populations (table 2). The incidence of all anaphylactic reactions associated with the rush protocol was estimated at 10–17% [9, 12, 16–18, 22]. Severe reactions requiring

Table 2. Safety profile in different rush protocols

Study/country	Patients	Duration of rush protocol days	Bee/wasp allergy	% of all systemic reactions	SAE	Total dose of allergen, µg
Brehler et al. [18]/Germany	335	3–6	32/303	31.2	–	406.111–411.111
Pasaoglu et al. [25]/Turkey	14	7	7/7	28.5 (all reactions in 1 woman)	–	NR
Wenzel et al. [17]/Germany	178	7	25/153	17.9	10	555.55
This study/Poland	118	5	28/90	15.2	7	486.46
Westall et al. [12]/Australia	68	5	8/60	38	11	NR
Mingomataj et al. [28]/USA	37	4	22/15	43 (33 patients)	–	428.48

NR = Not reported.

the use of adrenaline have been reported with different frequencies. The highest rate was described in the selected population of patients with bee venom allergy [23].

In a similar study performed on 101 patients, Sturm et al. [14] reported a decreased risk of systemic anaphylactic reactions during the rush protocol (6.9%). This discrepancy may be partly explained by the lower cumulative allergen dose used in this study in comparison with ours (332.51 and 486.46 µg, respectively). Provided that the efficacy of the treatment remains unchanged, this difference in the incidence of side effects calls for unification of rush protocols towards the optimal cumulative dose.

No randomized studies were made to compare the safety profile between different protocols. Conflicting data pointing to the conventional [24], rush [14, 16, 17, 25] or ultrarush [18, 19] method as safe result from comparing different populations, extracts, preparations (aqueous or depot) and a variety of comorbidities in different populations. Brehler et al. [18] showed a decreased incidence of side effects during 2-day ultrarush VIT as compared with 3- to 6-day and 7- to 9-day protocols. In this study, the risk of systemic side effects was decreased when the protocol was shortened to 2 days. Birnbaum et al. [19] even described a 210-min-lasting regimen. It is worth mentioning that the cumulative dose of allergen achieved in the ultrarush method is lower than in the rush method.

The mechanism of inducing tolerance in the VIT is not clear [15, 26]. It is postulated that affecting the threshold of mast cell and basophil activation may be responsible for rapid allergen tolerance [26]. Retrospective analysis of the efficacy of both methods and an understanding of the molecular basis behind VIT may help choose a better protocol.

Risk factors of adverse events in the present study were female gender, bee venom allergy and rush protocol. Similar observations were made previously where adverse reactions during VIT were more frequently observed in women [18], in patients allergic to honeybee venom [9, 12, 14] and during the rapid vaccine dose intensification [9, 19]. Other factors, including age, asthma and atopy or concurrent treatment with β-blockers or angiotensin-converting enzyme inhibitors were occasionally implicated as risk factors.

The superiority of pretreatment with H₁ receptor alone to the H₁-H₂ combination confirms previous findings. Increased safety of VIT may be obtained by pretreatment with antihistamines [23, 27]. Brockow et al. [20] showed that the use of H₁ receptor antagonists alone, or in combination with H₂ receptor antagonists, significantly reduced the risk of both local and systemic side effects during VIT. Moreover, administration of these agents enhanced the efficacy of VIT. In this study, all patients received pretreatment with H₁ receptor antagonists, whereas 45 patients received H₂ receptor antagonists in addition. The incidence of anaphylactic reactions in patients treated with both H₁ and H₂ receptor antagonists was doubled compared with those receiving H₁ receptor antagonists alone. Similarly, the percentage of SAE was higher in the group pretreated with H₂ receptor antagonists (8.8% with H₂ blockers vs. 4.1% without). This observation may account for the role of H₂ receptor in tolerance induction [21].

This study showed that the majority of VIT-related anaphylactic reactions occurred on the fourth day of the rush protocol, when a concentration of 100 µg/ml of the allergen was reached. The maintenance phase of VIT was associated with a significantly lower risk of side effects compared with the initiation phase. In our series, the risk

of an anaphylactic reaction after a single injection was 0.46%, and the risk of grade IV anaphylactic reactions was 0.05%. Similarly, in the multicenter study [9] including 840 patients, the risk of the occurrence of anaphylactic reactions during the maintenance phase was 0.5%. Despite the relatively low risk of adverse anaphylactic reactions during VIT, their severity warrants further research aiming at the improvement in therapy safety.

In conclusion, severe systemic reactions during the rush phase most frequently occur at a concentration of 100 µg/ml of allergen, on the fourth day of immunotherapy and in patients with bee venom allergy. During the maintenance phase, systemic side effects mostly occur during the administration of the first dose of allergen (50 µg). In most cases, administration of H₁ receptor blockers alone, rather than in combination with H₂ receptor blockers, is most effective in reducing side effects.

