

Should routine measurements of serum venom-specific IgG be a standard of practice in patients receiving venom immunotherapy?

In this issue of the JOURNAL Golden et al.¹ present data relating the level of serum venom-specific IgG to the response to intentional insect sting challenges in venom-allergic patients receiving maintenance venom immunotherapy (VIT). They conclude that measurement of this parameter identifies patients at greater risk for sting reactions, despite VIT, and they recommend routine monitoring of the level of serum venom-specific IgG after "maintenance treatment is established (usually 4 to 6 months) and again after 1 to 2 years of therapy." If levels are low, less than 3 $\mu\text{g/ml}$, "adjustments in dose or frequency of VIT are warranted to raise the level and the clinical protection." In my opinion, review of these data, review of other relative data, and the secondary consideration of cost factors and accessibility of these tests, does not support this recommendation, and in fact suggest the opposite—routine measurement of venom IgG antibody titers is not warranted.

Elevated levels of serum venom-specific IgG have been associated with immunity to insect stings. Initial observations were made in beekeepers who are highly immune to bee stings and, as a rule, have high levels of serum venom-specific IgG, often in direct correlation to the number of stings received during the beekeeping season.² In addition, the occasional beekeeper who becomes allergic has lower levels of IgG antibody. The protective effects of passive immunization of insect-allergic patients with hyperimmune gamma globulin obtained from beekeepers provided more specific documentation of the role of IgG antibodies.^{3,4} Finally, successful VIT has been associated with elevated levels of serum venom-specific IgG.⁵

On the other hand, clearly other factors exist that mediate clinical protection or lack of reaction to subsequent insect stings in individuals who have had prior venom anaphylaxis. In unselected patients who have had venom anaphylaxis and do not receive VIT, approximately 40% do not react to re-stings, either intentional sting challenges or field re-stings.^{6,7} These patients usually lack "protective" IgG antibody. The response to intentional sting challenges in these untreated patients cannot be correlated with serum

venom-specific IgG titers.^{8,9} After cessation of VIT, tolerance to insect stings is present frequently in the absence of significant titers of IgG antibody. Patients who have received VIT for 3 to 5 years and have persistent positive venom skin tests tolerate intentional sting challenges from 1 to 3 years after cessation of VIT, often in the absence of "protective" levels of IgG antibody.¹⁰⁻¹²

In their report, Golden et al.¹ describe the effect of intentional re-stings in venom-allergic patients who are receiving VIT. These patients were divided into two groups on the basis of the levels of yellow jacket venom IgG antibody. Using an arbitrary parameter of 3 $\mu\text{g/ml}$ as the dividing point between responders and nonresponders, the authors report that after sting challenges, 10 of 46 patients who had low antibody levels had systemic reactions, whereas only 2 of 63 patients with high IgG levels had systemic reactions. The patient group with low antibody responses was intentionally enriched to obtain adequate numbers. As pointed out in their report, approximately 85% of unselected patients receiving VIT mount adequate IgG antibody responses. Thus if 15% of patients treated by VIT do not respond immunologically, and of that group approximately 22% have re-sting reactions, then approximately 4% of an unselected group of patients receiving VIT might be subsequent treatment failures if re-stung. This figure is consistent with the incidence of reported treatment failures in the literature.^{5,13} To pursue this analysis it is also necessary to look at the nature of the re-sting reactions that occurred after sting challenge. In the Johns Hopkins study¹ only 2 of the 10 patients with low antibody titers had allergic symptoms that required treatment with epinephrine. Therefore of the estimated 4% re-sting reactors, approximately 20%, or less than 1%, of the total group of patients treated by VIT might be expected to have a significant re-sting reaction. Thus the first concern raised regarding the authors' recommendation for the routine measurement of IgG antibody as a standard of practice is the extremely low incidence of serious re-sting reactions in patients receiving VIT.

The second concern is the reproducibility of the relationship between the IgG antibody level and the occurrence of an allergic reaction to the re-sting. In Table III in the article,¹ specific patient data are presented. Eight of the 12 patients had more than one intentional sting challenge. Four patients, D.B., J.C.,

From State University of New York at Buffalo School of Medicine.
Reprint requests: Robert E. Reisman, MD, Buffalo Medical Group,
295 Essjay Rd., Williamsville, NY 14221.

