Title

Immunotherapy for Hymenoptera venom allergy compared with real-life stings: are we doing our best?

Keywords: hymenoptera venom allergy, venom immunotherapy, real-life stings

Main text

To the Editor.

It is known that a Hymenoptera sting cannot be avoided with absolute certainty in a patient affected by Hymenoptera venom allergy (HVA). Venom immunotherapy (VIT) is the only therapeutic tool that can potentially prevent systemic reactions.[1] Its rationale is represented by the ability to induce several immunological modifications that determine the establishment of a state of tolerance.[2] VIT was introduced into clinical practice over 40 years ago.[1] In time, the category of patients that can benefit from the administration of VIT has been defined, i.e., those whose initial reaction is represented by systemic manifestations.[3] Moreover, its efficacy rates have been highlighted to be 77%–89% and 91%–96% in the treatment of allergy to apid venom[4,5] and vespid venom,[6–8] respectively. Besides, the advancement of scientific knowledge has outlined both the methods of preparation of the extract of Hymenoptera venom and the characteristics of the duration, efficacy, safety and contraindications of this therapy.[9] The same applies to the definition of the treatment protocols, which first provide for an induction phase, according to a conventional, clustered, rash and ultra-rash protocols, and subsequently a maintenance phase, with a dosage equal to 100 μg and with a duration equal to 3–5 years.[3] As part of the maintenance phase, the choice of the dosage of 100 μg dates back to 1978, together with the first controlled study carried out for this purpose.7 Although this first study was carried out in 1978, the 100 μg dosage used in the VIT maintenance phase was adopted in almost all subsequent studies as the evidence of the efficacy of VIT using this dosage was confirmed.[3] It has been reported that the amount of venom released during a sting varies in different species of Hymenoptera and even within the same species. In particular, honeybees, yellow jackets, paper wasps and bumblebees release a quantity of venom equal to 50–140 mcg, 1.7–3.1 mcg, 4.2–17 mcg and 10–31 mcg, respectively. [10,11] On the other hand, the quantity of venom released in the case of a hornet sting is not known, which in any case seems to have its intrinsic danger, also in consideration of the weight of its venom sack, estimated at 260 mcg.[12] The quantity of venom released at each puncture was studied many years ago through two laboratory methods, the Coomassie blue

dying binding method and the Lowry assay.[11] Specifically, the Coomassie blue dying binding method has shown greater reliability than the Lowry assay.[11] This laboratory method is based on the fact that the different Hymenoptera are first chilled in ice and then placed on the parafilm.[11] The latter surfaces were subjected firstly to Hymenoptera puncture are then dried and stored at -20° C.[11]

Afterward, the pieces of parafilm were extracted, and the protein concentration of the venom of the different species of Hymenoptera determined.[11] However, it was not possible to rigorously estimate the exact amount of venom released in each sting, as the volume of injected venom can be very variable, specifically in the order of at least five times.[11] To the best of our knowledge, there is no subsequent confirmation of these data in the literature. Given that the amount of venom that is released during a sting varies in the different species of Hymenoptera, the maintenance dosage of the VIT would appear in the range of the quantity of venom inoculated by the honey bee (100 mcg versus 50-140 mcg), while it would result in several times higher for the vespid VIT, particularly for *Vespula spp*. (100 mcg versus 1.7-3.1 mcg) and this may be responsible for a lower rate of failure of VIT for *Vespula spp*. compared to the honey bee.

Another aspect that could lead to the latter outcome is represented by the quality of venom used for VIT.[4,13] Specifically, honey bee VIT does not appear adequately characterized concerning its allergenic content.[14] Moreover, while the content of the relevant allergens, particularly therapeutic extracts for VIT, is mainly represented by Api m 1, and the other allergens make up to 0.6–2% of its dry weight, it has been shown that honeybee venom, in addition to Api m 1, contains multiple allergens such as Api m 2, Api m 3, Api m 4, Api m 5 and Api m 10.14 Moreover, it is also known that some patients show a prevalent sensitization for Api m 10, an allergen poorly represented in VIT.[14] The latter peculiarity may represent a further cause of the therapeutic failure of some patients treated with VIT preparations for honeybees with low content for Api m 10.[14] On the contrary, the allergenic content of particular therapeutic extracts of VIT for yellow jackets contains substantial amounts of Ves v 1 and Ves v 5, which represent two major allergens.[14]

In conclusion, for a better and accurate definition of the dose to be administered during VIT, studies with more modern technologies are necessary for the exact quantification of the venom injected by Hymenoptera. Furthermore, comparative studies between different VIT doses may be helpful in identifying the optimal efficacy and safety of the treatment. Finally, appropriate use of molecular diagnostics for the definition of the allergenic content inside of extracts used for VIT, in comparison to specific individual sensitization, is advisable to study the relationship between them, especially in a health context increasingly oriented towards precision medicine.

