EDITORIAL

Basophil activation test: a reliable biomarker for allergen immunotherapy?

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Allergen immunotherapy (AIT) is the only causative treatment of allergic rhinoconjunctivitis and asthma, with strong evidence of efficacy and safety for both diseases and both for children and adults.[1] The most important prerequisite for obtaining significant clinical improvement of respiratory allergies after AIT is that a correct causal correlation between allergen sensitization, exposure, and elicited symptoms is proved.[2] As a matter of fact, choosing the appropriate allergen extract for AIT is one of the most relevant clinical problems every allergist faces in everyday practice, particularly in patients with multiple sensitizations who represent the majority by now.[3] This clinical problem becomes a real puzzle in some particular climatic areas in which the most relevant allergenic plants pollinate in the same period.[4]

Therefore, the need of biomarkers assessing the probability of response to AIT before it is initiated, as well as biomarkers predicting the safety, long-term efficacy, and time to symptoms relapse when AIT is stopped, is crucial and still a hot topic in allergy and clinical immunology research.[5] With the help of reliable biomarkers, the clinician will be more confident in finding eligible patients for AIT, as this treatment can really be considered a good example of precision medicine.[6]

A plethora of in vitro or in vivo, invasive or noninvasive, cheap or expensive, systemic or topical biomarkers have been tested, but so far none has shown the profile of a perfect or at least very reliable biomarker.

Among the in vivo biomarkers for AIT, nasal and conjunctival challenges with allergen extracts are considered easy, generally well tolerated, and therefore suggested and widely used for clinical trials.[7] The principle on which nasal and conjunctival allergen challenges are based is that directly exposing the target mucosa (in this case the nasal or conjunctival mucosa) with a known dose or concentration of a possible causative allergen extract, should induce typical allergic symptoms in a roughly dose manner,[8] giving the opportunity to the clinician to choose to treat the patient with one allergen extract rather than another. Unfortunately, this technique is not free of possible confounders.

First of all, the topical administration of an allergen extract dose can also induce a nonspecific irritating reaction that may perfectly mimic an allergic reaction. Moreover, even if the use of visual analogue scales or specific symptoms score are fully validated for nasal allergen challenge, the inter-subject variability in perceiving and referring symptoms and their severity is still high. Also, some patient factors, including the chronic use of systemic and topical corticosteroids and allergy drugs or the presence of additives into the allergen extract, may respectively decrease or increase the reactivity to the test.[8] In addition, an acute nasal allergen challenge may incompletely model a naturally occurring disease, in which the repeated daily exposure to allergen modifies the mucosal inflammatory cell profile, possibly altering the response to allergen exposure.[7] Finally, nasal allergen challenge is formally contraindicated in several common conditions such as previous episodes of anaphylaxis, severe lower airway diseases, and chronic treatment with β-adrenolytic or angiotensin-enzyme converting inhibitor. All these characteristics make the nasal challenge (and also the conjunctival one) an imperfect biomarker, which is still underutilized in clinical practice.

Leśniak et al,[9] in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*), showed that the basophil activation test (BAT) is a reliable surrogate marker of positive nasal allergen challenge, with a very high negative predictive value: a negative BAT virtually rules out a positive nasal challenge with that specific allergen.[9] BAT is an in vitro flow cytometric assay analyzing the response of basophils to immunological triggers, such as allergens, in terms of expression of activation molecules on the cell membrane. Exposing

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the patient's basophils to a relevant allergen is expected to induce an increase in the expression of molecules such as CD63 and CD203c; this should not happen in patients for whom the tested allergen sensitization is clinically irrelevant. With this in mind, BAT has been mainly used in food allergy and drug allergy diagnosis.[10] The study of Leśniak et al[9] applied the above assumption to test the sensitivity and specificity of BAT in predicting nasal allergen challenge in a group of patients possibly eligible for AIT. Their results highlight that BAT can be a potential good biomarker at least for determining to which allergen treat the patient. This study limited its attention to the pretreatment assessment of the causative allergenic source, and it has not been designed to monitor the patients during and after AIT treatment; therefore, it does not tell us anything about the possible role of BAT as a biomarker for assessing the probability of response to AIT before it is initiated. Further studies are needed to determine if the AIT selected by means of BAT is more efficacious than treatments selected only using clinical criteria.

In conclusion, the study by Leśniak et al[9] adds an element to the complex search for biomarkers for AIT, indentifying BAT as a useful diagnostic test to select the causative allergen to be treated by AIT. It is likely that in order to further refine treatment choice and consequently its effectiveness, it will be necessary to combine the BAT with other tools in panels of biomarkers.

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