# Advances in hymenoptera venom immunotherapy

Beatrice M. Bilò and Floriano Bonifazi

**Purpose of review**

Venom immunotherapy is highly effective treatment, capable of improving health-related quality of life. This overview examines advances in various aspects of this treatment.

**Recent findings**

New findings on the immunological mechanisms of the early and long-term efficacy of venom immunotherapy have been made. The decision to start and then to stop venom immunotherapy is best made on an individual case basis and should take into account medical and other factors, like the influence on patient quality of life. Venoms for use in immunotherapy should be selected according to the geographical distribution of each species and partial cross-reactivity between certain types of venom. Rapid protocols seem to be as safe as slower ones, though the major incidence of bee venom immunotherapy side-effects remains. Patients suffering from mast cell diseases seem to be at greater risk for an adverse reaction during treatment, without influencing its efficacy that much until the immunotherapy is actually ongoing. A number of new strategies for venom immunotherapy, mostly based on genetic engineering, have been described, and so far only a few have been used in humans.

**Summary**

Although there has been progress in the past few years, much remains to be accomplished.

**Keywords**

efficacy, future strategies, indications, mechanisms, safety, venom immunotherapy

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Department of Internal Medicine, Immunology, Allergy and Respiratory Diseases, University Hospital, Ancona, Italy

Correspondence to Beatrice M. Bilò, Department of Internal Medicine, Immunology, Allergy and Respiratory Diseases, University Hospital, Ancona, Italy
Tel: +39 071 5963804; fax: +39 071 5963253;
e-mail: b.bilo@ao-umbertoprimo.marche.it

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**Abbreviations**

| | |
|---|---|
| **HRQL** | health-related quality of life |
| **PLA** | phospholipase |
| **RAST** | radioallergosorbent test |
| **VIT** | venom immunotherapy |

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## Introduction

Though insect sting allergy illustrates most of the dilemmas in the immunology, pathophysiology, diagnosis and treatment of anaphylaxis, this field still presents mysteries [1] mainly concerned with the natural history of venom sensitization, and risk factors for bad outcome in both treated and untreated patients.

Moreover, poor awareness of the disease and the available venom immunotherapy (VIT) in the general population, especially the healthcare service, need to be improved as $20^{th}$ century epidemiological studies continue to reveal that a substantial number of emergency department admissions had a known history of a previous allergic sting reaction [2], indicating auto-injectable epinephrine (Epipen) was not available to patients and that above all they were not undergoing VIT.

There is no doubt that VIT is a highly effective treatment [3–5], which aims to lessen the risk of a subsequent systemic reaction, prevent morbidity and mortality and improve health-related quality of life (HRQL), as demonstrated in yellow-jacket-allergic patients [6]. In contrast, the Epipen is perceived as burdensome and an unsuitable definitive treatment by most venom-allergic patients [7•].

This overview examines advances in the following aspects of VIT: mechanisms, indications and contraindications, selection of venoms, treatment protocol, safety and efficacy, duration and future strategies.

## Mechanisms

Though VIT is well documented as the only path towards insect sting tolerance, the mechanism involved is not completely known.

The effects of VIT on venom-specific IgE and IgG antibodies are well documented [8], though neither concentration (or a change in concentration) of IgG nor the IgE/IgG ratio correlates closely with the clinical response to immunotherapy [5]. The proposal of blocking antibodies has recently been re-evaluated on the basis of observations of altered specificity and affinity during immunotherapy and effects on memory B cells and antigen-presenting cells [9].

Lymphocyte subsets and cytokine responses indicate the induction of a peripheral T-cell tolerance with a prominent role of IL-10 initially and, as one recent study



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reports, an increased expression of osteopontin during long-term VIT [10].

Previous studies reveal a decrease in IL-4 production by $CD4^+$ Th2 cells and an increase in IFNγ Th1 cell production during conventional VIT [11], but subsequently a decrease in both IL-4 and IFNγ production [12] or no variation in Th1 cytokines was detected [13].

