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ORIGINAL ARTICLE

A simple 3-day "rush" venom immunotherapy protocol: documentation of safety

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Abstract
Background: Venom immunotherapy (VIT) is the only effective treatment for hymenoptera hypersensitivity, but conventional protocols require a few weeks.
Objective: We present the safety of a 3-day "rush" protocol that requires only 7 injections and 255 mgr cumulative dose before the 100 μg maintenance dose.
Methods: Forty-nine patients (33 males, 16 females) of mean age 43.57 ± 12.9yrs received "rush" VIT. Only 7 injections were required until the maintenance dose of 100 mgr was reached on Day 5. On Day 1, four injections were administered with initial dose of 5 mgr and total dose of 75 μg. On Day 3 a cumulative dose of 180 mgr was administered in three injections (40 mgr, 60 mgr and 80 mgr). A dose of 100 mgr was administered on Day 5. Twenty-nine individuals were treated with Honey-Bee venom; 18 with Common wasp; 5 with Paper Wasp; while 13 patients received Mixed Vespid preparation. Inclusion criteria were documented IgE-mediated allergy with intradermal sensitivity to $\leq$0.1 mgr/ml venom concentration and concomitant detection of specific venom IgE $\geq$0.35 kU/l.
Results: All patients reached the maintenance dose. Forty-nine patients received 65 immunotherapy courses, resulting in 1520 injections. Thirty-three systemic reactions: 7 during building phase (1.5%); and 26 in the maintenance dose (2.4%) were observed in 9 patients. The percentage of reactions/total injection number was 2.2%; all reactions were mild-to-moderate. Fourteen patients reported documented field stings at least two months after VIT onset with only one reported mild systemic reaction.

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Conclusion: We propose a simple ''rush'' VIT protocol in an outpatient setting as an easy-to-perform alternative option for VIT induction phase.

Introduction

Systemic hypersensitivity reactions to Hymenoptera stings are estimated to occur in 0.3 to 7.5% of the general population according to well-designed epidemiological studies.[1] It is reported that at least fifty individuals die because of insect stings every year in the USA, and the true mortality rate may be even higher because sudden deaths may be mistakenly ascribed to other causes, such as heart attacks or strokes.[2]

Venom Immunotherapy (VIT) is regarded as the only effective treatment for insect venom allergy; it reduces the risk of future systemic reactions and improves the quality of life.[3] Furthermore, it is estimated that VIT provides protection to future stings in about 95% of individuals with a previous history of a systemic reaction.[2] Generally, the results seem to be more encouraging in Common wasp (Cw), the so called Yellow Jacket in the USA, in comparison with Honey bee (Hb) venom allergic patients, and in children compared to adults.[4,5]

Since venom extracts for immunotherapy were introduced almost four decades ago, several VIT protocols have been proposed in order to maximise protection, minimize side-effects and optimize patient convenience. With the conventional slow protocols it may take 3–6 months to attain the maintenance dose,[6–8] while with ''rush'' and ''ultra rush'' protocols, the maintenance dose is being reached within several days and hours respectively.[9–13] Rush and ultra rush protocols provide protection for future field stings earlier than the conventional slow protocols, a useful development for highly exposed individuals such as bee-keepers and for patients referred to the specialist just prior to the start of the insect season. Although these protocols have been associated with higher incidence of side-effects, recent studies confirm that their safety is comparable to slower regimens[10,14,15] and so they could represent the treatment of choice even in patients who have previously experienced systemic reactions during conventional VIT.[16]

We present our five-year experience with a 5-day rush protocol with only 7 injections to reach the maintenance dose.

Patients-methods

Forty nine consecutive individuals (33 males, 16 females) of mean age 43.57 ± 12.9 years (range 14–72) with a documented history of systemic reactions to Hymenoptera stings were included in a prospective study during a five-year time period. All patients underwent a rush VIT protocol with aqueous venom preparations; Alyostal® Venin Vespula, Alyostal® Venin Polistes, and Alyostal® Venin Apis Mellifera (Stallergenes SA, France) were used in patients treated with single venoms, while Pharmalgen® Mixed Vespid Vespula spp, Dolichovespula arenaria, Dolichovespula maculata, (ALK Abello, Denmark) in mixed-vespid treated patients. During maintenance phase the same venom extracts were also used. The diagnosis of insect sting allergy was based on definite history of a previous systemic reaction to an insect sting combined with the in vivo ± in vitro documentation of specific IgE sensitisation to insect venom, according to the guidelines of the EAACI Interest Group of Insect Venom Hypersensitivity.[17] For methodological reasons, allergic was considered every patient with skin reactivity and simultaneous detection of serum specific IgE against the same hymenoptera species. The reported systemic reactions caused by field stings were classified according to the Ring and Messmer classification system,[18] presented in Table 1.

