Predominant Api m 10 sensitization as risk factor for treatment failure in honey bee venom immunotherapy

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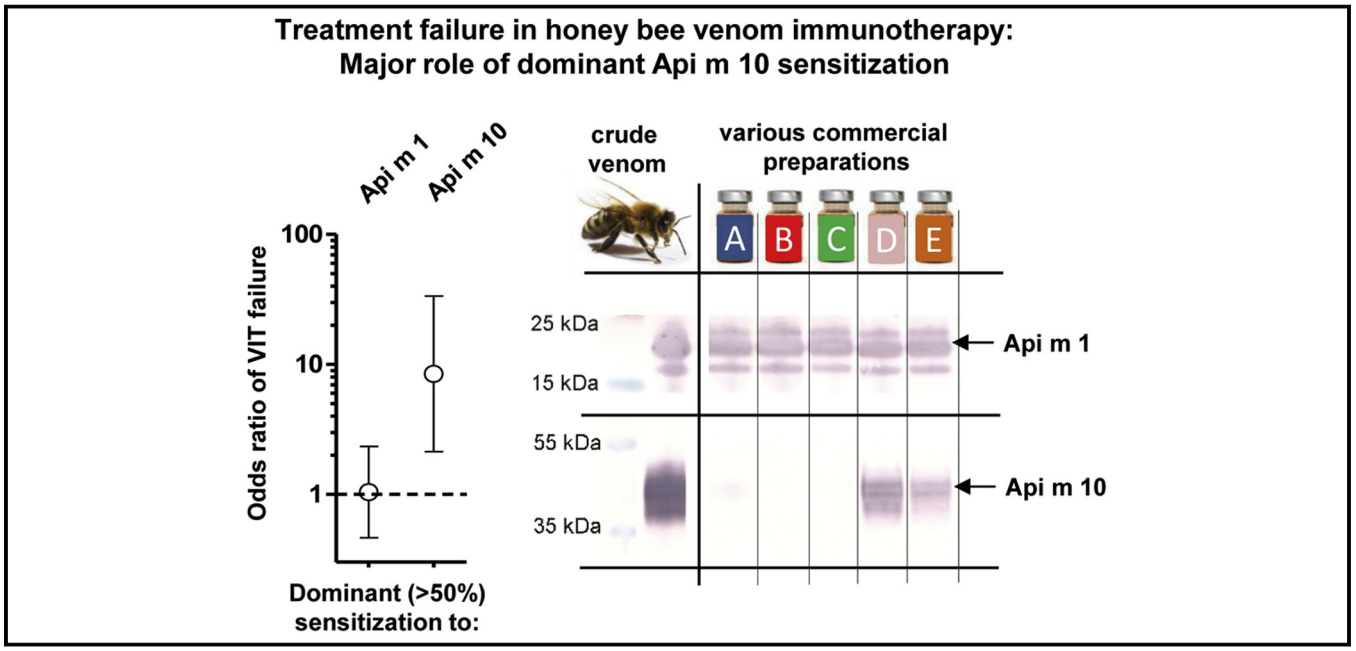
GRAPHICAL ABSTRACT



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Background: Component resolution recently identified distinct sensitization profiles in honey bee venom (HBV) allergy, some of which were dominated by specific IgE to Api m 3 and/or Api m 10, which have been reported to be underrepresented in therapeutic HBV preparations.

Objective: We performed a retrospective analysis of component-resolved sensitization profiles in HBV-allergic patients and association with treatment outcome.

Methods: HBV-allergic patients who had undergone controlled honey bee sting challenge after at least 6 months of HBV immunotherapy (n = 115) were included and classified as responder (n = 79) or treatment failure (n = 36) on the basis of absence or presence of systemic allergic reactions upon sting challenge. IgE reactivity to a panel of HBV allergens was analyzed in sera obtained before immunotherapy and before sting challenge.