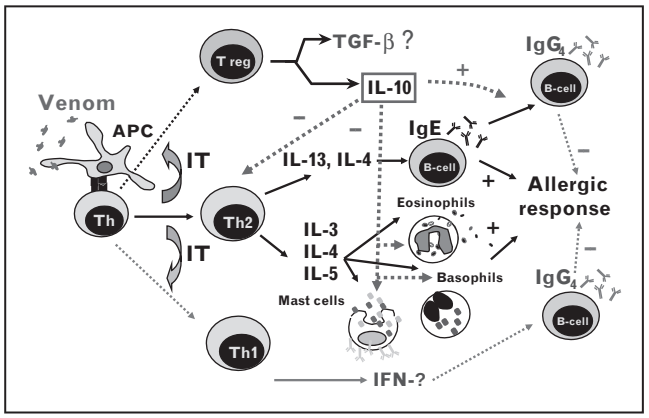
This discrepancy could be due to the heterogeneity of culture conditions but especially to the different VIT protocols and consequent allergen doses. Indeed, conventional VIT delays a decrease in IL-4 production for 2 months after starting VIT, whereas rush VIT induces the same decrease as early on as the first day of treatment [14].

Immunosuppressive IL-10 was shown to be responsible for VIT-induced IL-4 decrease [15], while, unlike in mucosal allergies, no increases in TGF-β production were observed during VIT (Fig. 1) [16••]. The different routes of natural allergen exposure as well as the induction of chronic events of allergic inflammation, absent in venom allergy, could explain these findings.

Tr1 cells are defined by their ability to produce high levels of IL-10 and TGF-β [17] and there is now clear evidence that IL-10 (or TGF-β-producing) Tr1 cells are generated *in vivo* in humans during the early course of immunotherapy, suggesting that high and increasing doses of allergen induce Tr1 cells in humans [16••].

Accordingly, using an ultra-rush protocol in vespid-allergic patients, a decrease in IL-4 production in the hours after the start of VIT, as well as $CD4^+CD25^+$ Treg cells and IL-10-producing T cells (Tr1) increase, has been demonstrated [18••]. Interestingly, it seems that these events occur earlier on and at a higher level in patients with less severe reactions than in those with anaphylaxis [18••].

**Figure 1 Venom immunotherapy: possible immune mechanisms**




APC, antigen presenting cell; IT, immunotherapy.

Very early effects of VIT are also associated with an early decreased mediator release from mast cells and basophils, though the mechanism of this desensitization effect is as yet unknown [16••,19••]. Ultra-rush protocols significantly increase the release of mediators of anaphylaxis into circulation without inducing a systemic anaphylactic response in the majority of cases. This piecemeal release of mediators may decrease the granule content of mediators and affect the threshold of mast-cell and basophil activation [19••,20].

An increase in intracellular cAMP levels immediately after vespid rush VIT parallel to a decrease of allergen-induced release of histamine and sulphfidoleukotrienes from basophils was demonstrated very recently [21•]; this intracellular modification might account for the decreased reactivity of basophils to allergen after 1 week of VIT, although this seems not to be a long-term effect as values returned to baseline after 6 months [21•].

Early-stage rush VIT protection may also be attributed to the direct suppressive effect of IL-10 on the effector cells (mast cells, basophils) (Fig. 1) [16••,19••].

## Indications and contraindications

The indications for VIT are based on the history of a systemic reaction, a positive venom skin or radioallergosorbent test (RAST), the knowledge of the natural history and established risk factors for severe outcome [22,23••].

The risk of a future allergic reaction, however, can only be expressed statistically since no available test can accurately predict the outcome of the next sting. This circumstance makes it difficult to specify what level of statistical risk justifies VIT.

Recommendations for the use of VIT vary from country to country. While there is a good consensus that VIT is indicated for severe systemic sting reactions, there is less agreement on whether adults and especially children with mild (cutaneous) reactions are suitable candidates, as the prognosis in dermal reactors is usually good [3,24]. Though current opinion on providing patients with a history of a mild reaction with an Epipen differs among experts [24,25•], its negative effect on HRQL could mean that treatment with autojectable epinephrine alone is probably inappropriate.

The updated European Guidelines state that in both children and adults with a history of a systemic, non-life-threatening reaction (urticaria, erythema, pruritus) other factors may influence the decision to initiate VIT which

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**Table 1 Indication for venom immunotherapy [5]**

| Type reaction | Diagnostic tests Skin test or IgE | Decision regarding venom immunotherapy |
|---|---|---|
| Adults/children | | |
| Respiratory and cardiovascular symptoms | Positive | Yes |
| Urticaria if risk factors or quality of life impairment present | Negative | No |
| | Positive | Yes |
| | Negative | No |
| Large local | Positive or negative | No |
| Unusual | Positive or negative | No |

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include occupations or hobbies for which the risk of exposure is high, the culprit insect itself, concomitant cardiovascular diseases, other pathologies, like mastocytosis, and psychological factors arising from anxiety which can seriously impair patient HRQL [5] (Table 1).

