

Issues in stinging insect allergy immunotherapy: a review

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Purpose of review

The treatment of insect allergy by desensitization still continues to present with some unanswered questions. This review will focus mainly on articles that have dealt with these issues in the past 2 years.

Recent findings

With the publication in 2007 of Allergen Immunotherapy: a practice parameter second update, many of the key issues were reviewed and summarized. Other recent studies deal with omalizumab pretreatment of patients with systemic mastocytosis and very severe allergic reactions to immunotherapy. It would appear that venom immunotherapy is somewhat unique compared to inhalant allergen immunotherapy in that premedication prior to rush protocols may not be necessary and that intervals of therapy may be longer than with allergen immunotherapy. The use of concomitant medications such as beta-blockers may be indicated in special situations. Angiotensin-converting enzyme inhibitors can be stopped temporarily before venom injections to prevent reactions. The issue of when to discontinue immunotherapy remains unsettled and should be individualized to patient requirements.

Summary

The newest revision of the Immunotherapy Parameters provides much needed information concerning successful treatment with immunotherapy of Hymenoptera-sensitive patients.

Keywords

Hymenoptera venom immunotherapy, immunotherapy, omalizumab and immunotherapy, rush immunotherapy

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Introduction

Many of the key issues in insect allergy immunotherapy are patient selection, evaluation, testing, treatment, dosage and schedules for therapy, use of concomitant medication, remote therapy, and when to discontinue treatment. This review will focus on articles that dealt with these issues published primarily in the past 2 years. With the publication in 2007 of Allergen Immunotherapy: a Practice Parameter second update [1^{••}] (AIPP2), many of the above issues have been discussed, reviewed, and summarized.

Subcutaneous immunotherapy was shown to be effective for treatment of Hymenoptera insect allergy as well as for other insects such as fire ants [1^{••}] (page S34). In addition in a recent review, Golden [2] states 'venom immunotherapy (VIT) is probably the most effective form of immunotherapy available to our profession.'

Patient selection

Indications for VIT or fire ant whole-body extract from AIPP2 [1^{••}] Summary Statement 22: 'VIT should be

strongly considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE antibodies. In the USA, patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants. Adults and children with a history of systemic reactions to the imported fire ant (*Solenopsis* species) who have positive skin test results or venom-specific IgE antibodies should be treated with allergen immunotherapy. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.' However, increased risk of severe sting anaphylaxis occurs in beekeepers and their families [3].

Patients with systemic mastocytosis are at risk for more severe insect venom reactions. A review of anaphylaxis in patients who have systemic mastocytosis [4] showed that

insect stings were the most common cause of anaphylaxis and most of these were very severe. De Olano *et al.* [5] reported on 21 patients with systemic mastocytosis who underwent venom immunotherapy. Six patients of the 21 or 29% experienced systemic reactions during the buildup phase. Two patients were discontinued; one voluntarily dropped out and the other because of severe reactions. Overall there was 75% protection rate from VIT in this group of patients. In a letter to the editor, Bonnadonna *et al.* [6] reported on an additional 16 patients with systemic mastocytosis who were successfully treated with immunotherapy.

Evaluation, testing

From AIPP2 [1^{••}]: ‘Venom skin test results are positive in more than 65% of patients with a history of a systemic reaction to a Hymenoptera sting compared with 15% of the population that has not had a systemic reaction. In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended. If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific IgE tests, or both be repeated 3–6 months later. Approximately 5 to 10% of patients with negative venom skin test results with a history of a systemic reaction have a positive venom-specific IgE test result.’ If the skin test is negative and the in-vitro test positive, AIPP2 recommends VIT in patients who have sustained severe anaphylaxis to an insect sting. The last section deals with patients with negative venom skin test results and negative venom-specific IgE test results being successfully treated with VIT if the selected venom is based on the results of a sting challenge [1^{••}] (S49).

The American Academy of Allergy Asthma & Immunology (AAAAI) Insect Committee’s modified working guidelines state that a negative venom skin test result or in-vitro assay result is not a guarantee of safety, and patients with suspected higher risk should be counseled about avoidance strategies, use of epinephrine injectors, and the emergency and follow-up care of the acute allergic reaction. The AAAAI Insect Committee also acknowledged that the management of patients with a positive history and negative venom skin test results requires clinical judgment and ongoing research [1^{••}].

Treatment: subcutaneous injections as the route of immunotherapy, sublingual immunotherapy, omalizumab

All of the past studies have used subcutaneous injections as the route of immunotherapy (SCIT). A review of Medline sources did not retrieve reported sublingual

routes [sublingual immunotherapy (SLIT)] for venom hypersensitivity treatment.

