



Treatment of Hymenoptera venom allergy: an update

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Purpose of review

To review and summarize the studies published between 2012 and 2014 about the use of venom immunotherapy (VIT) to treat Hymenoptera hypersensitivity.

Recent findings

Several studies reconfirm the effectiveness of VIT in both children and adults, and provide a better understanding of its immune-modulating effects. There are concerns about its cost-effectiveness; however, VIT versus self-injectable epinephrine alone when stung is the preferred treatment of choice for affected individuals when quality-of-life issues are considered. Ultrarush VIT may be as effective in children as in adults but is associated with a high risk of systemic allergic reactions (SARs). Controversy continues about the use of angiotensin-converting enzyme inhibitors and their potential for increased SARs while on VIT. Individuals with mast cell disorders, female sex, honeybee allergy, and those receiving rush or ultrarush VITs are at higher risk for SARs. Elevated baseline serum tryptase levels greater than 20 µg/l, SARs during VIT, and honeybee sensitivity are risk factors for VIT failure.

Summary

VIT remains the gold standard to treat Hymenoptera-allergic individuals to prevent future sting-induced SARs in both children and adults.

Keywords

anaphylaxis, Hymenoptera allergy, systemic allergic reaction, venom immunotherapy

INTRODUCTION

Stings by Hymenoptera insects, including bees, wasps, yellow jackets, hornets, and ants, are relatively common and most stings lead only to minor local reactions without any significant short-term or long-term complications. However, for some individuals, these stings can induce systemic allergic reactions (SARs) and even death. In the United States, 0.5–3.3% of adults have a SAR following a Hymenoptera sting [1]. The incidence is lower in children, with SARs occurring in 0.15–0.8% [2]. Hymenoptera stings also account for a significant number of SAR visits to emergency departments, with 0.03–0.48 deaths per 1 000 000 individuals per year [3]. Hymenoptera sting reactions are also responsible for decreased quality of life and significant anxiety regarding future stings, even in those who only suffer from local or large local reactions (LLRs).

Allergen immunotherapy has been used to treat allergic rhinitis, allergic conjunctivitis, and allergic asthma for over 100 years. However, venom immunotherapy (VIT), documented as being effective first

in 1979, has been used for less than 40 years. Whole-body extract (WBE), not venom, is used to treat ant-induced SARs.

This review highlights the scientific literature published between 2012 and 2014 regarding the use of VIT to treat Hymenoptera insect allergy. Some seminal studies published prior to this period are included to provide a more comprehensive review.

EFFICACY AND INDICATIONS

VIT is the most effective method to treat SARs from Hymenoptera insects and decreases morbidity and mortality from future stings. Improvements in

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KEY POINTS

- VIT is the most effective treatment for Hymenoptera sting-induced SARs.
- Controversy exists about the cost-effectiveness of VIT and the ideal subject for whom it should be prescribed.
- Safety of VIT is always a concern, especially in high-risk populations and with rapid buildup protocols. However, most SARs from VIT are mild.
- No deaths from VIT are reported in the world's literature.

quality of life, especially in those who are at high risk for stings, also occur. Such therapy prevents future sting-induced SARs in 75–95% once a maintenance dose of 100 µg of a single venom to which an individual is allergic is reached. Control groups with venom sensitivity not treated with VIT have a 40–60% chance of a SAR with subsequent stings [4]. It is usually administered for 3–5 years and, when discontinued, is protective against future SARs in most individuals for at least 7 years [5]. A 2012 Cochrane review of six randomized studies demonstrates efficacy in protecting venom-allergic individuals from future SARs and a significant improvement in the quality of life [6]. Although not well studied, individuals who are allergic to imported fire ant (IFA) also receive protection from future SARs when treated with high-dose WBE IFA vaccines which contain venom proteins [7,8].