Although capable of preventing large local reactions as well [26], VIT is not usually recommended in patients with such reactions due to the low risk of a subsequent systemic sting reaction. When confronted with extremely anxious patients with HRQL impairment or highly exposed subjects who need repeated per annum corticosteroid shots, however, the physician may consent to performing VIT.

Administration of immunotherapy to patients on β-blockers is contraindicated as they can aggravate anaphylactic reactions and also interfere with treatment. If the cardiac risk in venom-allergic patients is higher than the risk of a systemic reaction during VIT, VIT is appropriate in subjects on β-blockers [27].

Severe allergic reactions, including anaphylaxis, have been described in patients taking ACE inhibitors subsequent to being stung or receiving immunotherapy [5]. Although this risk is difficult to quantify exclusively on case reports, a recent review advises that ACE inhibitor therapy should be avoided where possible [28].

## Selection of venoms in Europe

Selection is based on identification of the Hymenoptera species involved and on venom cross-reactivity [22]. Several of the European species of the vespid family differ from those found in the USA. Furthermore, popular names for vespids in the USA and Europe are different and may lead to confusion (Table 2) [3].

Criteria for the selection of venom to be used for VIT were recently summarized [5]. In particular, considering the incomplete cross-reactivity between Vespinae and paper wasps (*Polistes*) and the different geographical distribution of each species, treatment with *Vespula* venom alone is

**Table 2 Vespid species in the USA and Europe**

| | Europe | | USA | |
|---|---|---|---|---|
| Genus | Species | Popular name | Species | Popular name |
| *Polistes* | *Gallicus Dominulus* | Wasp | *Annularis Fuscatus Exclamans* | Paper wasp |
| *Vespula* | *Vulgaris Germanica Rufa* | Wasp | *Vulgaris Germanica Maculifrons* | Yellow jacket |
| *Dolichovespula* | *Media Saxonica* | Wasp | *Maculata Arenaria* | Hornet |
| *Vespa* | *Crabro Orientalis* | Hornet | *Crabro* | European hornet |

usually sufficient in the temperate European climate. In the Mediterranean area patients who test positive to both venoms should be treated with both, unless RAST-inhibition reveals cross-reactivity [5].

A weaker cross-reactivity between European and American paper wasps was recently demonstrated [29,30••]. The species *Polistes dominulus* and *Polistes gallicus* are European paper wasps; *P. dominulus* has also spread to the northeastern United States and also been reported in Australia. The species *Polistes exclamans*, *Polistes annularis* and *Polistes fuscatus* are indigenous to North America and not present in Europe. All these findings raise the need to introduce, at least in Europe, the *Polistes gallicus* or *dominulus* extract (the latter only recently being available in some European countries) into clinical practice for diagnostic and therapeutic purposes, to replace the American *Polistes* species mixture presently being used [29,30••,31].

Honeybee and bumblebee venoms show marked cross-reactivity [22]. Immunotherapy with honeybee venom alone may be sufficient in non-professionally exposed bumblebee-allergic patients with bee venom primary sensitization, whose reaction is most likely due to cross-reactivity.

In occupationally exposed patients, who are frequently stung by bumblebees, purified bumblebee venom for immunotherapy, when available, is recommended due to the low or absent cross-reactivity with honeybee venom [32•].

Unlike in the southeastern USA, allergic reactions to ants are a rare occurrence in Europe [33], nor is a venom extract commercially available.

## Selection of venoms in the USA

Consensus data on which venoms to include for VIT are unavailable [24].

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Some authors believe it prudent to prescribe VIT with any venom which gives a positive skin test or RAST result since there have been cases for which VIT was tailored towards the primary culprit insect, but the patients subsequently reacted to an insect to which they had previously been sensitized [1].

Fire ant immunotherapy is performed with whole body extracts which contain sufficient venom allergens to provide reasonable clinical protection; fire ant venoms are available in Australia (Jack Jumper) where a very successful controlled trial was performed [34].

In the USA no approved diagnostic or therapeutic extracts for the bumblebee or Mediterranean wasp (*Polistes dominulus*) are commercially available [1].

## Treatment protocol and safety

To maximize protection, minimize side-effects and optimize patient convenience, slow to ultra-rush induction protocols have been designed. With rush and ultra-rush protocols the time required to reach the maintenance dose takes a few days or only hours respectively, with subsequent boosters before initiating a monthly schedule. This method is particularly useful in highly exposed subjects (e.g. beekeepers) or in patients referred to the specialist just prior to the start of the insect season, in order to reach the protective dosage as quickly as possible. Rush VIT is a routinely used core treatment in Europe [5], but is not a readily available technique at most American medical centres [1].

