Ann Allergy Asthma Immunol 121 (2018) 276–277

Contents lists available at ScienceDirect

Hymenoptera venom immunotherapy

Past, present, and future

John Oppenheimer, MD[*,†]; David B.K. Golden, MD[‡]

[*] Department of Internal Medicine, New Jersey Medical School, Newark, New Jersey
[†] Pulmonary and Allergy Associates, Morristown, New Jersey
[‡] Department of Medicine, Johns Hopkins University, Baltimore, Maryland

ARTICLE INFO

Article history:
Received for publication May 31, 2018.
Accepted for publication June 7, 2018.

We have learned a great deal about Hymenoptera immunotherapy since 1925, when Dr Braun first reported the effective use of immunotherapy in a bee allergic patient. In his report, he described snipping off the posterior 1/8 inch of the body then grinding it up, extracting it in saline, and filtering the solution, demonstrating a positive skin test response and then using the same material to perform immunotherapy.[1] A plethora of publications in the 40 years after that first report reinforced the efficacy of whole-body extract (WBE) for immunotherapy to Hymenoptera. Although in 1965 Loveless and Fackler[2] published their sentinel article demonstrating that the efficacy was actually carried in the venom, this work sadly went unnoticed or refuted, and the standard of care remained the use of WBE. That was the same year that the Insect Committee of the American Academy of Allergy endorsed WBE as effective treatment.[3] It was not until 13 years later, when Lichtenstein and colleagues[4] described a controlled clinical trial of venom immunotherapy, that the allergy world shifted to use of Hymenoptera venom in immunotherapy. What have we learned since and where are we likely to go in the future in the treatment of Hymenoptera allergy?

The first step is to examine the question of how we were fooled by WBE. There were 2 key mistakes: one was pointed out by Dr Lichtenstein after publication of the key controlled clinical trial of VIT, and the other was learned only after many years of study of the natural history of this disease.[4] Although Mary Loveless pioneered the use of venom, rather than WBE, for immunotherapy, the standard of medical reporting at the time was anecdotal and based on uncontrolled and often subjective observation of individual patients. The experience of allergists, as endorsed by the American Academy of Allergy, made them resistant to the idea that WBE did not work, and at the time there was no commercially available venom for clinical use. Practicing allergists really had no choice unless they were willing to follow Dr Loveless' practice of trapping insects, preparing a venom extract, and sometimes stinging people in the garden as a booster dose. Dr Lichtenstein recognized the power of the placebo-controlled clinical trial. By the early 1970s, the methods for production of venoms were being refined by Benton and colleagues[6] at Vespa Laboratories and King and colleagues[7] at Rockefeller University. King and colleagues[7,8] also identified the component allergens in the Hymenoptera venoms, permitting the standardization of allergen extracts for the first time in history. Venoms remain the only allergen extracts that are standardized in absolute terms (micrograms per milliliter) rather than relative potency units (allergy units or bioequivalent allergy units per milliliter) or descriptive qualitative terms (protein nitrogen units per milliliter or wt/vol). This confluence of new approaches culminated in a clinical trial that showed that WBE was no better than placebo and that venom was 98% effective.[5]

It was that clinical trial that provided some early insights on the natural history of the disease.[5] It demonstrated that even those at risk for anaphylaxis may not react each time they are stung, which led to a placebo efficacy rate of 40%! Seminal studies at Johns Hopkins, in the first few years after VIT was approved for clinical use, highlighted several key features of the natural history, including the very low risk of subsequent anaphylaxis in children with cutaneous systemic reactions (which constitutes most affected children) and in patients of all ages who had solely large local reactions.[9,10] The previous reports that supported efficacy with WBE had included many of the very low-risk patients who would likely not have had an anaphylactic reaction to a subsequent sting even without immunotherapy.

Interestingly, this first clinical trial foreshadowed 2 other pitfalls in insect sting allergy. First, one-third of the candidates for the study were excluded because of negative skin test results. It was 25 years later that the dilemma of negative venom skin test results was unraveled.[11] Second, the study protocol required that before sting challenge of patients after reaching maintenance doses of treatment, subcutaneous injection of 50 μg was to be given, and if there was no

Reprints: John Oppenheimer, MD, Pulmonary and Allergy Associates, 8 Saddle Rd, Cedar Knolls, NJ 07927 E-mail: nallopp22@gmail.com.