The World Allergy Organization (WAO) subcutaneous immunotherapy SAR grading system also provides an excellent grading system for SARs following Hymenoptera stings [9] (Table 1). VIT is indicated for most individuals with a history of a Hymenoptera-induced SAR and evidence of specific IgE sensitization via the use of appropriate skin prick and intradermal tests or in-vitro serum IgE tests to Hymenoptera insect venoms. It is also effective for individuals who have LLRs, especially those who are at high risk for multiple stings because of their occupation or susceptibility to a sting [10,11].

Such therapy is particularly helpful for individuals with venom hypersensitivity who have mast cell disorders (systemic mastocytosis, mast cell activation syndrome, monoclonal mast cell activation syndrome) or an elevated baseline serum tryptase above 11.4 µg/l, which can occur in disorders such as chronic urticaria, chronic renal failure, and myelodysplasia [12,13]. For example, VIT prevented SARs following subsequent stings in 86% of treated individuals in a prospective study [14] of 84 individuals

with systemic mastocytosis and Hymenoptera venom allergy.

Indications for VIT in children are more complex. Although children may be at higher risk for Hymenoptera stings, they are less likely to have SARs than adults. When SARs do occur, most are limited to cutaneous reactions only, including diffuse erythema and flushing, urticaria, and pruritus. Only 10% of children with systemic, cutaneous reactions will have a future SAR upon re-sting and most of these are mild and cutaneous only [15]. VIT is indicated for children less than 16 years of age with grade 2 to grade 4 reactions following Hymenoptera sting and is effective to prevent future SARs [16[¶]]. Children with grade 1 cutaneous reactions to Hymenoptera stings should not receive VIT. However, a child who presents with cutaneous symptoms as well as upper respiratory and ocular symptoms and does not meet the criteria for a grade 2 reaction is a candidate for VIT. Those with grade I cutaneous reactions following IFA stings should receive VIT because of the risk of a future sting-induced SAR, especially in endemic areas [17].

SAFETY

VIT is associated with the potential for adverse side-effects, especially in high-risk populations. Local and large local reactions are relatively common and occur in almost 50% of individuals. A total of 2–20% of individuals receiving VIT have a SAR during VIT, although most of these reactions do not require the use of epinephrine [6,18]. Approximately 3% of 818 individuals had SARs, with only 5 experiencing grade 2–4 reactions during VIT buildup in a retrospective review by Stoevesandt *et al.* [19]. Several characteristics increase the risk of SAR during VIT: female sex, honeybee allergy, those with baseline serum tryptase levels greater than 11.4 µg/l, and in those receiving rush or ultra-rush protocols [13,19].

Although there are no absolute contraindications for VIT, caution should be used in individuals with a history of coronary artery disease and in those with uncontrolled asthma or other severe chronic respiratory diseases. Beta-adrenergic blocking medications (β-blockers) should be discontinued, when possible, as they can exacerbate SARs causing them to be more difficult to treat. Angiotensin-converting enzyme (ACE) inhibitor use also has been associated with a higher risk of SAR during VIT. However, this risk was not demonstrated by Stoevesandt *et al.* [20] in their study of 743 Hymenoptera-allergic individuals. Some experts recommend discontinuation of ACE inhibitors prior to initiating VIT, especially in high-risk populations, in spite of these data [21]. Angiotensin receptor blocking (ARB) medications

