
Insect sting allergy and venom immunotherapy

David B. K. Golden, MD

Objective: To review specific aspects of venom immunotherapy (VIT) in the context of allergen immunotherapy (AIT) in general.

Data Sources: Immunotherapy Collegium II presented at the 2005 Annual Meeting of the American College of Allergy, Asthma and Immunology.

Study Selection: Discussions of VIT during Immunotherapy Collegium II.

Results: The decision to recommend VIT is based on a detailed history and confirmatory diagnostic tests, as well as a knowledge of the natural history of the disease and its impact on quality of life. Skin tests and radioallergosorbent tests are complementary in that neither can detect all cases of insect sting allergy. Unlike inhalant AIT, rush regimens are as safe as slower regimens for initial VIT, and 4- to 8-week maintenance intervals are typical for VIT. In contrast to inhalant AIT, large local reactions are common and expected with VIT and should not limit the maintenance dose. VIT induces full immune tolerance in 85% of patients after 5 years, whereas this occurs in 30% to 50% of patients with inhalant AIT. VIT is often discontinued after 5 years even though skin test results are usually still positive, but a 10% to 15% chance of reaction persists for many years and is greater in patients who had near-fatal reactions before treatment, those who had systemic reactions during VIT, those with honeybee allergy, and those treated for less than 5 years. Children who receive 3 to 5 years of VIT have a lasting immune tolerance for 10 to 20 years afterward.

Conclusion: The appropriate use of VIT for prevention of insect sting allergy requires knowledge of the natural history of the disease and would benefit from a better understanding of the mechanisms of successful immunotherapy for the induction of immune tolerance.

Ann Allergy Asthma Immunol. 2006;96(Suppl 1):S16–S21.

INTRODUCTION

In keeping with the theme of Immunotherapy Collegium II, presented at the 2005 Annual Meeting of the American College of Allergy, Asthma and Immunology, this article will focus on specific aspects of venom immunotherapy (VIT) in the context of allergen immunotherapy (AIT) in general. One of the most important aspects of AIT is appropriate patient selection, and one of the basic considerations when initiating VIT is the history. An insect sting can cause a normal local reaction, a large local reaction (a late-phase IgE-dependent reaction causing severe and prolonged swelling), a cutaneous systemic reaction (hives, angioedema, flush, but no other manifestations), or anaphylaxis (with hypotension, dizziness, dyspnea, or throat symptoms). The details of the history are of great importance, and they are an integral part of our decision making in beginning VIT, during immunotherapy, and when considering discontinuing immunotherapy.

The indications for VIT require a detailed history, confirmation by venom skin test or radioallergosorbent test (RAST), and a knowledge of the natural history. Without knowing what is going to happen without treatment, we do not really know whether (or why) to proceed with treatment. Another consideration is quality of life, because patients who

may not technically require VIT might still benefit from it in measurable ways. Published reports on quality of life in insect allergy showed the benefit of VIT, whereas patients who were given only epinephrine had deterioration in quality of life.¹

Our diagnostic tests, venom skin tests, and RASTs have good sensitivity and specificity, but we must remember that neither is perfect.² The skin test is preferred because of its greater sensitivity. Among patients with positive venom skin test results, 15% to 20% have negative RAST results; therefore, these cases would have been missed by RASTs alone. If the RAST result is negative and there is a convincing history, skin tests are required. We tend to forget that the converse is also true: in patients with negative skin test results, 10% to 15% have a positive RAST result. Therefore, in the face of a convincing history and a negative skin test result, we must check the RAST result, which can be considerably elevated even though the skin test result is negative.

Does the RAST or skin test predict the severity of the reaction? Not reliably. There is a linear correlation between skin test sensitivity and severity of the sting reaction, but too many outliers exist at both ends of the spectrum.³ There are people who have strong positive skin test results, such as large local reactors, who infrequently have systemic reactions to stings. Conversely, there are patients who have a weak or negative skin test result and yet have a severe systemic reaction to a subsequent sting. We need to realize that neither test is perfect, and we should therefore use them in a complementary fashion.

Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland.
This study was supported by National Institutes of Health grant 2R01-AI08270 and National Institutes of Health General Clinical Research Center grant 5MO1-RR02719.

