

EDITORIAL

Clinical & Experimental Allergy

Basophil activation test in the diagnosis of insect venom allergies

This editorial discusses the findings of the paper in this issue by Korosec et al. [20] pp. 1730–7.

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Life-threatening anaphylactic reactions to hymenoptera stings occur in 0.8–5% of the general population. Treatment of this IgE-mediated allergy with specific immunotherapy is highly effective. About 80–100% of those who formerly displayed a systemic reaction no longer do so when re-stung following the initiation of treatment. The diagnosis of insect venom allergy and the indication for specific immunotherapy is based on patient history, skin testing and demonstration of hymenoptera venom-specific IgE antibodies. Stepwise incremental venom skin tests are recommended. The sensitivity of skin prick tests (SPT) is lower than that of intradermal tests. These *in vivo* and *in vitro* tests are performed to demonstrate IgE-mediated reactions. In many cases, the results of these tests form the basis of the indication for immunotherapy with the relevant insect [1].

Another method of identifying IgE-mediated reactions is the analysis of IgE-bearing basophils. In the 1970s the Lichtenstein group used basophil histamine release to characterize the allergenic components of insect venom and as a diagnostic method for a small number of patients [2]. Later, sensitivity and specificity for venom-induced histamine release was determined in a large group of insect venom-allergic patients [3]. Measurement of de novo synthesized sulphidoleukotrienes after allergen stimulation was introduced in 1993 by de Weck et al. [4] and used for the diagnosis of insect venom allergy. The concept of flow cytometric measurement of CD63 expression as a marker of basophil activation was published in

1991 [5]. The CD63 marker is a 53 kDa glycoprotein present on the lysosome membrane and is expressed with a high density on activated basophil membrane. In patients with insect venom allergy, the basophil activation test (BAT) with hymenoptera venom achieved better results than histamine release and equal results to leukotriene C4 release [6]. The sensitivity of the test was 85–100%; specificity was 83–100% in several studies showing the reliability of the test for insect venom allergy [7–9].

CD203c (ectonucleotide pyrophosphatase/phosphodiesterase 3 as a type II transmembrane protein), is another basophil-specific activation marker not expressed on other blood lymphocytes. It is upregulated in response to IgE receptor cross-linking similar to CD63, but it has been shown that CD203c and CD63 upregulation appears to be regulated by different pathways and follows different kinetics [10]. For the BAT using CD203c, a sensitivity of between 89% and 100% and a specificity of between 89% and 92% was found in patients allergic to insect venom [11–13].

BATs can also help to solve several problems in the diagnosis of insect venom allergy. In cases with negative skin tests and negative RAST or contradictory results, several researchers have shown that BATs (if possible in combination with a cellular antigen stimulation test) are useful in demonstrating IgE-mediated reactivity [8, 14, 15].

Double positivity has also proved problematic: this means patients with allergic reactions to honey bee or *Vespa* stings also have specific IgE for the other venom, making it difficult to select which venom to use for immunotherapy. Double positivity in diagnostic tests may be caused by true double sensitization to both venoms, or by cross-reactions that occur either on a peptide basis or may be related to so called cross-reacting carbohydrate determinants. In some cases, BATs can support the decision to use immunotherapy with one insect [8, 9, 15].

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To date, there is no *in vitro* marker capable of proving the success of insect venom immunotherapy. The BAT was shown to be of little value up to 6 months immunotherapy [7], but after 3 years of immunotherapy, basophil reactivity to sub-maximal stimulation conditions was significantly reduced [16] and might correlate with tolerated stings [17]. Whether success can be predicted in single cases is, however, doubtful.

While some research has been published showing that high sensitivity of basophils predicts side-effects in venom immunotherapy, others did not observe any such correlation [18, 19]. Correlation with the severity of anaphylactic reactions in anamnesis could not be shown for BATs [8, 9], nor were suitable tests performed to answer the question of whether BAT can be a marker of anaphylactic reaction.

The study published by Korosec et al. [20] in this issue of *Clinical & Experimental Allergy* investigates the usefulness of the BAT in 47 patients with insect venom allergies and negative venom-specific IgE and SPT. Seventy-five percent demonstrated a positive basophil CD63 response, whereas 46% had positive intradermal venom skin tests. Of 20 patients who demonstrated negative intradermal test results, 12 patients had positive BAT (60%), 10 patients had a negative BAT, while only one was detected by intradermal testing (10%).

Guidelines for the diagnosis of insect venom allergy recommend that skin tests should be performed to determine the threshold value. Initially, increasing concentrations of insect venom for prick test (0.1–1–10–100 µg/mL) should be used; this should be followed by intradermal tests (0.001–0.01–0.1–1 µg/mL). Intradermal tests are generally believed to be more dangerous than prick tests as regards systemic reactions. The study shows that the CD63 activation test in particular could be more useful and more sensitive than intradermal skin testing. Thus, it might be worth performing BAT before intradermal testing in patients with an insect venom allergy and inconclusive diagnostic results.

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