Table 1. Reactions to allergen immunotherapy

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of one organ system present	Symptom(s)/sign(s) of more than one organ system present	<i>Lower respiratory</i> Asthma (e.g. ↓FEV1 or PEF by 40%) NOT responding to inhaled bronchodilator	<i>Lower or upper respiratory</i> Respiratory failure with or without loss of consciousness	Death
	OR	OR	OR	
<i>Cutaneous</i> Generalized pruritus, urticaria, flushing, or sensation of heat or warmth	<i>Lower respiratory</i> Asthma: cough, wheezing, shortness of breath (e.g. ↓FEV1 or PEF by <40%) responding to an inhaled bronchodilator	<i>Upper respiratory</i> Laryngeal, uvula, or tongue edema with or without stridor	<i>Cardiovascular</i> Hypotension with or without loss of consciousness	
OR	OR			
Angioedema (not laryngeal, tongue, or uvular)				
OR				
<i>Upper respiratory</i> Rhinitis (e.g. sneezing, rhinorrhea, nasal pruritus, and nasal congestion)	<i>Gastrointestinal</i> Abdominal cramps, vomiting, or diarrhea			
OR	OR			
Throat clearing (itchy throat)	<i>Other</i> Uterine cramps			
OR				
Cough perceived to originate in the upper airway, not the lung, larynx, or trachea				
OR				
<i>Conjunctival</i> Erythema, pruritus, or tearing				
OR				
<i>Other</i> Nausea, metallic taste, or headache				

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are felt to be well tolerated and a suitable alternative for such individuals [22].

VIT is usually not started during pregnancy because of the risk of a VIT-induced SAR which could place the fetus at risk. Exceptions exist, particularly when there is a high risk of a sting-induced SAR, for example, a pregnant individual who lives on a farm or is involved in bee keeping. Individuals who already are at maintenance can continue such therapy throughout their pregnancy; however, some clinicians halve the dose as well as the interval between injections to decrease the risk of VIT SARs [23].

COST-EFFECTIVENESS

The cost-effectiveness of any form of treatment has come under increased scrutiny. VIT is no exception.

Concerns remain about its cost-effectiveness, even though it is effective to prevent future SARs and thus reduces morbidity and mortality. It is estimated that VIT in the United Kingdom would cost an additional £18 million compared with no such therapy and use of as needed epinephrine autoinjectors and an oral antihistamine, that is, diphenhydramine 50 mg, upon re-sting in sensitized individuals [24]. A study [25] of bee and vespid allergic individuals in Holland suggests that VIT be reserved for those at high risk because of outdoor and occupational exposure, whereas as needed epinephrine devices are acceptable for those not at high risk for such an exposure. Arguments remain about the fact that VIT not only reduces morbidity and mortality from re-stings, but also improves the quality of life and reduces anxiety of venom-allergic individuals,

making such therapy cost-effective [26[¶]]. Those who received self-injectable epinephrine rather than VIT viewed the epinephrine device as burdensome and were apprehensive about using it in a study of yellow-jacket-sensitive individuals. More than 90% of the individuals who received VIT viewed it in a positive manner and chose to continue it. Of those who initially received only the epinephrine device, almost 70% preferred to switch to VIT after 1 year [11]. This study suggests that factors other than just mortality should be considered in determining VIT cost-effectiveness.

IMMUNE MODULATION

VIT causes a shift from a predominantly T_H2 response to T_H1 , with decreases in IL-4, IL-13, and concomitant increases in IFN- γ . It also suppresses basophil activity and decreases both venom-specific IgE and increases in IgG4 [27,28]. A higher specific IgG4 level was found in tolerant beekeepers compared with honeybee-allergic individuals, suggesting that IgG4 actively inhibits IgE binding to allergen, thus explaining the protection from future SARs during VIT [29]. IL-10, important for immunosuppression, is increased during VIT; this change occurs particularly early in individuals treated with rush VIT protocols [30]. Lipoxin A4, which reduces inflammation associated with asthma, increases in individuals receiving VIT, possibly serving as a trigger for additional IL-10 production [31]. Such therapy also leads to early reductions in soluble CTLA-4, a marker normally increased in Hymenoptera-venom-allergic individuals, indicating development of immune tolerance [32]. Regulatory T cells (Tregs) also play an important role in that there is increased homing of these cells to regional lymph nodes, which may help modulate effector T-cell responses through IL-10 and prevent the overproduction of inflammatory (T_H1) cytokines such as IFN- γ [33].