Received for publication April 8, 2005.

Accepted for publication in revised form April 28, 2005.

The risk of reaction in untreated patients varies widely.⁴⁻⁸ When the outcome of subsequent stings is analyzed in many published studies of patients with a history of systemic reaction and positive venom skin test results, the mean reaction rate is 46%. However, a tremendous range exists among the studies, from 65% to 30%. Some of the reasons for this range are related to the natural history of the disease and the patients included in different studies (Table 1). Some of those studies actually included patients with large local reactions who have a low risk of systemic reaction.^{9,10} Some included children who had cutaneous systemic reactions and were also known to have a relatively low risk of systemic reaction.^{11,12} Even adults with cutaneous systemic reactions have a relatively low risk of future systemic reaction. At highest risk are individuals, including children, who had a more severe systemic reaction. In the study we recently published showing the 10- to 20-year follow-up of children, those with moderate or severe reactions did not necessarily outgrow the allergy. They had a 30% reaction rate, which is similar to the reaction rate in untreated adults after 10 to 20 years. We now realize that children with more severe reactions remain at risk in the long run.¹²

VIT is probably the most effective form of immunotherapy available to our profession. There were only 2 controlled clinical trials on VIT: one was performed at Johns Hopkins by Hunt et al⁵ and the other was performed by Muller et al in Switzerland.¹³ Both showed essentially the same results. The Johns Hopkins study was controlled both by placebo and by the previously standard treatment for 50 years: whole-body extract. Among the patients treated with venom, only 1 of 55 reacted to a sting, demonstrating the 98% efficacy of VIT. It was interesting that the reaction rate among patients treated with placebo or whole-body extract was not 100%. The fact that only 60% reacted spurred studies, still ongoing, to try to understand what makes a sensitized individual react, or not react, to a given sting. There is no proven predictor of reactivity in each individual. All we can say is that there is a

statistically elevated risk in certain patients, but we cannot exactly predict who is going to react or not.

VIT is not usually recommended to patients with large local reactions because of the low risk of a subsequent systemic reaction to a sting. Some would benefit from improved quality of life because of their fear of developing a systemic reaction. Others who have frequent exposure would like to be able to prevent the severe swelling and the need for prednisone multiple times each year. The group at Wilford Hall has reported that fire ant extract immunotherapy prevents large local reactions, and in our pilot study we found that VIT-treated patients had a greater than 50% reduction in size and duration of swelling, compared with minimal change in untreated patients.^{14,15} I hope to be able expand on this study in the next few years with a multicenter clinical trial of VIT for large local reactions.

VIT can present many complexities, but I will focus on a few specifics. As with all types of immunotherapy, we must consider who should receive the treatment, how to begin the treatment regimen, optimal maintenance dose and interval, and, of course, the duration. VIT is in many ways a model for AIT, and yet there are some differences (Table 2). For example, the initiation regimen can be a relatively slow traditional regimen that might build up during 4 to 6 months or a relatively rapid regimen that reaches maintenance dose after 6 to 8 weekly injections. We have shown that with venom they are equally safe.¹⁶ In fact, Bernstein et al and others¹⁷⁻²⁰ have reported that a 2- to 3-day rush immunotherapy regimen with venom is as safe as any other. With inhalants, on the other hand, many studies have shown that rush regimens are not necessarily as safe and can cause more systemic reactions. Another consideration is the maintenance dose, which is uniform for VIT. Every patient is expected to reach the full dose of 100 μ g of each venom, because lower doses may not be fully effective. In contrast, in inhalant immunotherapy the maintenance dose is adjusted "as tolerated," depending on local (or systemic) reactions. Local reactions, sometimes quite large, are expected with venom and may slow the treatment schedule but should not prevent us from reaching full dose. On the other hand, despite proven target doses, we generally try to avoid large swellings with inhalant AIT, which tends to limit the dose in some patients.

