

EXPERT
REVIEWSVenom immunotherapy:
clinical efficacy, safety and
contraindications

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Venom-specific immunotherapy (VIT) is considered for the treatment of patients with IgE-mediated systemic allergic reactions (SARs) after developing a Hymenoptera venom allergy. Tolerance is achieved in a majority of patients after only a few days or even hours of rush immunotherapy. After VIT discontinuation, the allergy returns in up to 15% of patients. During VIT, the majority of patients have local reactions at the site of venom injections. SARs to VIT are much more frequent in honeybee-treated patients than in wasp-treated patients. Increased baseline serum tryptase and increased allergen-specific sensitivity of basophils are other factors that might be associated with systemic reactions (SRs) during VIT. Severe SRs occur mainly during the build-up phase but can also occur in the maintenance phase of the VIT, even in patients with a well-tolerated dose-increase phase. Pre-treatment with humanized anti-IgE antibodies (omalizumab) is effective in patients with repeated SARs; however, this use of omalizumab is off-label. In highly exposed patients with a history of very severe reactions, there are virtually no absolute contraindications for VIT.

KEYWORDS: anaphylaxis • basophil allergen sensitivity • contraindications • Hymenoptera venom allergy • immunotherapy • side effects • tryptase

Between 0.3 and 7.5% of people report systemic allergic reactions (SARs) after being stung by a honeybee, wasp or hornet [1]. A phone survey in Austria found that 39.1% of the reactions were mild (grade I) and 43.5% were moderate (grade II) according to the Ring and Messmer classification [2]. In highly exposed populations such as in beekeepers, the prevalence of SARs can even exceed 30% [1]. Reactions caused by the European hornet (*Vespa crabro*) sting seem to be a risk factor for life-threatening reactions [3]. Patient-related risk factors for severe reactions include advanced age, elevated basal serum tryptase and concomitant cardiovascular diseases [4].

Contradictory results have been shown in clinical studies concerning whether concomitant treatment with β -blockers or angiotensin-converting enzyme inhibitors (ACEI) is a risk factor for more severe SARs [4,5].

Up to 0.5 per 1 million people die per year due to Hymenoptera venom allergy [1]. In addition to presenting a risk of a fatal outcome, allergy to insect stings has a negative impact on quality of life [6]. Venom

immunotherapy (VIT) is effective for the prevention of serious allergic reactions to Hymenoptera stings. It is the therapy of choice for patients who have experienced a severe sting reaction – Mueller grade III (dyspnea) or IV (hypotension) – particularly if there is a substantial risk of further stings [7]. VIT might also be offered to patients with milder IgE-mediated SARs when exposure is high; to patients with relative contraindications for adrenaline, such as concomitant cardiovascular disease; or when the fear of being stung seriously impairs a patient's quality of life. In the USA, patients older than 16 years with a systemic reaction limited to the skin are also candidates for VIT [8]. In addition, frequent and disabling local reactions might be indications for VIT in the USA [8].

VIT protocols

VIT protocols are presented in TABLE 1. In the build-up phase, the patient receives injections with increasing amounts of the allergen. The starting dose in VIT is between 0.001 and 1 μ g of venom [9]. The basic principle is that

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Table 1. Built-up protocol in venom immunotherapy: Conventional protocol [10].

Concentration	Volume (ml)	Dose (µg)
1 µg/ml	0.05, 0.1, 0.2, 0.4	0.05, 0.1, 0.2, 0.4
10 µg/ml	0.05, 0.1, 0.2, 0.4	0.5, 1, 2, 4
100 µg/ml	0.02, 0.05, 0.07, 0.1, 0.2, 0.4, 0.6, 0.8, 1	2, 5, 7, 10, 20, 40, 60, 80, 100

Injections are given once weekly.

the next dose is approximately double the previous dose. In conventional protocols, the patient receives an injection every week [10]. In cluster immunotherapy, the patient is administered several injections of increasing doses (generally 2 or 3 per day, on non-consecutive treatment days) at 30-min intervals [11]. In a rush immunotherapy build-up schedule, the patient receives incremental doses at intervals of 1 or 2 h over few days until the maintenance dose is achieved [12]. In ultrarush therapy, the VIT dose-increase phase is performed in one day [12,13]. The maintenance dose for the majority of patients is 100 µg of venom, which is equivalent to approximately two bee stings and a much higher number of wasp stings. The maintenance interval should be kept at 4 weeks for the first year and then extended for 2 weeks each year until it reaches 3 months [14].