Selection of immunotherapy specimens was based on clinical history combined with skin testing results ± serum specific IgE concentrations: patients with non-definite identification of the offending insect received VIT to all Hymenoptera species to which IgE sensitisation was detected. Mixed vespid specimen was used in patients who definitely stated history of reaction to European Hornet and in those with simultaneous Cw and Hornet reactivity.[19]

In vivo tests

Skin Prick tests were performed with standardised pure venom extracts of Hb, Cw, Paper Wasp, White Faced Hornet, and Yellow faced hornet venom (ALK-Abello, Denmark) at a concentration of 10 μg/ml. Histamine dihydrochloride (10 mg/ml) and normal saline dilution (0.9%) were used as positive and negative controls, respectively. Prick test was considered positive if a wheal at least 3 mm greater than the wheal produced by the control solution occurred.

Prick tests were followed by intradermal tests at progressively increasing concentrations (from 0.001 mgr/ml with ten-fold increase up to 1 mgr/ml). Intradermal tests were considered positive if a typical wheal and flare reaction pattern occurred after 20 mins with wheal diameter

Table 1 Classification of severity of reactions according to Ring and Messmer[18]

Grade	Skin	Gastrointestinal tract	Respiratory tract	Circulation
I	Pruritus, urticaria, flush			
II	Pruritus, urticaria, flush	Nausea	Dyspnoea, rhinorrhoea	Tachycardia, hypotension
III	Pruritus, urticaria, flush	Vomiting, incontinence	Bronchospasm, cyanosis	Loss of conscioussness
IV	Pruritus, urticaria, flush	Vomiting, incontinence	Respiratory arrest	Cardiac arrest

$\geq$5 mm at a concentration of 1 μg/ml or less. For methodological reasons, patients with positive intradermal testing only at 1 μg/ml were excluded from the study population.

In vitro tests

The concentration of serum specific IgE to Hb, Cw, Paper Wasp, White Faced Hornet; and Yellow faced hornet was measured with Pharmacia-UniCap-System™ (Pharmacia Diagnostics, Uppsala, Sweden). Any value $\geq$0.35 kU/l was considered as ''positive''.

Immunotherapy protocol

All patients received a 3-day rush protocol with aqueous venom extracts of Hb, Cw, Paper Wasp, and Mixed Vespid (Cw, Yellow Hornet, and White faced Hornet). The exact induction protocol is presented in Table 2. Only 7 injections were required until the maintenance dose of 100 μg for single venom preparations, and 300 μg for mixed vespid specimen, was reached on Day 5. On Day 1 four injections were administered with an initial dose of 5 μg and a cumulative dose of 75 μg. On Day 3, the cumulative dose of 180 μg was given divided into three injections (40 μg, 60 μg and 80 μg respectively). No premedication was used. All patients received the next injection of maintenance dose one week after the induction phase and then time intervals were further increased progressively. A six-week interval was achieved at the end of the first year, 8 weeks in the second year, and 12 weeks after three years of treatment.

All injections were applied subcutaneously to the outside surface of the upper arm. Vital signs and peak expiratory flow rate of all patients were recorded before every injection and at the end of the process. Full emergency resuscitation equipment was available at all times. There was an interval of 45 to 60 mins between two subsequent injections. In patients receiving more than one extract, the same protocol was performed; equal doses of both specimens were administered consecutively with a 90-min time interval. No hospitalisation was required. All patients signed an informed consent before VIT onset.

Local and systemic reactions after immunotherapy injections as well as field stings were recorded and any reported reaction was classified according to the classification system mentioned above.

Results

Forty-nine allergic patients received 65 immunotherapy courses, resulting in 1520 injections (455 during the building phase and 1065 during the maintenance phase). The VIT courses according to the venom species were: 29 to Honey Bee; 18 to Common Wasp; 5 to Paper Wasp; and 13 to Mixed Vespid preparation. Thirty-three of 49 patients received a single insect extract, while the remaining 16 received more than one specimen; in particular, 7 patients received Hb+Cw specimens, 8 Hb+Mixed Vespids and 1 Pw+Cw respectively.