Maintenance intervals also vary in immunotherapy. With inhalants the treatment interval is usually in the range of 1 to

Table 1. Risk of Systemic Reaction in Untreated Individuals With Positive Skin Test Results Related to History and Age*

Original sting reaction severity	Age at reaction	Risk of systemic reaction, %	
		1-9 y	10-20 y
No reaction	Adult	17	
Large local	All	10	5
Systemic			
Cutaneous	Child	10	5
	Adult	20	10
Anaphylaxis	Child	40	30
	Adult	60	40

*Reproduced with permission from Golden DBK. Insect sting allergy. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, eds. *Middleton's Allergy: Principles and Practice*. 6th ed. St Louis, MO: Mosby; 2003:1475-1486.

Table 2. Allergen Immunotherapy: Venom vs Inhalant

	Venom	Inhalant
Rapid vs slow regimen	As safe	More risky
Maintenance dose	Uniform	As tolerated
Local reactions	Expected	Avoided
Maintenance interval, wk	4-8	1-4
Duration, y	3-10	3-10
Long-term tolerance, %	85	30
Exposure	Infrequent	Daily/seasonal
Diagnostic priority	Sensitivity	Specificity

4 weeks, whereas with venoms it is more typically 4 to 8 weeks. The duration of immunotherapy has not been fully studied, but there is not necessarily a difference between venom and inhalants. On the other hand, the tolerance induced by long-term immunotherapy appears to be different with venom than with inhalants. Durham et al and others²¹⁻²⁷ have reviewed some of the long-term benefits of immunotherapy. A true long-lasting elimination, not just reduction, of their symptoms occurs in perhaps 30% to 50% of the patients who stop inhalant immunotherapy, but 85% of patients who discontinue VIT after 5 years will never react to another sting.²⁸ The ability to achieve such immune tolerance may depend on the pattern of allergen exposure. Inhalant allergens are associated with frequent exposure, whether it is daily or seasonal, whereas stings are infrequent and may occur years apart. Another interesting difference between VIT and inhalant AIT has to do with the selection of patients for treatment. The priority for insect allergy favors sensitivity of diagnostic tests. We feel more inclined not to miss a case with venom because of the potentially disastrous consequences. With inhalant allergy we favor optimum specificity of the test and generally avoid intradermal skin tests, because their sensitivity is relatively lower than that of puncture skin tests. In doing so, we accept that we may miss a few cases, but the consequences will not be fatal. We are more inclined to risk the so-called unnecessary treatment with venom in some patients, because we do not want to miss a case that will lead to a severe sting reaction.

When we begin VIT, several decisions must be made. The build-up regimen can range from 6 hour ultra-rush to a 2- to 3-day rush regimen (which is the norm in Europe), a 6- to 8-week modified rush regimen, or a traditional regimen of 3 to 6 months of weekly injections. The maintenance interval is described in the product package insert as being 4 weeks indefinitely. Almost no published literature exists on the 6- to 8-week regimen that is now accepted in the practice parameters.²⁹ Some recent publications report the safety of a 12-week maintenance interval, especially for prolonged therapy.³⁰ During immunotherapy, premedication with antihistamines on the day of each injection significantly reduced the occurrence of both local reactions and even some systemic reactions.^{31,32} In the study by Muller et al,³² it even seemed to have a therapeutic benefit, because challenge sting caused fewer systemic reactions in patients who had received antihistamine before each shot. This is not yet understood and has not yet been confirmed in other studies.

The standard maintenance dose is 100 μ g of each venom. Although some claim 50 μ g to be equally effective, there is evidence to the contrary, showing that 200 μ g is clearly more effective and is indicated in some patients.³³ Although mixed vespid venom treatment has shown 98% efficacy, single venom therapy is 85% to 90% effective, and honeybee treatment is only 75% to 85% effective.³⁴ I should clarify that we have always defined efficacy as the total elimination of systemic reaction, not just reduced reaction. In a study of VIT treatment failures, Rueff et al³³ showed that when the dose

was increased to 200 μ g the patients were fully protected against systemic reactions to stings. Although this is not necessary in every patient, the problem is that it is hard to identify a patient in whom treatment will fail before failure occurs. We have reported that we could identify most patients in whom treatment will fail by measuring the venom-specific IgG antibody level.³⁵ In our study, patients with an IgG level greater than 3 μ g/mL had a 1.6% reaction rate to sting challenge, whereas those who had a lower IgG level had a 27% reaction rate to sting challenge. However, some patients who had a low IgG level did not react to a sting. This is understandable, since even untreated patients at highest risk do not always react to a sting. Although we could increase the dose in patients who have a low IgG level, this would lead to overtreatment of some patients.