1/1/39901

S.M., and E.R., had two or three sting challenges, at which time the serum IgG antibody levels were 3 $\mu\text{g}/\text{ml}$ or less. These four patients had inconsistent responses to the sting challenge, with no reaction or a reaction occurring after different challenges. Two of the patients, W.T. and J.D., did have consistent allergic reactions after two sting challenges when levels of IgG were 3 $\mu\text{g}/\text{ml}$ or less. Thus these data raise a question about the applicability of this IgG antibody parameter to the response to sting challenge in individual patients.

The third concern is the validity of the recommendation to raise the venom dose if the serum antibody titer is low. There have been anecdotal reports that such an approach is successful. However, the clinical and immunologic data presented in this paper do not document that this dose increase is necessarily effective. Several observations reported in this paper are pertinent to this aspect of the discussion. The venom dose was increased from 100 μg to 200 μg in three patients, D.B., S.M., and E.R. (Table III). Patient D.B. did subsequently tolerate an insect re-sting. After two sting challenges, patient S.M. initially had no reaction but subsequently had a systemic reaction. Patient E.R. continued to react after the increase in yellow jacket venom dose. The immunologic response after the increased venom dose was reported in three patients. Two patients (S.M., E.R.) actually had a fall in serum venom specific IgG titers and patient D.B. had a modest rise, but remained below the 3 $\mu\text{g}/\text{ml}$ level.

Other effects of venom dosing on the antibody response are shown in Tables III and V. Four patients, (T.B., J.C., S.H., W.T.) had a drop in IgG antibody levels despite persistent venom therapy (Table III). In Table V, the authors present the relationship of treatment dose and specific antibody levels for the total group. Increasing the yellow jacket venom dose to 200 μg did not raise the levels of yellow jacket-specific IgG as compared with the titers in those patients receiving doses of 100 μg . Antibody levels less than 3 $\mu\text{g}/\text{ml}$ were found in 14 of 46 patients (30%) receiving 100 μg yellow jacket venom doses and in 11 of 24 patients (46%) receiving 200 μg yellow jacket venom doses. Thus the third concern is the suggestion that raising the dose of venom is effective therapy for patients who are "potential" or real treatment failures, although appearing to be sensible, cannot fully be supported by these data.

Several other disturbing aspects of the results relate to the authors' recommendations. First, the data are derived entirely from yellow jacket stings. Although a substantial number of patients received honeybee stings (40) and all had no reaction, the authors do not present information regarding the antibody responses in these patients. The data on yellow jacket sting re-

actions cannot be applied to patients receiving treatment for more than 4 years. Why the time cutoff? Finally, it is not clear why the authors selected yellow jacket venom for measurement of the immunologic response and the challenging antigen in the large number of patients who were receiving treatment with multiple venoms. Why not measure hornet or wasp venom-specific IgG or a combination thereof? It also should be noted the 36 of 46 patients who had low serum antibody levels, and did not react to a sting challenge, would be treated with increasing doses of venom if the authors' recommendations are followed.

Another study by Müller et al.¹⁴ found no relationship between levels of honeybee venom phospholipase A₂-specific IgG and the response to sting challenges in patients treated with honeybee venom. Interestingly, the levels of IgG antibody were actually higher in the group of patients who had reactions after sting challenge than in the group of patients who did not react. The authors further concluded that for an individual patient "no single antibody estimation or combination of various antibodies was predictive of the outcome of a sting challenge."

In addition to the critical assessment of the scientific data used to make the recommendation regarding routine measurements of IgG antibody titers, economic factors and the availability of the laboratory for making these determinations are important. This reliable quantitative measurement of serum venom-specific IgG is performed at the Johns Hopkins University Laboratory. It is not clear how many other laboratories in the country can perform the assay in the same manner. The cost for a single venom IgG antibody assay is \$44.00 and for a panel of five venom antibody assays is \$176.00.* If recommendations to measure IgG antibody titers are followed, then presumably assays should be done to all venoms administered, often three or four. The cost of increased venom dosing will, of course, be variable, but it could be very significant, particularly if a mixed vespid preparation, usually given in a dose of 300 μg , is increased to 400 or 500 μg .

How then should the practicing physician use these data in the practical management of patients receiving VIT? First, is there any test that should be done to monitor the response to VIT? In my opinion, the routine measurement of serum venom-specific IgG is not necessary. No specific tests are needed to monitor patients other than periodic skin tests to determine whether sensitivity is still present and treatment is still necessary.