In patients with SRs to a VIT injection, an insect sting during VIT, beekeepers and patients with mastocytosis, the maintenance dose should be increased to 200 µg [7,15,16].

The duration of VIT is 3–5 years. Patients with reactions to insect stings during immunotherapy, those with relapse and patients with mastocytosis are encouraged to receive immunotherapy throughout their lives.

Efficacy of VIT

Tolerance is achieved in a majority of patients after only a few days of rush immunotherapy [17]. In a sting challenge controlled study performed by Hunt *et al.*, only one Hymenoptera venom-treated patient of 19 experienced a systemic reaction (mild) compared with 14 of 23 placebo- or whole-body extract-treated patients (whose reactions were severe). Goldberg and Confino-Cohen performed a sting challenge in 67 bee-allergic patients immediately after reaching the maintenance dose of 100 µg. In total, 6.6% of the patients developed a systemic reaction, and those patients continued to receive VIT on a maintenance dose of 200 µg [18].

Immunotherapy also improves quality of life [19]. A randomized prospective study compared the effects of VIT with those of an EpiPen. The group randomized to VIT showed a statistically significant improvement in their health-related quality of life scores, whereas in those randomized to the EpiPen group, the health-related quality of life scores were unchanged or even decreased [6].

Treatment failure, which is defined as a reaction to a sting in patients on maintenance VIT, was observed more often in

patients receiving honeybee VIT (11%) than in those receiving wasp VIT (4%) [20]. In a sting challenge study consisting of 1532 patients, predictors of VIT failure were concomitant use of ACEI, honeybee venom allergy and a systemic allergic reaction during VIT [21]. Elevated tryptase in the absence of mastocytosis did not increase the risk of treatment failure. A longer duration of VIT reduced the risk of treatment failure.

In a Swiss study, 16% of bee-allergic patients and 7.5% of wasp-allergic patients treated for 3–7 years developed systemic reactions after stopping immunotherapy. Most reactions were mild, but there was a tendency for an increase in the severity of reactions after repeated re-stinging [22]. The risk of relapse was the same in patients who were skin test-positive and those who were skin test-negative when the immunotherapy was stopped.

A fatal reaction 9 years after the discontinuation of immunotherapy has been described [23].

In a follow-up study of 229 patients (108 treated with honeybee, 100 treated with yellow jacket and 20 treated with both venoms), 55% of the VIT-treated patients were stung after the treatment [24]. After the first sting, 8% reported a systemic reaction. In patients stung more than once, a systemic reaction occurred in 17% of those who tolerated the first sting. Patients who reacted after discontinuation of immunotherapy were found to have higher basophil sensitivity (the sensitivity was comparable to that in a group of patients without immunotherapy) compared with a group of protected patients [25]. In a long-term sting challenge study, induction of tolerance after VIT was associated with a decrease in basophil sensitivity. In patients with incomplete tolerance, basophil sensitivity remained high [26]. A differential expression of a group of 89 genes was detected in patients during VIT [27]. However, the clinical and prognostic significance of the findings has not yet been evaluated.

Safety of VIT

A majority of patients develop painful local reactions at the site of venom injections that last from few hours to days. Additionally, there is considerable risk of a SAR following VIT injection. For this reason, VIT should be performed only in clinical settings where such reactions can be optimally treated, and patients must be observed at least 30 min after an injection [8]. Life-threatening anaphylactic reactions more than 30 min after an injection are extremely rare [28]. To avoid life-threatening SARs during VIT, concomitant internal diseases should be treated before starting VIT. Alternatives to drugs such as β-blockers and ACEI should be considered because indirect evidence has shown that severe SARs might be refractory to treatment in patients receiving these drugs, although reports of this are rare [8,29–31].