SELECTION OF VENOMS AND TREATMENT PROTOCOLS

Trying to identify the insect which causes the SAR is important. This may be accomplished by obtaining a detailed and accurate history or, when available, by examining the culprit insect. In many cases, it is difficult to correctly identify or even suspect the identity of the stinging insect. Skin prick and intradermal skin test as well as in-vitro venom-specific IgE tests are the preferred diagnostic tests but can be complicated to interpret because of the presence of cross-reacting carbohydrate determinants (CCDs) in individuals who appear to be sensitized to both honeybee and vespids.

Component-resolved diagnostic testing (CRD) can be used to determine whether dual sensitization is actually present or related to CCDs [34]. Please see the corresponding article about CRD for Hymenoptera allergy [35].

There is no consensus about which venoms to include for VIT. Some physicians choose to include all venoms to which the individual is sensitized, whereas others will include only venoms from the suspected insect which induced the SAR. Fifty-five percent of 635 individuals in a retrospective review with honeybee (*Apis*) or *Vespula* allergy were sensitized to both genera of insects. They received single-venom VIT based on their clinical history and interpretable differences in skin prick and/or in-vitro venom-specific IgE testing. Only 7.1% had SARs with future stings while on VIT and none was considered severe, indicating that single VIT is effective in most double-sensitized individuals [36]. Many of the venoms also are cross-reactive, so in individuals who require multiple venoms for VIT, mixed venom preparations [i.e. mixed vespids, containing yellow jacket (*Vespula* sp.), yellow hornet (*Dolichovespula arenaria*), and white-faced hornet (*Dolichovespula maculata*) venoms] may be utilized. These preparations are not commercially available in all parts of the world, but are available in the United States and Europe.

VIT is initiated using one of several buildup protocols, each reaching maintenance at different time intervals: slow or standard (8–15 weeks), cluster (6 weeks), rush (4–7 days), or ultrarush (1–2 days). Adverse reactions, that is, SARs, occur more commonly with rapid buildup schedules [37]. Arseneau *et al.* [38] demonstrated that approximately 25% of individuals had SARs associated with an ultrarush IFA allergen immunotherapy protocol that reached maintenance in less than 1 day. These adverse reactions are abrogated to some extent using oral H1 and H2 antihistamines and systemic corticosteroid premedication protocols (i.e. loratadine 10 mg, ranitidine 150 mg, and prednisone 20 mg, each twice a day, beginning 2 days prior to initiation with discontinuation at the end of the protocol). Ultrarush VIT was associated with a significantly higher risk of SARs, including more severe reactions, in a study of 93 individuals with jack jumper ant (*Myrmecia pilosula*) allergy who were randomized to receive rush (over 9 weeks) versus ultrarush (over 2 weeks) immunotherapy. A lower, 50 μ g dose of venom (not commercially available for jumper jack ant) in this experimental study [39] was associated with fewer SARs, but there were concerns about optimal efficacy using this dose. However, Patella *et al.* [40] found that individuals randomized to an ultrarush protocol using either honeybee or

yellow-jacket venoms did not have a significantly higher number of SARs during buildup or maintenance compared with those who received rush or standard buildup protocols. Ultrarush protocols also are effective in children but are associated with a significant risk of SARs. Köhli-Wiesner *et al.* [41] demonstrated that SARs occur in 16% of children treated with a 1-day ultrarush protocol for honeybee or wasp hypersensitivity and the authors concluded that the risk of a SAR is similar to that seen in comparable adult ultrarush protocols. The authors recommend that if ultrarush protocols are considered for use in children that they be initiated in an inpatient intensive care unit for appropriate monitoring.

Experts agree that a maintenance dose of venom between 50 and 200 µg provides protection from sting-induced SARs; 100 µg of venom for each insect is the standard dose prescribed. If an individual has a sting-induced SAR on 100 µg, the dose is increased to 150–200 µg, which is more protective [42]. Many individuals, including children, are adequately protected using a 50 µg dose of venom. For example, 54 children received VIT every 4–6 weeks for 5 years with a 50 µg maintenance dose of the venom to which they were allergic. None reported a SAR to a field sting in the 6–16 years following initiation of VIT [43].