All patients had experienced systemic reactions due to hymenoptera field stings, of I to III severity before initiation of VIT: 21 (43%) reported reaction severity I, 16 (33%) severity II, and 12 (24%) severity III. Mean duration of treatment was 2.4 years $\pm$1.2 ranging from six months to 5 years, with 31.0$\pm$15.1 injections per individual. All patients reached the maintenance dose of 100 μg (300 μg for Mixed Vespid extract). Large local reactions occurred in several patients; symptomatic treatment with topical application of ice and topical corticosteroid preparations were only used.

We recorded 33 systemic reactions, 7 during the building phase (1.5%) and 26 in the maintenance dose (2.4%). The percentage of reactions/total injection number was 2.2%. These reactions were observed in 9/49 (18.4%) patients of whom 7 (24.1%) received Hb venom and 2 (5.5%) received Cw venom. Five out of the reactors were treated with a single specimen; three with Hb and two with Cw while the remaining four reactors to Hb received treatment with a second specimen: two with Cw and two with Mixed Vespids. The risk of developing systemic reactions was estimated to be 0.046 per injection for Hb as compared to 0.0023 per injection for Cw. Five individuals (10.2%) experienced reactions during the rush protocol and 6 (12.2%) reacted during the maintenance phase, while 4/6 had not reacted during the building phase. The time distribution of these reactions during treatment is shown in Figure 1.

Referring to skin reactivity of immunotherapy reactors among 7 reactors to Hb, 5/7 were positive with 0.001 μg/ml intradermal testing and the remaining 2/7 with 0.01 μg/ml, while both patients reacting to Cw (2/2) had positive intradermal testing to 0.001 μg/ml. All skin prick tests were negative.

All systemic reactions were mild to moderate. Twenty five (75.7%) were classified as severity I and the remaining 8/33 (24.3%) as severity II. During the induction phase, all reactions were documented to be of severity I, and oral antihistamines were the only administered medication. In

Table 2 The 3-day venom immunotherapy protocol: induction phase

Injection	Day 1 (Monday) dose (μg)/volume (ml)	Day 3 (Wednesday) dose (μg)/volume (ml)	Day 5 (Friday) dose (μg)/volume (ml)
1	5	40	100
2	10	60	
3	20	80	
4	40		
Cumulative Dose (μg/ml)	75	180	100

For Mixed Vespid Specimen (300 μg/ml), each dose was tripled without modifying the administered volume per injection.

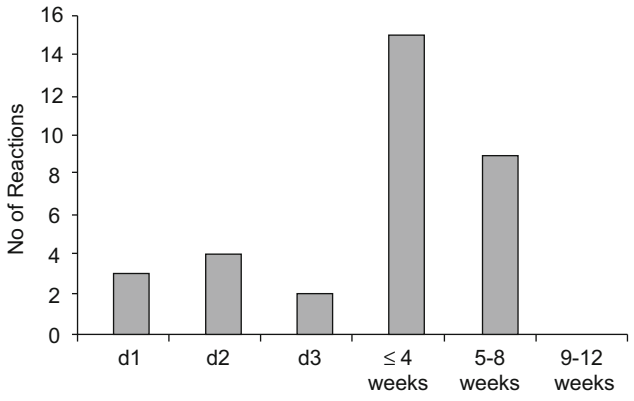

Figure 1 Timing of the reactions during VIT.

contrary, during the maintenance phase, three patients developed more severe symptoms, with cardiovascular involvement (tachycardia, hypotension) and respiratory (cough); in two of them, epinephrine injection was used. All three patients with more severe symptoms, including two of them who received epinephrine, were allergic to Hb venom.

Two of the 27 (7.4%) patients who failed to reach the maintenance interval of twelve weeks did so as a result of repeated systemic reactions during expansion of the time interval. The first was a 20-year old male allergic to Honey Bee Venom who experienced two reactions of severity I on day 1 of the rush protocol (at 0.2 and 0.4 ml respectively) and 4 reactions of severity II at maintenance: one at the first week interval injection, two at the six-week intervals and one at eight-week intervals. The reactor successfully continued VIT at six-week intervals reaching a maintenance dose of 150 μg. He reported two field stings of Honey Bee during the second year of treatment resulting both in minor local reactions. The second patient, a 26 year old female with history of Hb allergy, experienced a total of 15 mild reactions consisting of flushing, pruritus and urticaria during the maintenance phase. A maintenance dose of 150 μg (with antihistamine premedication) was successfully administered every six weeks.

With respect to clinical efficacy, 59 documented field stings were reported in 14 patients, at least two months after VIT onset. A beekeeper reported 24 field stings of which 10 were during the first year and 14 during the second year of treatment. Only one incident of mild urticaria was reported after a Hb sting, while in the rest of cases local reactions occurred.

