Review of: "Venom Immunotherapy and Aeroallergen Immunotherapy: How Do Their Outcomes Differ?"

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The authors have presented an excellent review of the differences between AIT and VIT. It is very thought-provoking to identify these differences and their possible explanations. This can also vary according to the perspective taken. It is important to recognize that the goals of AIT and VIT are different. The goal of AIT is not to achieve 100% protection against all symptoms of reaction, but to reduce symptoms to a level that is better-tolerated, and more manageable with medications. The goal of VIT is indeed to achieve 100% protection against all symptoms of systemic reaction. Even a mild systemic reaction to a sting while on VIT is considered a treatment failure and requires an increased maintenance dose. The primary goal is to reduce morbidity, not just, as the authors suggest, to eliminate mortality. While it is true that no fatal reactions have been reported in patients on VIT (100% efficacy), the frequency of complete protection against systemic reactions is not 100%, but 95% for vespid venom and 80% for honeybee venom at the 100 mcg maintenance dose.

The authors discuss the efficacy of AIT as being less predictable than for VIT. Perhaps the critical factor is the potency and consistency of composition of the allergen extract. Hymenoptera venoms were the first standardized extracts to become commercially available, followed soon after by dust mite extracts and later by grass and cat. It is not a coincidence that the most reliably effective agents for AIT (as pointed out by the authors) are dust mites and grass, and cat is also very effective (despite the single study to the contrary cited by the authors).

Efficacy is also dependent on the dose administered. This is true for VIT and for AIT. However, our approach to treatment is different. Because our goal with VIT is complete protection against systemic sting reaction we administer the same target dose to all patients and we take steps to achieve that dose even if there are adverse reactions along the way. However with AIT we often accept the “highest tolerated dose” and we (and our patients) accept the clinical improvement that is good but less than perfect.

It is ironic that despite the life-threatening nature of the disease (anaphylaxis), VIT has greater safety than AIT. The authors point out that asthma is the major risk factor for severe AIT reactions. This underscores the difference between treating a condition that is only sporadically active (sting anaphylaxis) and one that is chronic (allergic airway disease). Symptoms are ongoing for inhalants and are more susceptible to aggravation by AIT whereas exposure and symptoms are not present at the time of VIT injection.

Another way in which VIT differs from AIT is the relative safety of rush VIT (the same or better than semi-rush or traditional regimens) whereas rush AIT is associated with increased risk of systemic reactions. The reasons may be the same as suggested above.

The determinants of long-term efficacy and the ability for AIT/VIT to achieve sustained unresponsiveness remain

enigmatic. Why can we achieve clinical tolerance more reliably with VIT than with AIT? One possible reason is that we use a uniform high dose of standardized allergen for venom instead of a variable “highest tolerated” dose of inhalant allergens that are not always as well standardized for high allergen content. The authors allude to another fascinating difference: the frequency and consistency of exposure. Is the ability to induce tolerance better for VIT because the exposure is intermittent and infrequent? Is it better for inhalants with intermittent (seasonal pollen) exposure than for those with frequent or daily exposure (mite, cat)?

New ways to facilitate the rapid and safe induction of tolerance remain the holy grail of immunotherapy. The authors provide an excellent overview of potential targets for therapies that would reduce systemic reactions and permit a more robust immunologic and clinical response. Omalizumab has only partially fulfilled this promise but there remain patients in whom it did not prevent severe reactions to immunotherapy and others who tolerated maintenance doses but had recurrent systemic reactions when omalizumab was stopped after 6 months. There are intriguing reports of signaling pathway modifiers (eg, btk inhibitors or siglec ligands) that can block anaphylaxis, and new adjuvants that may permit better immune responses with lower doses of allergen (thus reducing the risk of systemic reaction).