Systemic reactions after immunotherapy injections are particularly common during the dose-increase phase of VIT [28]. In a

Table 2. Built-up protocol in venom immunotherapy: Cluster protocol [11].

Concentration	Volume (ml)	Dose (μ g)	Cumulative dose (μ g)	Day	Hour
0.01 μ g/ml	0.1	0.01		1	0
0.1 μ g/ml	0.1	0.1			0:30
1 μ g/ml	0.1	1			1
1 μ g/ml	0.1			8	0
	1				0:30
10 μ g/ml	0.1				1
	0.1			15	0
	0.5				0:30
	1				1
100 μ g/ml	0.1			22	0
	0.2				0:30
	0.2			29	0
	0.3				0:30
	0.3			36	0
	0.4				0:30
	0.4			43	0
	0.4				0:30
	0.5			50	0
	0.5				0:30
	1			57	

large multicenter study, systemic reactions were documented in response to 1.9% of injections during the dose-increase phase and 0.5% of injections during the maintenance VIT phase. Childhood does not seem to represent an increased risk [32]. Interestingly, the majority of studies show that side effects are less frequent in rush protocols than in slower protocols [12,33,34].

There is evidence that rush protocols make it possible to induce tolerance in a majority of patients who have experienced recurrent SARs during the build-up phase of conventional VIT [35].

SARs are much more frequent in honeybee-allergic patients than in wasp-allergic patients. A systematic review of the literature identified 22 studies, comprising 3665 patients, on the safety and tolerability of VIT that compared types of venom [36]. The incidence of systemic reactions was 25.1% in patients treated with honeybee venom and 5.8% in vespid venom-treated patients. In a study by Lockey *et al.*, the frequency of SRs during the build-up phase of VIT was 40% for honeybee venom and 12% for wasp venom [37]. Overall, 9% of the reactions were severe, 32% were moderate and 59% were mild. Slightly lower frequencies of objective systemic reactions – 21% for honeybee venom versus

4% for wasp venom – were reported by Mueller *et al.* [38]. Additionally, they noticed subjective systemic reactions in 20% of the patients overall. An European Academy of Allergy and Clinical Immunology multicenter study collected data from 840 patients (71% were wasp-allergic), totaling 26,601 injections, with a variety of treatment regimens. SARs occurred in 24–19% of patients treated with honeybee and wasp venom VIT, respectively [28]. The majority of reactions were very mild, and only one-third required treatment with antihistamines. Only 6 of 168 patients with systemic reactions required adrenaline. Rueff *et al.* reported rates of 16–5% for SARs in patients treated with honeybee and wasp venom VIT, respectively [39]. The major reason for such variability in the frequency of reported systemic reactions is probably the different classifications of adverse reactions used in different studies. Very mild, self-limited reactions and reactions with only subjective symptoms were not always recorded [40]. To overcome this problem, the World Allergy Association recently proposed a standard for reporting systemic side effects during immunotherapy [41].

The baseline serum level of tryptase is an indicator of the body's entire mast cell load. Increased baseline serum tryptase

is a factor that might be associated with SRs during VIT. Rueff *et al.* showed that increased baseline serum tryptase is associated with SRs during wasp VIT but not during honeybee VIT [39]. Potier *et al.* found elevated basal cell tryptase in 10.7% of patients on VIT; one-third of these patients were eventually diagnosed with mastocytosis [42]. Similarly, systemic mastocytosis was diagnosed in 5.8% of 379 consecutive patients with Hymenoptera sting anaphylaxis in a study by Bonadonna *et al.* [43]. VIT in patients with mastocytosis is associated with a higher rate of severe side effects; however, it is possible to achieve tolerance in the majority of patients. It may be necessary to use an elevated maintenance dose to protect individual patients with mastocytosis [44]. VIT is recommended for life in venom-allergic patients with mastocytosis because the fatal reactions after cessation of VIT have been reported [45].