Our studies of the IgG antibody response gave us some early insight regarding potential discontinuation of VIT. The venom IgG level was predictive of clinical protection only in the patients who had 4 years or less of treatment. In patients who had more than 4 years of VIT, even those with low IgG levels had a relatively low frequency of systemic reaction, which suggested that after 4 years some other protective mechanism was coming into play. Although we now know more about mechanisms of immunotherapy, most of the published data pertain to the protection achieved during early immunotherapy.^{36,37} We still have limited evidence of what is happening after more than 4 years of immunotherapy that leads to true immune tolerance.³⁸

During our observation of VIT for 5 years or more, we also noted that the mean venom IgE level declines steadily with time, reaching relatively low levels after 4 years. These findings led us to consider the possibility of discontinuing treatment after 5 years. For this study we recruited 74 patients who had at least 5 years of venom immunotherapy (mean, 6 years). When therapy was stopped, there had been a 1-log (10-fold) decline in both the skin tests and RASTs, but 75% of the patients still had positive venom skin test results.³⁹ Our first concern was whether the venom IgE level would rebound or whether resensitization would occur after a sting. Fortunately, these problems did not occur. After stopping treatment, the skin test result and venom-IgE level continued to decline in a linear fashion, even though we administered challenge stings to these patients every 1 or 2 years. We ultimately observed both challenge stings and field stings in 113 patients who had not been receiving treatment for up to 13 years.²⁸ In the first 4 years after stopping treatment, 10% of the patients had a systemic reaction to a sting. We believed the reaction rate would get lower and lower with time, but this has not occurred. After 5 to 13 years of not receiving treatment (mean, 9.6 years), the frequency of systemic reactions to stings was still 10%. These results showed that each sting had a 10% chance of causing a reaction even more than 10 years after discontinuing therapy. However, when a patient gets stung several times during a period of years, the chance that one of those stings will cause a systemic reaction

increases such that the cumulative relapse rate during our extended observations was almost 17%.

One of the risk factors for relapse after stopping treatment is the occurrence of a systemic reaction during immunotherapy, whether to an injection or a sting. We found such patients had a 46% relapse rate, whereas the patients who had no systemic reaction during immunotherapy had a relapse rate of 8%.⁴⁰ Our results confirmed the observation made by Muller et al.

When relapse occurs, the reactions are generally much less severe than before immunotherapy, even though there are occasionally severe reactions. The history of the pretreatment sting reaction is helpful in evaluating the risk of relapse. Both Reisman⁶ and Keating et al.⁴¹ showed that the patients with the more severe history had a higher risk of relapse. We did not find a higher frequency, but we are more concerned with the likelihood that if a patient with a severe history were to relapse, the reaction would be more likely to be severe. Therefore, people who have near-fatal or unconscious reactions should continue with immunotherapy for life. When we review the details on some of the patients who have relapsed, several specific points emerge. We have described patients who had negative skin test results the last time we tested them and yet they had a systemic reaction when they got stung. All had detectable venom IgE on RASTs. Therefore, negative skin test results during or after VIT are not a guarantee of safety when treatment is discontinued. We have also observed great variability, with some patients having a reaction to one sting but not to the subsequent or preceding sting. This variability is similar to what we see before treatment as well.