References

- Golden DBK: Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115:439–447.
- Muller U, Mosbech H, Blaauw P, Dreborg S, Malling HJ, Przybilla B, et al: Emergency treatment of allergic reactions to Hymenoptera stings. *Clin Exp Allergy* 1991;21:281–288.
- Charpin D, Birnbaum J, Vervloet D: Epidemiology of hymenoptera allergy. *Clin Exp Allergy* 1994;24:1010–1015.
- Novembre E, Cianferoni A, Bernardini R, Veltroni M, Ingargiola A, Lombardi E, et al: Epidemiology of insect venom sensitivity in children and its correlation to clinical and atopic features. *Clin Exp Allergy* 1998;28:834–838.
- Annala I: Bee venom allergy. *Clin Exp Allergy* 2000;30:1682–1687.
- Nittner-Marszalska M, Liebhart J, Liebhart E, Dor A, Dobek R, Obojski A, et al: Prevalence of Hymenoptera venom allergy and its immunological marker current in adults in Poland. *Med Sci Monit* 2004;10:324–329.
- Gawlik R, Nittner-Marszalska M: *Allergology in Practice*. Łódź, Mediton, 2003.
- Ross RN, Nelson HS, Finegold J: Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity. A meta-analysis. *Clin Ther* 2000;22:351–358.
- Mosbech H, Muller U: Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. *European Academy of Allergology and Clinical Immunology*. *Allergy* 2000;55:1005–1010.
- Wolf BL, Hamilton RC: Near-fatal anaphylaxis after Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1998;102:527–528.
- Poli F, Long G, Parmiani S: The safety and efficacy of immunotherapy with aluminum hydroxide-adsorbed venom extract of *Vespula* spp. An open, retrospective study. *Hymenoptera Allergol Immunopathol* 2001;29:191–196.
- Westall GP, Thien FC, Czarny D, O'Hehir RE, Douglas JA: Adverse events associated with rush Hymenoptera venom immunotherapy. *Med J Aust* 2001;174:227–230.
- Mueller HL: Insect allergy. *Pediatr Clin North Am* 1959;6:917–952.
- Sturm G, Kranke B, Rudolph C, Aberer W: Rush hymenoptera venom immunotherapy: a safe and practical protocol for high-risk patients. *J Allergy Clin Immunol* 2002;110:928–933.
- Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U: Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;60:1459–1470.
- Laurent J, Smiejan JM, Bloch-Morot E, Herman D: Safety of Hymenoptera venom rush immunotherapy. *Allergy* 1997;52:94–96.
- Wenzel J, Meissner-Kraemer M, Bauer R, Bieber T, Gerdson R: Safety of rush insect venom immunotherapy. The results of a retrospective study in 178 patients. *Allergy* 2003;58:1176–1179.
- Brehler R, Wolf H, Kutting B, Schnitker J, Luger T: Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. *J Allergy Clin Immunol* 2000;105:1231–1235.
- Birnbaum J, Ramadour M, Magnan A, Vervloet D: Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors. *Clin Exp Allergy* 2003;33:58–64.
- Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J: Efficacy of antihistamine pretreatment in the prevention of adverse reactions to hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1997;100:458–463.
- Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J, et al: Histamine regulates T-cell and antibody responses by differential expression of H₁ and H₂ receptors. *Nature* 2001;413:420–425.
- Przybilla B, Ring J, Griesshammer B, Braun-Falco O: Rush hyposensitization with Hymenoptera venoms. Tolerance and results of therapy. *Dtsch Med Wochenschr* 1987;112:416–424.
- Berchtold E, Maibach R, Muller U: Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy* 1992;22:59–65.
- Youlten LJ, Atkinson BA, Lee H: The incidence and nature of adverse reactions to injection immunotherapy in bee and wasp allergy. *Clin Exp Allergy* 1995;25:159–165.
- Pasaoglu G, Sin BA, Misirligil Z: Rush hymenoptera venom immunotherapy is efficacious and safe. *J Investig Allergol Clin Immunol* 2006;16:232–238.
- Jutel M, Akdis M, Blaser K, Akdis CA: Mechanisms of allergen specific immunotherapy – T-cell tolerance and more. *Allergy* 2006;61:796–807.
- Muller U, Hari Y, Berchtold E: Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol* 2001;107:81–86.
- Mingomataj E, Priftanji A, Qirko E, Dinh QT, Fischer A, Peiser C, et al: Specific immunotherapy in Albanian patients with anaphylaxis to hymenoptera venoms. *BMC Dermatol* 2002;2:11–16.