Second, what should be done with patients whose treatment fails? In these individuals, who represent

*The Johns Hopkins University Dermatology, Allergy and Clinical Immunology (DACI) Reference Laboratory fee schedule - 1/92.

less than 5% of treated individuals, the venom dosing should be raised. As noted, a number of anecdotal reports indicate that an increased venom dose prevents subsequent re-sting reactions. Unfortunately, in the small number of patients reported in the report by Golden et al., there is not adequate documentation of this clinical or immunologic response. Thus I believe that although patients whose treatment fails should have increases doses of venom, it is not clear that an IgG antibody response necessarily reflects the development of an immune status. These patients should, of course, carry epinephrine for self-administration.

Finally, when should measurements of venom IgG antibodies be done? One suggestion has been in patients who have had severe anaphylactic sting reactions characterized by symptoms such as loss of consciousness. In these patients, if IgG antibody titers are high, there might be more confidence that protection has been established. Nevertheless, it is important to point out that VIT is highly successful in patients who have had severe reactions, and thus routine measurement of this parameter, even in this situation, is medically unnecessary.¹⁵ Although the accurate measurement of serum venom-specific IgG is an important research tool and has clarified many aspects of the insect sting allergy field, no current clinical indication exists for its assay as part of the routine assessment of patients with insect sting allergy.

The Johns Hopkins group should be commended on this difficult, time consuming, study, which has added to our knowledge of the relationship of immunologic parameters to the clinical features of insect sting allergy. Our differences lie in the clinical interpretation of these data. The results do suggest that patients receiving VIT who have elevated titers of serum venom-specific IgG as a group are less likely to have re-sting reactions than patients with low antibody titers. As reviewed in this editorial, it is my conclusion, that on the basis of (1) the low incidence of serious re-sting allergic reactions in patients treated with VIT, (2) the lack of reproducible reactions to sting challenges in individual patients with low antibody titers, (3) the failure to document the clinical and immunologic effectiveness of increased venom doses, (4) the recommended application of these conclusions to only patients allergic to yellow jacket venom treated for less than 4 years, and (5) secondary economic and logistic considerations, the routine measurement of serum venom specific IgG is unnecessary.

Finally, it is important to reemphasize the remarkable progress that has occurred in the field of insect sting allergy over the past 15 years. Although very small numbers of treatments may continue to fail, the overall clinical effectiveness of VIT should provide

patients with the self-confidence and assurance to pursue normal life-styles without fear or anxiety concerning repeat venom anaphylaxis.

Robert E. Reisman, MD
Buffalo Medical Group
295 Essjay Rd.
Williamsville, NY 14221

REFERENCES

1. Golden DBK, Lawrence ID, Hamilton RH, 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;90:386-93.
2. Light WC, Reisman RE, Wypych JJ, Arbesman CE. Clinical and immunological studies of beekeepers. *Clin Allergy* 1975;5:389-95.
3. Lessof MH, Kagey-Sobotka A, Lichtenstein LM. Effects of passive antibody in bee venom anaphylaxis. *Johns Hopkins Med J* 1978;142:1-7.
4. Bousquet J, Fontez A, Aznar R, Robinet-Levy M, Michael FB. Combination of passive and active immunization in honeybee venom immunotherapy. *J ALLERGY CLIN IMMUNOL* 1987;79:947-54.
5. Valentine MD. Insect venom allergy: diagnosis and treatment. *J ALLERGY CLIN IMMUNOL* 1984;73:299-304.
6. 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;299:157-61.
7. 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* (In press).
8. Blaauw PJ, Smithius LOMJ. The evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital insect sting. *J ALLERGY CLIN IMMUNOL* 1985;75:556-62.
9. Parker JL, Santrach PJ, Dahlberg JE. Evaluation of *Hymenoptera* sting sensitivity with deliberate insect sting challenges: inadequacy of present diagnostic methods. *J ALLERGY CLIN IMMUNOL* 1982;69:200-7.
10. 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.
11. Müller V, 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;87:702-9.
12. Keating MU, Sobotka AK, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. *J ALLERGY CLIN IMMUNOL* 1991;88:339-48.
13. Reisman RE, Livingston A. Venom immunotherapy: 10 years experience with administration of single venoms and 50 µg maintenance doses. *J ALLERGY CLIN IMMUNOL* 1992;1189-95.
14. Müller U, Helbling A, Bischof M. Predictive value of venom-specific IgE, IgG and IgG subclass antibodies in patients on immunotherapy with honeybee venom. *Allergy* 1989;44:412-8.
15. Lantner R, Reisman RE. Clinical and immunologic features and subsequent course of patients with severe insect-sting anaphylaxis. *J ALLERGY CLIN IMMUNOL* 1989;84:900-6.