Many investigators have studied the duration of VIT. Some investigators have suggested that 3 years is sufficient, especially in children, but many studies had inclusion criteria, such as marked decline of venom RAST results and negative sting challenge results, during treatment.⁴²⁻⁴⁵ Other investigators have concluded that 5 years of VIT is better than 3 years. Keating et al.,⁴¹ with Yunginger's group at the Mayo Clinic, showed that the IgE reduction is more pronounced after 5 years than after 2 to 4 years. That same study showed a much lower reaction rate to stings when they had 5 years or more of VIT compared with 2 to 4 years. After years of study, the more recent data of Lerch and Muller⁴⁶ showed a significantly lower reaction rate with treatment of more than 50 months than with treatment of less than 50 months. Muller et al.³⁴ have shown that honeybee allergy is different than yellow jacket or wasp allergy in a number of ways. Honeybee allergic patients have more reactions to venom injections, more treatment failures during treatment, and more relapses after treatment. It is not yet clear whether the reaction rate decreases with time after stopping VIT. We have not found such a decline after 10 years, whereas there was an early trend to decreasing frequency of reaction in the study by Lerch and Muller. In summary, 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 also be taken into account.

We have recently reported our observations on the long-term outcomes in children with insect sting allergy with and without VIT.¹² Without treatment, the children with cutaneous systemic reactions had a 13% systemic reaction rate, similar to that observed by Valentine and Schuberth.¹¹ After 3 to 5 years of VIT, the reaction rate in children with a history of cutaneous systemic reactions was 0, even 10 to 20 years after stopping treatment. Children with moderate or severe systemic reactions to stings should certainly receive 3 to 5 years of VIT, because without it they had a 32% chance of systemic reaction as adults, whereas with VIT they had only a 5% reaction rate, even 10 to 20 years after treatment.

I have presented some of the major issues related to VIT in the context of AIT in general. There are interesting parallels and differences between VIT and inhalant AIT, which underscore the range of immunologic and environmental factors that influence the application and outcome of our treatments for allergic disease. The appropriate use of VIT for prevention of insect sting allergy requires knowledge of the natural history of the disease and would benefit from a better understanding of the mechanisms of successful immunotherapy for the induction of immune tolerance.

REFERENCES

1. Oude-Elberink JNG, deMonchy JGR, vanderHeide S, Guyatt GH, Dubois AEJ. Venom immunotherapy improves health-related quality of life in yellow jacket allergic patients. *J Allergy Clin Immunol.* 2002;110:174-182.
2. Golden DBK, Kagey-Sobotka A, Hamilton RG, Norman PS, Lichtenstein LM. Insect allergy with negative venom skin tests. *J Allergy Clin Immunol.* 2001;107:897-901.
3. Day J. A comparison of venom concentrations of 0.1 µg/ml and 1.0 µg/ml as indicator of sensitivity to honeybee stings. *J Allergy Clin Immunol.* 1986;77:142.
4. Golden DBK, Langlois J, Valentine MD. Treatment failures with whole body extract therapy of insect sting allergy. *JAMA.* 1981;246:2460-2463.
5. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med.* 1978;299:157-161.
6. Reisman RE. Natural history of insect sting allergy: Relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol.* 1992;90:335-339.
7. Franken HH, Dubois AEJ, Minkema HJ, vanderHeide S, deMonchy JGR. Lack of reproducibility of a single negative sting challenge response in the assessment of anaphylactic risk in patients with suspected yellow jacket hypersensitivity. *J Allergy Clin Immunol.* 1994;93:431-436.
8. vanderLinden PG, Hack CE, Struyvenberg A, vanderZwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol.* 1994;94:151-159.
9. Mauriello PM, Barde SH, Georgitis JW, Reisman RE. Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol.* 1984;74:494-498.

