The prevalence of Api m 10 sensitization and the modification of immunotherapy in bee venom allergy

Aleksandra Górska, Marek Niedoszytko, Marta Chełmińska, Karolina Kita, Ewa Jassem

Allergology Department, Medical University of Gdansk, Gdansk, Poland

Adv Dermatol Allergol 2021; XXXVIII (4): 699–700
DOI: https://doi.org/10.5114/ada.2021.108922

It is estimated that 56–94% of the adult population have been stung by a hymenopterous insect at least once in their lifetime, with one third of these cases being stung by a bee [1]. The prevalence of systemic reactions in the adult general population is 0.3–8.9% in Europe [2]. In beekeepers, this prevalence increases to 14–32% [3]. It is important to prevent any future allergic reactions based on correct diagnosis and management, including the prescription of an autoinjector with adrenaline, and specific venom immunotherapy in confirmed venom allergy [2]. Diagnosis is based on the clinical history with the classification of the type of the reaction, identification of the stinging insect and confirmation of the specific IgE-mechanism of the systemic reaction [4]. It is recommended to perform skin tests and to detect serum sIgE to insect venoms at least 2 weeks after the sting after the refractory period [1]. Although the sensitivity of serological tests with recombinant allergens is lower than traditional methods with extract allergens, molecular diagnostic approaches may improve the diagnosis accuracy in some patients excluding "false-positive" test results due to IgE directed against cross-reactive carbohydrate determinants (CCD). Furthermore, it has been recently published that negative skin test results with the *Apis mellifera* extract may be due to the lack of some allergens in the diagnostic and therapeutic extract [5]. Patients with a bee venom allergy often have a broad sensitisation profile with the most relevant being Api m 1, which could not be sensitised in up to 43% of cases [1, 6]. The combination of 2 allergens (Api m 1 and Api m 10) enables the diagnosis of 86.6% of cases; the combination of 6 allergens (Api m 1–5, Api m 10) has a sensitivity of 94.4% [3, 6]. Patients with a Vespula allergy are sensitised mainly to Ves v 1 and Ves v 5, and a combination of these 2 recombinant allergens enables the diagnosis in 92–94% of Vespula-allergic cases [7]. The effectiveness of venom immunotherapy (VIT) depends on the treatment duration, the dose of venom during maintenance therapy, and the type of venom used in treatment. Treatment failure is more frequent in bee VIT than in vespid VIT, ranging from 11% to 23% as compared to 0% to 9% [8]. The risk of treatment failure in honey bee venom allergy has been suggested to be associated with differences in the venom composition as compared to the sensitisation profile, as well as the HBV protein composition in preparations used for HBV immunotherapy [8]. The analysis of different HBV preparations has shown that Api m 3 and Api m 10 detected in crude HBV, are under-represented or absent in preparations used for VIT [6]. Patients with a predominant sensitisation to Api m 10 (> 50% sensitisation to Api m 10) treated with HBV immunotherapy without representation of Api m 10 are at an increased risk of treatment failure [8].

Considering the analysis by Frick *et al.* [8], which revealed that some of the preparations used for HBV immunotherapy displayed a lack of Api m 10, made us realise that some of our patients treated with venom immunotherapy received a preparation which can result in a lack of efficacy. Thus, we wanted to study the number of patients with Api m 10. Secondly, we found no information in the guidelines concerning the method of switching the venom therapy preparations produced by different manufacturers. Repeating the VIT build-up phase was impractical due to the number of patients.

Sera from 46 HBV-allergic patients treated with a maintenance dose of 100 ug of HBV were analysed. The venom immunotherapy had been performed for at least one to 3 years before sampling. Diagnosis of HBV allergy was based on a combination of the well-documented patient's history of an anaphylactic sting reaction, a positive result of skin tests performed according to the EAACI guidelines [4], and positive specific IgE (sIgE) to HBV (> 0.35 kUA/l; ImmunoCAP i1), as recently described [6]. Specific IgE to rApi m 10 was analysed in all patients treated with the VIT preparation without Api m 10. The risk of systemic adverse events during VIT was assessed

Address for correspondence: Aleksandra Górska MD, PhD, Allergology Department, Medical University of Gdansk, 17 Smoluchowskiego St, 80-214 Gdansk, Poland, phone: +48 600 912 624, e-mail: agorska@gumed.edu.pl
Received: 7.10.2019, **accepted:** 26.11.2019.