Very high basophil allergen sensitivity may also be an independent predictor of severe SRs during the build-up phase of honeybee VIT [46,47].

It should be kept in mind that very severe reactions can occur in the maintenance phase of VIT, even in patients with a well-tolerated dose-increase phase [48].

Table 3. Built-up protocol in venom immunotherapy: Rush protocol [12].

Concentration	Volume (ml)	Dose (μ g)	Cumulative dose (μ g)	Day	Hour
0.01 μ g/ml	1	0.01	0.01	1	0
0.1 μ g/ml	1	0.1	0.11		2
1 μ g/ml	1	1	1.11		4
10 μ g/ml	0.2	2	3.11		6
	0.3	3	5.11	2	0
	0.35	3.5	9.61		2
	0.35	3.5	13.11		4
100 μ g/ml	0.1	10	23.11	3	0
	0.15	15	38.11		2
	0.15	15	53.11		4
	0.2	20	73.11	4	0
	0.25	25	98.11		2
	0.25	25	123.11		5
	0.30	30	153.11	5	0
	0.35	35	188.11		2
	0.35	35	223.11		4

Various measures can be taken to decrease the frequency or severity of side effects. Pre-treatment with antihistamines reduces the number and severity of large local reactions and mild systemic reactions such as urticaria and angio-edema. It is

ever, most published case reports on omalizumab-pretreated patients have shown that even after patients have achieved the maintenance dose, systemic reactions return when omalizumab pretreatment is discontinued [54].

Table 4. Built-up protocol in venom immunotherapy: Ultrarush protocol [12].

Concentration	Volume (ml)	Dose (μ g)	Cumulative dose (μ g)	Minute
0.01 μ g/ml	1	0.01	0.001	0
0.1 μ g/ml	0.1	0.01	0.011	15
	0.4	0.04	0.051	30
	0.5	0.05	0.11	45
1 μ g/ml	0.1	0.1	0.21	60
	0.4	0.4	0.61	75
	0.5	0.5	1.11	90
10 μ g/ml	0.1	1	2.11	105
	0.4	4	6.11	120
	0.5	5	11.11	135
100 μ g/ml	0.1	10	21.11	150
	0.4	40	61.11	165
	0.5	50	111.101	180

advised that antihistamines be administered 1 h before injection until the maintenance dose has been shown to be well tolerated [49]. Antihistamine pretreatment might also increase the efficacy of VIT [50]. Depot extracts seem to be associated with fewer local side effects than aqueous preparations and have comparable efficacy [51]. In a systematic literature review, no difference in the incidence of SRs between aqueous and depot extracts was found for vespid venom VIT (5.8 vs 7.8%), but the incidence of SRs was significantly lower in patients treated with depot honeybee venom extract (11.1%) than in patients treated with aqueous extract (26.3%) [36]. To improve the tolerability of VIT, attempts are being made to remove peptides which are toxic but function as only minor allergens, such as melittin, from the venom extract [52].

Pre-treatment with humanized anti-IgE antibodies (omalizumab), although it is an off-label use of the drug, allows the application of a maintenance dose of venom in patients who experience repeated systemic reactions while receiving immunotherapy injections [53]. How-

Contraindications for VIT

Contraindications for VIT are not as strict as those for immunotherapy for respiratory allergic diseases. Absolute contraindications for starting VIT include severe uncontrolled asthma [55] and poor compliance with VIT [8].

Concerning the use of β -blockers during VIT, the decision must always take into account the risk of cardiac disease if the β -blocker treatment is withdrawn. In patients at high risk for anaphylaxis, VIT should be initiated under careful supervision, even if it is not possible to take the patient off β -blockers [56,57]. ACEIs are quite easily replaced with angiotensin receptor blockers [44,58].

There are no controlled studies regarding the effectiveness and risks of immunotherapy in patients with malignant diseases, immunodeficiency (including HIV) or autoimmune disorders [8].