Disclosures: Dr Oppenheimer reported working as a consultant/adviser for AstraZeneca, GlaxoSmithKline, Mylan, Novartis, and Teva; receiving royalties from UpToDate; and receiving research funding from AstraZeneca, Medimmune, Novartis, and Sanofi. Dr Golden reported serving on the speaker bureau (honoraria) and clinical trials for Genentech and Stallergenes/Greer.

https://doi.org/10.1016/j.anai.2018.06.006
1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

reaction, then 100 μg was to be given. Only if there was no reaction to the full-dose venom injection would the sting challenge proceed. Not a single patient had a reaction to the 100-μg injection, but 60% had a systemic reaction to the live sting.[5] Subsequent studies also found that of the patients who did not react to a first sting challenge, 20% reacted to a later sting challenge.[12,13] This finding again reinforces the unpredictability of the reaction to a sting and illustrates how easy it was for WBE to appear to be effective when low-risk patients are included, and even high-risk patients do not react to a sting almost half the time.

The future of Hymenoptera immunotherapy hinges on refining 2 of the basic principles that brought VIT to the market: understanding the natural history of the disease and the molecular characteristics of the venoms. There is a need for accurate risk stratification to distinguish those at highest risk for severe reactions from those who will probably never have a severe reaction to a sting. Ideally, there would be a test that would clearly identify patients who are at greatest risk for developing anaphylaxis. The basal serum tryptase is one such indicator.[14] The basophil activation test shows some promise in this regard. There is also the promise of recombinant venom allergens, extending the work of King and others, to identify those at greatest risk or at least to identify the specific insect culprit and navigate the problems associated with venom cross-reactivity.[15,16] Recombinant venom allergens do not have the cross-reacting carbohydrate determinants that can account for misleading cross-reactive serum IgE test results to natural venoms. Lastly, VIT has been the model for the study of the mechanisms of allergen immunotherapy.[17] There is still a need to identify a marker of sustained unresponsiveness (tolerance).

Mary Loveless was decades ahead of her time in identifying venom as the appropriate material for testing and treatment, in the use of cluster regimens of immunotherapy, and in the identification of IgG antibodies as a marker and mechanism of protection in venom immunotherapy, as later confirmed by Dr Lichtenstein's group.[2,18] We have learned a great deal since then, leading to a new era in diagnosis and prevention of insect sting anaphylaxis. Just think what the next generation of allergists will learn regarding the diagnosis and treatment of Hymenoptera venom allergy.

References

[1] Braun LIB. Notes on desensitization of a patient hypersensitive to bee stings. *S Afr Med Rec*. 1925;23:408–409.
[2] Loveless MH, Fackler WR. Wasp venom allergy and immunity. *Ann Allergy*. 1956;14:347–366.
[3] Insect Allergy Committee, American Academy of Allergy. Insect sting allergy, cooperative study. *JAMA*. 1965;193:115–120.
[4] Lichtenstein LM. Insect allergy: the state of the art. *J Allergy Clin Immunol*. 1979;64:5–12.
[5] Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med*. 1978;299:157–161.
[6] Benton AW, Morse RA, Stewart JD. Venom collection from honeybees. *Science*. 1963;142:228–230.
[7] King TP, Sobotka AK, Alagon A, Kochoumian L, Lichtenstein LM. Protein allergens of whote faced hornet, yellow hornet, and yellow jacket venoms. *Biochemistry*. 1978;17:5165–5174.
[8] King TP, Sobotka AK, Kochoumian L, Lichtenstein LM. Allergens of honey bee venom. *Arch Biochem Biophys*. 1976;172:661–671.
[9] Golden DB. Large local reactions to insect stings. *J Allergy Clin Immunol Prac*. 2015;3:331–334.
[10] 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.
[11] Golden DBK, Tracy JM, Freeman TM, Hoffman DR, Insect CA. Negative venom skin test results in patients with histories of systemic reaction to a sting [Rostrum article]. *J Allergy Clin Immunol*. 2003;112:495–498.
[12] 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.
[13] Golden DBK, Breisch NL, Hamilton RG, et al. Clinical and entomological factors influence the outcome of sting challenge studies. *J Allergy Clin Immunol*. 2006;117:670–675.
[14] Rueff F, Przybilla B, Bilo MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase: a study of the EAACI Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol*. 2009;124:1047–1054.
[15] Eberlein B, Krischan L, Darsow U, Ollert M. Double positivity to bee and wasp venom: improved diagnostic procedure by recombinant allergen-based IgE testing and basophil activation test including data about cross-reactive carbohydrate determinants. *J Allergy Clin Immunol*. 2012;130:155–161.
[16] Muller UR, Schmid-Grendelmeier P, Hausmann O, Helbling A. IgE to recombinant allergens Api m 1, Ves v 1, and Ves v 5 distinguish double sesnitization from crossreaction in venom allergy. *Allergy*. 2012;67:1069–1073.
[17] Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol*. 2005;115:439–447.
[18] 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.