Results: No differences were observed between responders and nonresponders regarding levels of IgE sensitization to Api m 1, Api m 2, Api m 3, and Api m 5. In contrast, Api m 10 specific IgE was moderately but significantly increased in nonresponders. Predominant Api m 10 sensitization (>50% of specific IgE to HBV) was the best discriminator (specificity, 95%; sensitivity, 25%) with an odds ratio of 8.444 (2.127-33.53; $P = .0013$) for treatment failure. Some but not all therapeutic HBV preparations displayed a lack of Api m 10, whereas Api m 1 and Api m 3 immunoreactivity was comparable to that of crude HBV. In line with this, significant Api m 10 $sIgG_4$ induction was observed only in those patients who were treated with HBV in which Api m 10 was detectable.

Conclusions: Component-resolved sensitization profiles in HBV allergy suggest predominant IgE sensitization to Api m 10 as a risk factor for treatment failure in HBV immunotherapy. (J Allergy Clin Immunol 2016;138:1663-71.)

Key words: Apis mellifera*, Hymenoptera venom allergy, HBV allergy, recombinant allergen, allergen-specific immunotherapy, treatment failure*

Abbreviations used
AUC: Area under the ROC curve
HBV: Honey bee venom
HB: Honey bee
LOD: Limit of detection
NLR: Negative likelihood ratio
OR: Odds ratio
PLR: Positive likelihood ratio
ROC: Receiver operating characteristic
sIgE: Specific IgE
VIT: Venom immunotherapy

Systemic allergic reaction to Hymenoptera stings affects 0.3% to 3.5% of the adult population.[1,2] Venom immunotherapy (VIT) protects allergic patients from systemic reactions to subsequent stings.[2,3] The effectiveness of VIT depends on a number of variables such as treatment duration, venom dose during maintenance therapy, and type of venom (honey bee [HB] vs vespid) used for immunotherapy.[4-6] Treatment failure is more frequent in HB VIT than in vespid VIT, ranging from 11% to 23% as compared with 0% to 9%.[4-7] A recent retrospective study on the outcome of more than 1600 sting challenges calculated an odds ratio (OR) of more than 5 for treatment failure in honey bee venom (HBV) allergy as compared with VIT in vespid venom allergy.[6] This increased risk of treatment failure in HBV allergy has been suggested to be associated with differences in venom composition, venom dose during natural exposure conditions, and differences in sensitization profiles.[4,7,8]

Advances in proteomics and molecular biology have allowed a detailed characterization of the protein composition of HBV. The best-characterized HBV allergens are phospholipase A2 (Api m 1), hyaluronidase (Api m 2), and the basic peptide melittin (Api m 4).[9,10] Additional HBV allergens of lower abundance have been cloned and characterized such as acid phosphatase (Api m 3),[11] dipeptidylpeptidase IV (Api m 5),[12] icarapin (Api m 10),[13,14] and others as recently reviewed.[15] Analysis of different venom preparations have shown that Api m 3 and Api m 10, while present in the crude HBV, are absent or underrepresented in preparations used for HBV immunotherapy.[13] These findings were supported by subsequent observations that in patients with dominant sensitization to Api m 10, IgE reactivity to HBV could be inhibited by crude HBV preparations but not by therapeutic HBV preparations.[8] In addition, HBV-allergic patients who had undergone VIT displayed a strong induction of $sIgG_4$ to Api m 1, Api m 2, and Api m 4, whereas no or little induction of $sIgG_4$ to Api m 3 and Api m 10 could be detected.[8] On the basis of these 3 lines of evidence, we hypothesized that the absence or underrepresentation of Api m 3 and Api m 10 in therapeutic HBV preparations may have an impact on the treatment outcome of VIT and that distinct sensitization profiles, for example, with predominant IgE reactivity to Api m 3 and/or Api m 10, may represent a potential risk factor for treatment failure of VIT in HBV allergy. To address this issue, we here retrospectively analyzed the molecular sensitization profiles in HBV-allergic patients who had undergone controlled HB sting challenge after at least 6 months of HBV.

METHODS

Patients

Sera from HBV-allergic patients who had undergone controlled HB sting challenge after at least 6 months of HBV immunotherapy at a maintenance dose of 100 μg BV were included in the study (n = 115) and classified as responder,

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