Omalizumab has been used successfully to decrease reactions to rush immunotherapy [7]. There has been one case study by Schulze *et al.* [8] involving a 15-year-old son of a beekeeper who had a systemic reaction with a 2-day Rush protocol at the 10 µg level. He was treated with 300 mg of omalizumab and then 2 weeks later, he completed the rush protocol to 100 µg without incident. One year later on maintenance therapy, he was challenged. This resulted in only a mild reaction thus indicating successful specific immunotherapy. Kontou-Fili [9] reported using 300 mg of omalizumab (twice the recommended dose based on IgE level and weight) 7 days and then eventually 1 hour before VIT in a patient with mastocytosis who previously had mild-to-moderate systemic reactions with most of his therapy. After omalizumab, he was able to tolerate 100 µg of bee venom without adverse effects.

Dosage for therapy

The recommended dose [10] is 100 µg of venom as maintenance. From AIPP2 [1^{••}]: ‘There are conflicting data over whether lower doses (50 µg) are less effective, but there are also data showing that 200 µg is more reliably effective’. Glerant *et al.* [11] showed that 200 µg resulted in a greater degree of change in venom-specific IgE antibody levels and skin test sensitivity than when maintaining a 100 µg dose. In a review of advances in venom immunotherapy by Bilo and Bonifazi [12[•]], they point out that European maintenance therapy frequently uses a depot preparation not available in the USA.

Schedules

One manufacturer’s package insert for venom immunotherapy [8] describes a buildup to maintenance in 15 doses; another uses a modified cluster approach and achieves maintenance in eight doses [13] (Table 1). Immunotherapy following these schedules or modifications of them are usually done in an outpatient environment with appropriate precautions and treatment for anaphylaxis available. Very rapid or ultrarush immunotherapy schedules that reach maintenance levels in 2.5–4 h have been described [14,15]. Rush protocols for administration of Hymenoptera venom have not been associated with the high incidence of systemic reactions observed with inhalant immunotherapy [1^{••}] (S59). Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush immunotherapy is usually unnecessary. In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant whole-body extract, there was no statistically significant differences in the systemic reaction rates between the premedication

Table 1 Comparison of two-package insert schedules

Number of days	Amt ALK [11] (μ g)	Hollister–Stier [8] (μ g)	Week ^a
1	0.001 0.01 0.1	0.05	1
8	0.1 0.5 1.0	0.1	2
15	1 5 10	0.2	3
22	10 20	0.4	4
29	20 30	0.5	5
36	30 30	1.0	6
43	40 40	2.0	7
50	50 50	4.0	8
57	100	5.0	9
64		10	10
71		20	11
78		40	12
85		60	13
92		80	14
99		100	15

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^a Assuming one office visit per week.

and placebo premedication group (3.6% of the premedication group vs. 6.7% of the placebo group, $P = 0.87$) [1••] (page S59). Pasaoglu *et al.* [16] reported on 14 patients who underwent a 7-day rush immunotherapy with an increase in specific IgG4 levels but no change in specific IgE levels and skin tests. One patient treated with bee venom developed four mild systemic reactions on being given four out of 469 injections. They concluded that the rush protocol was safe and effective.

Steiss *et al.* [17] modified an ultrarush protocol for in hospital use for children aged 4–18 years. Thirty-eight children received eight injections 30–60 min apart, seven on the first day. There were no reactions in 25 (58%) of the patients, 11 (25.6%) had extensive redness, and seven (16.2%) had local reactions with higher doses (60–80 μ g.) Another use of ultrarush venom desensitization was reported by Oren *et al.* [18] in a patient who had severe systemic reactions to conventional VIT. Ultrarush VIT was successfully accomplished by premedication with 40 mg of prednisone, 180 mg fexofenadine, and 150 mg of ranitidine in a 2-day protocol.

Intervals of therapy

Most studies with venom immunotherapy have shown that the interval between maintenance injections may be increased to 3 months. Two studies that have dealt with extending this period to 6 months have had conflicting

results, Baenkler *et al.* [19] reported continuous VIT at 6-month intervals was safe and effective in a total of 176 patients ranging from 1 to 25 years of treatment. In 162 re-stings, there was one systemic, seven nonserious reactions, and 154 local reactions. Contrarily, Goldberg and Confino-Cohen [20] concluded that administration at 6-month intervals did not provide suitable protection after one patient had a systemic reaction at 4 months, and two field stings resulted in mild systemics, and in 14 sting challenged patients, three (21%) developed systemic reactions. For comparison, a recent study by Hafner *et al.* [21] looked at responses of 100 patients who had VIT and for at least 3 years before discontinuing therapy and were accidentally re-stung with the insect to which they were allergic. Ninety-two had only local reactions and eight or 8% had systemic allergic reactions.