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Tables

Table 1. Correlation between the quantity of venom released during a sting varies in the different species of Hymenoptera, venom molecular allergens, molecular allergen content in therapeutic extracts, and efficacy of VIT. *(IQ: inoculated quantity; VMA: venom molecular allergens; MACTE: molecular allergen content in therapeutic extracts; references present in online supplementary.)*

Hymenoptera	**IQ[1,3]**	**VMA[4]**	**MACTE[5]**	**Efficacy**
Honey bee	50-140 mcg	Api m 1, Api m 2, Api m 3, Api m 4, Api m 5, Api m 6, Api m 7, Api m 8, Api m 9, Api m 10, Api m 11, Api m 12	*Api m 1, Api m 2:* present in all therapeutic extracts in high amounts. *Others:* strongly undereperesented	77-84%[6,7]
Yellow jackets	1.7-3.1 mcg	Ves v 1, Ves v 2, Ves v3, Ves v 4, Ves v 5	undefined	93,5%[8]
Paper wasps	4.2-17 mcg	Pol a 1, Pol a 2, Pol a 5, Pol d 1, Pol d 3, Pol d 4, Pol d 5	undefined	95,5%-96,1%[9]
Hornet	Not calculated; estimated weight of venom sack estimated 260 mcg	Vesp c 1, Vesp c 5	undefined	93,8 %[10]
Bumblebee	10-31 mcg	Bom t 1, Bom t 4	undefined	85%[11]

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Authors

Luca Pecoraro[1,2#](M.D.)

Mattia Giovannini[3#](M.D.)

Francesca Mori[3](M.D., Ph.D.)

Francesca Saretta[4](M.D., Ph.D.)

Simona Barni[3](M.D.)

Riccardo Castagnoli[5](M.D.)

Stefania Arasi[6](M.D., Ph.D.)

Carla Mastrorilli[7,8](M.D., Ph.D.)

Lucia Liotti[9](M.D.)

Lucia Caminiti[10](M.D., Ph.D.)

Elio Novembre[3](M.D., Ph.D.)

from the Rare Allergic Diseases Commission of the Italian Society of Pediatric Allergy and Immunology

Affiliations

1) Department of Medicine, University of Verona, Policlinico GB Rossi, Verona, Italy.luca.pecoraro@asst-mantova.it
2) Pediatric Unit, ASST Mantua, Mantua, Italy. luca.pecoraro@asst-mantova.it
3) Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy.francesca.mori@meyer.it; simona.barni@meyer.it; mattiag88@hotmail.it; elio.novembre@unifi.it
4) Pediatric Department, Latisana-Palmanova Hospital, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy.francescasaretta@gmail.com
5) Department of Pediatrics, Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. riccardo.castagnoli@yahoo.it

6) Predictive and Preventive Medicine Research Unit, Multifactorial and Systemic Diseases Research Area, Pediatric Allergy Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.
7) Pediatric Unit and Emergency, University Hospital Consortium Corporation Polyclinic of Bari, Pediatric Hospital Giovanni XXIII, Bari, Italy.carla.mastrorilli@icloud.com
8) Department of Medicine and Surgery, University of Parma, Parma, Italy. carla.mastrorilli@icloud.com
9) Pediatric Unit, Senigallia Hospital, Senigalia, Italy. lucialiotti@libero.it
10) Department of Human Pathology in Adult and Development Age “Gaetano Barresi”, Allergy Unit, Department of Pediatrics, AOU Policlinico Gaetano Martino, Messina, Italy.lucycaminiti@yahoo.it

Corresponding Author:

Elio Novembre[3](M.D., Ph.D.)

Allergy Unit, Department of Pediatrics, Meyer Children’s University Hospital, Florence, Italy.; elio.novembre@unifi.it

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