The risk of side effects during VIT is highly variable, ranging from 0 to 46%, and, for reasons which still have to be fully understood, this is more related to the nature of the venom (honeybee versus vespid venom) than to the regimen itself [5]. Indeed, very recent rush and ultra-rush protocol studies have confirmed their safety [35,36], which is at least equal to slower protocols. These protocols seem to be applicable and also tolerated in patients with a history of a systemic reaction during conventional VIT [37].

The higher incidence question of adverse reactions with honeybee VIT has been investigated using different approaches devised to improve safety, for example, pretreatment with antihistamines, which may reduce the number/severity of large local reactions and mild systemic reactions.

In one study [38], antihistamine premedication seemed to enhance the clinical efficacy of VIT, though further studies will have to confirm this.

In bee and Vespula venom-allergic patients depot extracts seem to cause fewer side effects, especially local ones, than do aqueous preparations, with comparable efficacy demonstrated by sting challenge and in-field stings [39–41]. Depot extracts cannot be used for rush or ultra-rush protocols, but many European specialists switch to depot preparations after the updosing phase. These preparations have not been granted FDA approval yet and will require further controlled studies to demonstrate their superiority.

Side effects from VIT may be more frequent and severe in patients with mastocytosis; risk factors for adverse reactions in this patient population (e.g. type of mastocytosis, venom used for VIT, protocol) require further evaluation [23••].

The recommended maintenance dose of Hymenoptera venom is 100 μg, equivalent to approximately two bee stings and a much higher number of *Vespula* stings. This dose gives better protection than a 50 μg dose in adults; there are no specific data on the effective dose in children. A dose of 200 μg is recommended when a systemic reaction follows an insect sting in spite of VIT with 100 μg and in highly exposed populations such as beekeepers [3,5]. According to some authors, an elevated maintenance dose (usually 200 μg) from the start of VIT should be administered to honeybee-allergic patients with concomitant mastocytosis and also considered in vespid venom-allergic subjects with additional risk factors [23••].

The general consensus is that the maintenance interval should be kept at 4 weeks for the first year, extended to 6 weeks in the second year, and then to 8 weeks if VIT is continued over 5 years [5,24]. The number of studies assessing the feasibility of extending the maintenance interval up to 12 weeks included too small a sample of patients with mainly vespid allergy, or relied on reactions to field stings only, which presently does not justify administering maintenance VIT at three-monthly intervals indiscriminately to all patients.

It is to be hoped that within the next few years multicentre clinical trials will yield results enabling us to select patients in whom the interval between injections can be extended without risk.

## Efficacy and duration

The efficacy of VIT has been confirmed in prospective controlled and uncontrolled studies [3,5] and in one meta-analysis [4] (level of evidence Ia), demonstrating the higher protection rate of vespid VIT than honeybee VIT.

Most American patients receive mixed vespid venoms, with an injectable maintenance dose of 300–400 μg, which provides about 98% protection [1].

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The protection rate of bumblebee venom immunotherapy, demonstrated by sting challenge and in field stings, has been estimated to be greater than 90% [32•].

Some authors have shown that VIT efficacy in patients with mastocytosis may be reduced [42]. Two female patients died when re-stung by a yellow jacket despite venom immunotherapy, which nevertheless occurred several years after discontinuing immunotherapy [43]. Contrarily, this indicates that patients with mastocytosis should continue lifelong VIT, increasing the dose, where possible.

The question of how long VIT should last in order to provide long-term protection after discontinuation is a long-standing issue and is extensively discussed elsewhere [5,44]. To sum up, the studies in which long-term protection up to 7 years after stopping VIT of at least a 3-year duration were evaluated on the basis of field stings or sting challenges revealed more frequent relapses than those with a shorter follow-up (protection rate of about 80% versus 83% to 100%), with a more favourable outcome in *Vespula* than in bee venom-allergic patients and in children than in adults [5]. There are no data on the outcome after more than 15 years of VIT.

It is likely that short and long-term results are more favourable with the much higher total dose given in the USA than with the 100 μg applied elsewhere. More European data on the discontinuation of VIT in allergic vespid patients with 100 μg maintenance dose are needed.