The interval of injections is gradually increased to every 4–6 weeks once the VIT maintenance dose is reached. Longer dosing intervals have been studied in an attempt to improve patient compliance. Sixty-seven patients received either conventional maintenance dosing, every 4–6 weeks, or extended maintenance dosing, every 3–4 months, in a prospective study by Simioni *et al.* There was no significant difference in the number of SARs between the two groups, suggesting that maintenance dosing every 3–4 months is as effective as conventional dosing in preventing future sting-induced SARs [44].

VIT failure, which occurs in 6–6.5% of individuals, can be related to several factors [45]. Honeybee VIT, serum tryptase levels greater than 20 µg/l, adult-onset cutaneous mastocytosis, and SARs during the VIT buildup and maintenance phase increase this risk. ACE inhibitor use is also associated with VIT failure, possibly because of increased kinin production during SARs caused by these medications. In a study [46] of 1532 Hymenoptera-allergic individuals, ACE inhibitor use was associated with the highest risk factor for failure of VIT.

DURATION OF THERAPY

Consensus expert opinion recommends a treatment period of 3–5 years with VIT for Hymenoptera-allergic individuals. Some require lifelong therapy,

including those with mast cell disorders. Others who may require lifelong therapy are those with more severe SARs or with reduced quality of life after treatment is stopped. Discontinuation of VIT can be considered in individuals who have completed therapy for 3–5 years and, in particular, who show a significant reduction or resolution of venom-specific IgE and convert to negative skin testing (see list below). Individuals who have completed at least 5 years of VIT have a 10% chance of a SAR with subsequent stings, even 10 years after the therapy is discontinued [47]. Sting challenge tests also are used to determine when VIT should be discontinued. Although there are concerns about the reproducibility of sting challenge tests, those who successfully pass such a challenge have improvements in the quality of life, giving individuals confidence about discontinuing VIT [48]. Considerations for discontinuing VIT are as follows:

- (1) consider discontinuation of VIT if
 - (a) completion of 3–5 years of therapy;
 - (b) conversion to
 - (i) negative skin testing;
 - (ii) negative venom-specific IgE testing;
 - (c) negative sting challenge test;
 - (d) increase in venom-specific IgG4 levels;
- (2) consider lifelong VIT if
 - (a) near-fatal SAR following initial sting;
 - (b) diagnosis of mast cell disorder (systemic mastocytosis, mast cell activation syndrome, and monoclonal mast cell activation syndrome) or elevated baseline serum tryptase greater than 11.4 µg/l;
 - (c) positive skin testing after 5 years of VIT;
 - (d) serious (grade 2–4) SAR sustained during VIT.

The basophil activation test also may be helpful in determining when to discontinue such therapy. CD63 expression, a marker of basophil activation, increases in venom-allergic individuals and can be used for the identification of the suspected venom which induced the SAR. A study by Eržen *et al.* followed 23 individuals treated with honeybee VIT and performed CD63-basophil activation testing (BAT) prior to initiation, after 1 year, and again after VIT was completed (approximately 5 years). No significant changes were seen after 1 year; however, 85% of individuals had significantly decreased CD63 expression after 2–4 years of VIT [49].

CONCLUSION

Hymenoptera sting-induced SARs lead to significant morbidity and mortality. Concerns remain about

the cost of VIT; however, no other treatment provides similar efficacy, especially when patient preference and quality of life are considered. Safety, including SARs triggered by VIT, especially with rush and ultrarush protocols, is always a concern, and caution should be exercised in high-risk populations, that is, women, honeybee allergy, and mast cell disorders. However, VIT remains the best option to prevent future SARs, reduce LLRs, as well as improve the quality of life for Hymenoptera-allergic individuals.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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