during qualification for changing the preparation of VIT. Among the 46 patients in our study group, a positive result of specific IgE to rApi m 10 (≥ 0.35 kUA/l) was found in 30 (65%) of cases. The mean result was 3.9 kUA/l (range: 0–48.3 kUA/l). Among patients with Api m 10 sIgE, a positive result of 43.3% had predominant sensitisation to Api m 10. A basal serum tryptase level (sBT) was determined in all patients during qualification to VIT with the range of 1.1–76 µg/l. In 4 cases, elevated sBT > 11.4 µg/l was found, in all these subjects the diagnosis including bone marrow biopsy was done, resulting in diagnosis of indolent systemic mastocytosis in 2 of them. In all patients with positive Api m 10 and 3 subjects with a high risk of insect stings (bee keepers), regardless of the Api m 10 result, the treatment was modified according to the protocol: 1. The dose used in immunotherapy was decreased to 50% of the last injection: 2. The second dose, which was used further in maintenance treatment (100 µg) was injected after 3 weeks. Actually patients were switched from the aqueous extract preparation to the depot preparation. As preventive treatment H1 blockers in quadruple dose were administered (double dose 12 h and 1 h before administering the VIT preparation). We did not observe any systemic adverse reaction during the change of the medication and further treatment. The protocol of treatment modification used was safe in all of the studied patients (n = 33).

There are various induction protocols performed to achieve the maintenance dose of 100 µg without side effects, with clinical protection and sufficiently good adherence. Management of the immunotherapy depends on the protocol and can be switched from an aqueous extract to a depot extract by the same manufacturer with no impact on the efficacy or safety [9]. There are no guidelines in the literature on the management of switching the VIT preparation. The recent multicentre study reported that switching VIT from one manufacturer to another is a safe option if necessary, and in patients who had previously tolerated VIT even without reducing the previous maintenance dose [10], except the patients who experienced systemic reaction during VIT, the modification of treatment should be performed using ultra-rush or rush protocol in centres experienced in Hymenoptera venom immunotherapy [1].

Concluding, we revealed that specific IgE to Api m 10 is a prevalent component in bee venom-allergic patients. The protocol of treatment modification based on switching the VIT preparation used was safe in all studied patients. Further studies may be focused on the question if the VIT should be tailored to the specific IgE to allergen components present in the patient sera or contain the whole allergen. We assumed that due to the possible fatal reaction the second option is more appropriate.

Acknowledgments

Data were presented in the poster form during the European Academy of Allergy and Clinical Immunology Congress, 26–30 May 2018, Munich, Germany.

Conflict of interest

The authors declare no conflict of interest.

References

1. Bilò MB, Pravettoni V, Bignardi D, et al. Hymenoptera venom allergy: management of children and adults in clinical practice. J Investig Allergol Clin Immunol 2019; 29: 180-205.
2. Biló MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. Allergy 2011; 66: 35-7.
3. Müller UR. Bee venom allergy in beekeepers and their family members. Curr Opin Allergy Clin Immunol 2005; 5: 343-7.
4. Golden DB, Moffitt J, Nicklas R, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol 2011; 127: 852-4.
5. Blank S, Seismann H, Michel Y, et al. Api m 10, a genuine A. mellifera venom allergen, is clinically relevant but underrepresented in therapeutic extracts. Allergy 2011; 66: 1322-9.
6. Köhler J, Blank S, Müller S, et al. Component resolution reveals additional major allergens in patients with honeybee venom allergy. J Allergy Clin Immunol 2014; 133: 1383-9.
7. Ebo DG, Faber M, Sabato V, et al. Component- resolved diagnosis of wasp (yellow jacket) venom allergy. Clin Exp Allergy 2013; 43: 255-61.
8. Frick M, Fischer J, Helbling A, et al. Predominant Api m 10 sensitisation as risk factor for treatment failure in honey bee venom immunotherapy. J Allergy Clin Immunol 2016; 138: 1663-71.
9. Alessandrini AE, Berra D, Rizzini FL, et al. Flexible approaches in the design of subcutaneous immunotherapy protocols for Hymenoptera venom allergy. Ann Allergy Asthma Immunol 2006; 97: 92-7.
10. Bilò MB, Martini M, Berra D, et al. Hymenoptera venom immunotherapy: how to safely switch to the same venom of a different manufacturer. J Investig Allergol Clin Immunol 2018; 28: 205-8.