A number of risk factors for the recurrence of systemic reaction following Hymenoptera stings after stopping VIT have since been identified and include insect type, old age, severity of pretreatment reactions, generalized allergic side effects to VIT injections, incomplete protection upon re-sting during VIT, presence of mast cell diseases [5].

On the premise that the duration of VIT should be decided after a thorough patient–physician discussion of the issues involved, the present recommendations for stopping VIT take into account all these findings and are very similar in Europe [5] and America [24]. Indeed, they state that longer-term or lifelong treatment should be considered in patients with any of the above high-risk characteristics.

Some patients with low risk of relapse, however, prefer to perform long-term VIT out of a sense of security and for improved quality of life. Presently, we do not know if an improvement in HRQL remains even after stopping VIT.

## Future strategies

Much remains to be done to improve the safety and efficacy of immunotherapy, including VIT [19••].

Thanks to modern molecular biology, a considerable number of major venom allergens from both honeybee and various vespids are available today in recombinant form, paving the way towards novel therapeutic techniques.

Major T-cell epitope peptides can be prepared synthetically or expressed as recombinant fragments. A mixture of three dominant T-cell peptides of phospholipase (PLA) has been used for immunotherapy in a preliminary bee venom allergy study in only a few patients, with no side effects, and complete protection in three and partial protection in two of the five patients who were given a bee sting challenge [45].

In a double-blind, randomized, placebo-controlled trial in bee venom-allergic patients, using three long synthetic overlapping peptides (LSPs), mapping the entire PLA2 amino acid sequence, this therapy induced T-cell anergy, immune deviation toward a Th1-type T-cell cytokine response, enhanced IL-10 secretion, and PLA2-specific IgG4 production. LSP immunotherapy was safe and did not cause any severe systemic reactions. The efficacy of treatment with these long peptides, however, was not verified by a sting challenge [46].

In DNA vaccination DNA-plasmids encoding the relevant allergens are injected. The successful DNA vaccination of sensitized mice has, amongst other allergens, been reported with plasmids from bee venom PLA2 [47]. To date DNA vaccination has not been used for VIT in humans.

Many Hymenoptera venom-allergic patients, however, are sensitized to several different venom allergens from vespids or honeybees. Therefore, treatment with one major allergen in recombinant unrefolded or point mutated form, with peptides or DNA-plasmids encoding it, may be insufficient. A fusion protein composed of the two major allergens of bee venom PLA2 and hyaluronidase (HYA) was constructed through genetic engineering and characterized by destroyed conformational B-cell epitopes but intact T-cell epitopes of the two allergens [48]. The fusion protein induced T-cell proliferation and both Th1 and Th2-type cytokine responses; on the other hand, IgE reactivity was abolished and basophil degranulation reduced. The use of the fusion protein for VIT could minimize anaphylactic side effects and increase efficacy compared with the whole venom-based treatment.

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Another model used a recombinant chimeric protein consisting of the whole amino acid sequences of three major bee venom allergens (PLA2, HYA and melittin). The fragments were designed to preserve all relevant T-cell epitope peptides while conformational B-cell epitopes were destroyed. Treatment of mice with this chimeric protein led to a significant reduction of specific IgE development towards the native allergen, producing a protective vaccine effect *in vivo* [49].

Anti-IgE monoclonal antibody pretreatment could permit more rapid and higher doses of allergen immunotherapy and enhance its safety as well as play an important role in insect venom-allergic patients intolerant to VIT. The first case of a beekeeper's young bee venom-allergic relative who experienced an anaphylactic reaction towards the first VIT honeybee doses to later tolerate an ultra-rush VIT together with one single dose of omalizumab premedication was recently published [50]. Further studies on larger patient populations are required to ascertain whether treatment with anti-IgE can only be performed during the increase phase or even during the first maintenance injections as well, and if so, for how long without placing the patient at risk after discontinuation.

## Conclusion

Insect sting allergy and VIT remain an excellent model for the study of anaphylaxis and immune tolerance. VIT is probably the most effective form of immunotherapy available to physicians.

Patient knowledge that VIT prevents anaphylactic reactions to future stings improves HRQL, which itself constitutes an important reason for offering immunotherapy to insect-allergic patients.

The efficacy of bee VIT, however, is less than that of vespid venom, and its side effects more frequent.

Thus, there is considerable room for further improvement in the safety and efficacy of VIT.

A number of new strategies for venom immunotherapy, mostly based on genetic engineering, have been described and we are eagerly awaiting the advent of their application in clinical practice.

## References and recommended reading

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