Discussion

Numerous VIT protocols ranging from slow to ultra-rush have been proposed in order to achieve the optimal balance between efficacy, safety and patient convenience. Rush VIT is routinely used in European countries,[4] while American colleagues seem to be more sceptical. Golden suggested a modified rush regimen[20] which is commonly used in US patients, mostly on an outpatient basis, where the 100 μg maintenance dose is being reached with eight weekly administered doses, in contrary to the 4–6 months required in traditional slow protocols[2]. In this study we present our clinical experience with an easy to perform 3-day VIT protocol, which is the first to our knowledge which reaches the maintenance dose in only 7 injections.

Sturm et al. presented a 4-day rush VIT regimen performed in hospitalised patients.[10]. A total of 17 injections were needed until the maintenance dose was reached. Besides this, pre-treatment with intravenous dimenthidine maleate was administered every morning, 60 mins before the initiation of injection series. Wenzel et al. have proposed a 7-day rush protocol that required 4 injections per day and a cumulative dose of 555.55 μg until the 100 μg dose was reached[11]. More recently Pasaoglou et al. described a VIT protocol of 7 days and a total number of 14 injections in order to achieve the maintenance dose.[15] In our 5-day rush protocol the maintenance dose of 100 μg is accomplished after only seven injections with a cumulative dose of 255 μg for each venom extract without pre-treatment and with no hospitalisation required. We believe that this protocol provides a safe rush alternative for VIT and the most patient-friendly option.

We did not use any prophylactic treatment with antihistamines, with the exception of one patient who experienced recurrent systemic reactions. Antihistamine premedication is controversial because it may mask mild side effects and prevent the adjustment of dose schedule, but these allegations were not documented in controlled studies,[21] while elsewhere it is claimed that antihistamine pretreatment may even enhance efficacy of allergen specific immunotherapy.[22]

The frequency of systemic reactions VIT in different centres ranges from 0% to 67.3%.[10] Regarding rush VIT protocols, the reported frequency of systemic reactions was 13–46% among Hb allergic patients and 0–21% among Cw allergic individuals.[9,10,14] In our study 18.4% of patients experienced systemic reactions, 24% of those being allergic to Honey bee and 5.5% allergic to Cw. This reaction rate is relatively low despite the fact that no premedication was used. Moreover, the reaction rate was not different in patients receiving VIT with more than one specimen. In an EAACI multicentre study with data from 840 patients who had undergone different VIT regimens from 19 European centres; 20% patients experienced systemic reactions, while 1.2% of total injections elicited reactions; female sex, rapid dose increase and bee venom allergy were risk factors for systemic reactions.[8] Our findings are consistent regarding Hb as the offending venom for increased adverse reactions; however we failed to determine the female sex as a risk factor, as has been reported in other studies.[6,13,23] The reported frequency of systemic reactions per injection was 0.47% in a study of 101 patients with insect venom allergy who received rush VIT protocol.[10] In the same study, the risk of developing systemic reactions per injection of Hb and Cw extract was estimated at 0.79% and 0.12%, respectively.

Regarding the time interval between injections at maintenance phase, most centres suggest that maintenance interval should be kept at 4 weeks for the first year, then extended to 6 weeks in the second year and then to 8 weeks, if the VIT is continued after 5 years of treatment.[4,23] However, recent studies support the safety and efficacy of prolonging the maintenance interval to 12 weeks.[16,24,25] One hundred and sixty patients, mostly allergic to Hb, received VIT at a 3-month interval; only 3.8% of patients failed to

reach this interval, mostly due to failure to reach the maintenance dose. We have extended the time interval between injections to 12 weeks irrespectively of the offending insect. Only 2/27 (7.4%) of those allergic to Hb, did not reach the maintenance interval because of systemic reactions experienced in earlier stages of treatment, a relatively low failure rate compared to the 30% reported in Hb allergic patients by Kochuyt et al.[24]; both continue VIT receiving an increased maintenance dose of 150 μg at 6-week intervals according to previous reports.[26]

Comparative evaluation of different VIT schedules regarding safety and effectiveness is problematic because of the lack of an international standard classification of side effects and also the fact that no ideal laboratory or clinical parameter exists so as to identify clinical efficacy of treatment. Only 1/14 (7.1%) patients who experienced field stings during treatment reported a mild systemic reaction, compared to the 8.3% in Hymenoptera allergic patients[16] and to almost 7% in imported fire ants' treated patients.[27]

In conclusion, we report the use of a simple and patient-friendly rush protocol in an outpatient setting for VIT induction phase.

Conflict of interest

The authors have no conflict of interest to declare.

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