10. Graft DF, Schuberth KC, Kagey-Sobotka A, et al. A Prospective study of the natural history of large local reactions following Hymenoptera stings in children. *J Pediatr*. 1984;104:664–668.
11. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med*. 1990;323:1601–1603.
12. Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children with and without venom immunotherapy. *N Engl J Med*. 2004;351:668–674.
13. Muller U, Thurnheer U, Patrizzi R, Spiess J, Hoigne R. Immunotherapy in bee sting hypersensitivity: bee venom versus wholebody extract. *Allergy*. 1979;34:369–378.
14. Walker R, Jacobs J, Tankersly M, Hagan L, Freeman T. Rush immunotherapy for the prevention of large local reactions secondary to imported fire ant stings. *J Allergy Clin Immunol*. 1999;103:S180.
15. Golden DBK, Hamilton RG, Kelly D, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Venom immunotherapy for large local reactions to insect stings: a pilot study [abstract]. *J Allergy Clin Immunol*. 2004;113:S74.
16. Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med*. 1980;92:620–624.
17. Bernstein JA, Kagan SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. *Ann Allergy*. 1994;73:423–428.
18. Birnbaum J, Charpin D, Vervloet D. Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy*. 1993;23:226–230.
19. Birnbaum J, Ramadour M, Magnan A, Vervloet D. Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors. *Clin Exp Allergy*. 2003;33:58–64.
20. Goldberg A, Confino-Cohen R. Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy. *Ann Allergy*. 2003;91:405–410.
21. Jacobsen L, Nuchel-Peterson B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts, IV: results from long-term (6 year) follow-up. *Allergy*. 1997;52:914–920.
22. Eng PA, Reinhold M, Gnehm HPE. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy*. 2001;57:306–312.
23. Cools M, vanBever HP, Weyler JJ, Stevens WJ. Long-term effects of specific immunotherapy, administered during childhood in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. *Allergy*. 2000;55:69–73.
24. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol*. 1995;96:879–885.
25. DesRoches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, V: duration of the efficacy of immunotherapy after its cessation. *Allergy*. 1996;51:430–433.
26. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow up study in patients with grass pollen rhinitis. *Allergy*. 1988;43:523–529.
27. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass pollen immunotherapy. *N Engl J Med*. 1999;341:468–475.
28. Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol*. 2000;105:385–390.
29. Moffitt JE, Golden DBK, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol*. 2004;114:869–886.
30. Goldberg A, Confino-Cohen R. Maintenance venom immunotherapy administered at 3-month intervals is both safe and efficacious. *J Allergy Clin Immunol*. 2001;107:902–906.
31. Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 1997;100:458–463.
32. Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific allergen immunotherapy. *J Allergy Clin Immunol*. 2001;107:81–86.
33. Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses. *J Allergy Clin Immunol*. 2001;108:1027–1032.
34. Muller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol*. 1992;89:529–535.
35. Golden DBK, Lawrence ID, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. *J Allergy Clin Immunol*. 1992;90:386–393.
36. Akdis CA, Blesken T, Akdis M, et al. Role of interleukin 10 in specific immunotherapy. *J Clin Invest*. 1998;102:98–106.
37. Akdis M, Verhagen J, Taylor A, et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med*. 2004;199:1567–1575.
38. Plaut M, Rotrosen D. Tolerance induced by allergen immunotherapy. In: Lockey RF, Bukantz SC, Bousquet J, eds. *Allergens and Allergen Immunotherapy*. 3rd ed. New York, NY: Marcel Dekker; 2004:681–682.
39. Golden DBK, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: outcome after five years. *J Allergy Clin Immunol*. 1996;97:579–587.
40. Golden DBK, Kwiterovich KA, Addison BA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. *J Allergy Clin Immunol*. 1998;101:298–305.
41. Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. *J Allergy Clin Immunol*. 1991;88:339–348.
42. Urbanek R, Forster J, Kuhn W. Discontinuation of bee venom immunotherapy in children and adolescents. *J Pediatr*. 1985;107:367–371.
43. Haugaard L, Norregaard OFH, Dahl R. In-hospital sting challenge in insect venom-allergic patients after stopping venom immunotherapy. *J Allergy Clin Immunol*. 1991;87:699–702.

-
44. Muller U, Berchtold E, Helbling A. Honeybee venom allergy: results of a sting challenge 1 year after stopping venom immunotherapy in 86 patients. *J Allergy Clin Immunol.* 1991;87:702–709.
 45. Reisman RE. Duration of venom immunotherapy: relationship to the severity of symptoms of initial insect sting anaphylaxis. *J Allergy Clin Immunol.* 1993;92:831–836.
 46. Lerch E, Muller U. Long-term protection after stopping venom immunotherapy. *J Allergy Clin Immunol.* 1998;101:606–612.

Requests for reprints should be addressed to:
David B. K. Golden, MD
Johns Hopkins Asthma and Allergy Center
5501 Hopkins Bayview Blvd
Baltimore, MD 21224
E-mail: dgolden1@jhmi.edu