Autoimmune and malignant diseases are considered contraindications for inhalant allergen-specific immunotherapy because there is a fear that immunotherapy might aggravate those diseases. In a Danish study, 18,841 people on immunotherapy were compared with 428,484 individuals with allergic diseases treated with drugs only and followed for 10 years. Subcutaneous immunotherapy was associated with lower mortality and lower incidences of acute myocardial infarction and autoimmune disease [59]. In a case series, VIT appeared to be safe and effective in patients with a malignant disease in remission as well as in patients with underlying autoimmune diseases, including rheumatoid arthritis, Crohn's disease and autoimmune thyroiditis [60,61].

Immunotherapy with mites and pollens has been recommended for patients with early to midstage HIV disease [62]. The benefits and risks of allergen immunotherapy in patients with immunodeficiencies or autoimmune disorders should be assessed on an individual basis [8].

VIT is well tolerated by the majority of patients with underlying mast cell disease (elevated baseline serum tryptase and/or mastocytosis) [39]. Only a few patients with mastocytosis have been reported to experience repeated reactions during immunotherapy that were severe enough to necessitate early suspension of treatment [45].

Because of the risk of systemic reactions, VIT should not be started during pregnancy. In well-tolerated VIT, it is safe to continue maintenance injections during pregnancy [63].

Expert commentary

VIT is a very efficient method of treating patients prone to severe anaphylactic reactions to Hymenoptera insect stings. Because even severe anaphylactic reactions rarely result in a fatal outcome, the most obvious outcome of VIT is a greatly improved quality of life for allergic individuals. The efficacy of VIT is generally at least 85% if the absence of a severe sting reaction is the outcome measure. However, although extremely

rarely, VIT is associated with potentially life-threatening side effect. For that reason, VIT should be performed only by healthcare professionals experienced with this type of treatment.

In highly exposed patients with a history of very severe reactions, there is virtually no absolute contraindication for this treatment. Some circumstances that are contraindications for immunotherapy with inhalant allergens are an even clearer indication for VIT. Individuals in such situations include those who are, owing to comorbidities, at high risk of dying if anaphylaxis occurs, such as patients with cardiovascular comorbidities, patients on β -blockers and patients with mast cell disorders.

Systemic reactions during inhalant allergen immunotherapy are a reason to stop treatment. In venom-allergic patients, however, systemic reactions during VIT indicate that the patient is at extremely high risk of a severe reaction if stung by an insect and thus make the indication for VIT even more straightforward.

Five-year view

New laboratory techniques, such as measurement of specific basophil sensitivity and cluster analysis of patient characteristics and laboratory data, would enable the detection of allergic subjects at particular risk of a severe reaction after a Hymenoptera sting and are therefore excellent candidates for VIT. The same techniques would also enable identification of patients who are prone to severe side effects during VIT and therefore require the use of individualized and safer protocols and eventually pre-treatment with anti-IgE antibodies.

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Key issues

- Venom immunotherapy (VIT) is effective for the prevention of serious allergic reactions to Hymenoptera stings. Tolerance is achieved in majority of patients after only a few days of rush immunotherapy.
- Patients receiving VIT showed a statistically significant improvement in their health-related quality of life scores compared with those given an epinephrine autoinjector.
- Treatment failure is observed more often in patients receiving honeybee VIT than in those receiving wasp VIT.
- Systemic reactions after immunotherapy injections are particularly common during the dose-increase phase of VIT and occur in up to 40% of honeybee-treated patients. The majority of reactions are mild. However, very severe reactions can occur in the maintenance phase of VIT, even in patients with a well-tolerated dose-increase phase.
- Mastocytosis is associated with a higher rate of severe side effects during VIT. Very high sensitivity of basophils to allergens is also an independent predictor of severe systemic reactions (SR) during the build-up phase of honeybee VIT.
- Contraindications for VIT are not as strict as those for immunotherapy for respiratory allergic diseases.
- The risk of relapse is as high as 15% and increases with an increased number of re-stings.

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