Concomitant medication

Medications that may augment the response to immunotherapy include antihistamines and monteleukast. Mueller *et al.* [22] reported years ago that the use of antihistamines, specifically terfenadine during the rush phase of VIT, appeared to augment the immune response to insect venom desensitization. A study by Wohrl *et al.* [23] that compared 10 mg of monteleukast and 5 mg of desloratadine with placebo found that the development of local reactions was significantly delayed by monteleukast.

Drugs that may increase side effects of VIT include beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. While, in general, immunotherapy should not be administered to patients who are receiving beta blocking medications, the Immunotherapy Parameters state: 'However, immunotherapy is indicated in patients with life-threatening stinging insect hyper-sensitivity who also require beta-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction [1••] (page S34).'

Muller and Haeberli [24] studied 1389 VIT followed for 34 months. There were 25 patients who received concomitant beta-blocker medications. Three (12%) of the 25 patients receiving beta-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving beta-blockers. Systemic reactions after a field sting or challenge occurred in one out of seven (14.3%) cardiovascular patients receiving beta-blocker medications compared with four out (13.8%) of 29 cardiovascular patients not receiving beta-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving beta-blocker medications. They concluded the 'combination of beta-blockers with venom immunotherapy may be

indicated in heavily exposed patients with severe cardiovascular disease.'

ACE inhibitors have been associated with severe allergic reactions in sensitive individuals who were stung or received venom immunotherapy. A review by Stumpf *et al.* [25] concluded ACE inhibitors may exacerbate the response to insect venom and that it seems prudent that insect venom patients should avoid taking ACE inhibitors. They also suggest 'in patients in whom VIT is appropriate, temporary discontinuation of the ACE inhibitor prior to each venom injection may prevent subsequent adverse reactions.' One manufacturer's package insert [11] recommends treatment with ACE inhibitors be stopped for at least 24 h prior to receiving VIT.

Remote therapy

Home administration, Summary Statement 62: In rare and exceptional cases, when allergen immunotherapy cannot be administered in a medical facility and withholding this therapy would result in a serious detriment to the patients' health (e.g., VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient basis. If this approach is used, informed consent should be obtained from the patient, and the person administering the injection to the patient must be educated about how to administer immunotherapy and recognize and treat anaphylaxis (S62). The Immunotherapy Parameters conclude: 'Therefore each case should be considered individually by weighing the benefits and risks. For children who have had a history of anaphylaxis to stinging insects or have severe allergic disease, the benefits of allergen immunotherapy might outweigh the risks' [1**].

Discontinuing treatment

The subject of when to discontinue venom immunotherapy is still not completely settled. From AAIP2 [1**] 'Summary Statement 55b: Although there are no specific tests to distinguish which patients will relapse after discontinuing VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years' (S36).

With regard to how long immunotherapy should be considered the document suggests: 'Long-term follow-up studies suggest that a 5-year immunotherapy treatment course for Hymenoptera hypersensitivity might be sufficient for most allergic individuals. However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported. Nevertheless, systemic

reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe.' [1**] It is important to note ... 'Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE. Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment. The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those with less than 5 years of treatment.' Golden [2] summarized this issue in this way: 'the patients in whom treatment should not so readily be stopped are the ones with the extreme or near-fatal history, the ones who had a systemic reaction during immunotherapy, the honeybee allergic patients, and those with less than 5 years of treatment. Obviously, age, underlying medical conditions, and frequency of exposure should be taken into account.' Patients who have systemic mastocytosis may need treatment for an indefinite period of time based on the data of de Olano *et al.* [5].

Conclusion

The newest revision of the Immunotherapy Parameters provides much needed information concerning treatment with immunotherapy of Hymenoptera-sensitive patients. In addition, there is a place for anti-IgE therapy in certain situations such as supersensitive patients, those needing rush protocols, or patients with systemic mastocytosis. It would appear that venom immunotherapy is somewhat unique compared to inhalant allergen immunotherapy in that premedication prior to Rush protocols may not be necessary and that intervals of therapy may be longer than with allergen immunotherapy. The use of concomitant medications such as beta-blockers may be indicated in special situations. ACE inhibitors can be stopped temporarily before venom injections to prevent reactions. The issue of when to discontinue immunotherapy remains unsettled and should be individualized to patient requirements.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 365).

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This publication is essential reading for practitioners of any type of allergen or venom immunotherapy.

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