

The practical role of serum allergen-specific IgE as potential biomarker for predicting responder to allergen immunotherapy

Expert Rev. Clin. Immunol. 10(3), 321–324 (2014)



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Allergic asthma and rhinitis are characterized by IgE-mediated inflammation consequent to the exposure to a specific allergen. Therefore, IgE production may be considered the hallmark of allergy. Actually, allergen immunotherapy (AIT) is the unique causal treatment for respiratory allergy. Indeed, successful AIT can induce a physiologic immune tolerance toward the causal allergen. There is evidence to show that AIT is safe and effective; its indication has been rigorously stated by robust position papers. AIT efficacy assessment is mainly based on symptom reduction and drug saving. AIT responder quote may range between 60 and 90% of AIT prescription. As AIT is expensive and long-lasting, the availability of a marker able to predict AIT responder is a crucial relevance. This issue has been the topic of several studies. Very recently, it has been preliminarily reported that a cut-off of serum specific IgE levels could define AIT-responder. However, further rigorous studies will confirm this view.

Allergen immunotherapy

Allergic asthma and rhinitis are characterized by IgE-mediated inflammation consequent to exposure to a specific allergen. Therefore, IgE production may be considered the hallmark of allergy, such as an indispensable factor for being allergic. Actually, allergen immunotherapy (AIT) is the unique causal treatment for respiratory allergy. Indeed, successful AIT can induce a physiologic immune tolerance toward the causal allergen [1]. In other words, AIT may be considered a disease-modifier as it is able to prevent typical complications of the natural history of allergy. AIT consists in administering a high dose of the causal allergen for a long time period. AIT has been evidenced to be safe and effective, and its indication has been rigorously stated by robust position papers [2,3]. AIT efficacy assessment is mainly based on symptom reduction and drug saving.

On the other hand, the percentage of AIT responders depends on several factors including appropriate indication, adequate allergen extract choice, type of causal allergen, duration and severity of symptoms, sufficient treatment duration and patient compliance. Anyway, responder quote may range between 60 and 90% of AIT prescription. As AIT is expensive and long lasting, the availability of a marker able to predict AIT responder is a crucial relevance. This issue has been the topic of several researches, but presently a sure marker for predicting AIT response is still lacking.

Searching for an AIT efficacy biomarker

Allergic reaction is sustained by a complex network of immune response toward the causal allergen. Historically, allergy was considered depending on Th2 polarization, such as increased production of Th2-dependent cytokines,

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KEYWORDS: allergen immunotherapy • allergen-specific IgE • allergic rhinitis • asthma • biomarker
• responder • serum • total IgE

mainly IL-4 and IL-13, able to start, amplify and maintain inflammatory phenomena. Presently, other T-cell subsets are involved in allergy pathogenesis, including Th9, Th17, Th23, and above all, Treg. Indeed, allergy may be characterized by an allergen-specific and functional defect of Treg that in turn causes intolerance toward the causal allergen. For this reason, successful AIT restores Treg function and induces the physiological tolerance for the causal allergen, changing the cytokine scenario. To this end, cytokine pattern change was associated with AIT response, but no cytokine has been clearly established as a marker for AIT response or for defining AIT responder [4].

IgE as a biomarker for allergy

Recognizing the causal allergen is a mandatory requirement (*condicio sine qua non*) for appropriate AIT prescription, mainly concerning the wide prevalence of polysensitized patients. The first diagnostic step is to detect allergen-specific IgE production by skin prick test (SPT) or by serum assay: a positive response confirms the presence of sensitization. The second one is to distinguish simple sensitization from true allergy, such as the symptom occurrence after the exposure to the sensitizing allergen (*post hoc ergo propter hoc*). However, SPT is not able to surely discriminate between sensitization and allergy. In this regard, Letran *et al.* performed an interesting study for investigating component-resolved diagnosis in patients with pollen allergy [5]. They concluded that there is the necessity of the habitual use of this kind of protocol in routine allergy practice. In fact, the introduction of component-resolved diagnosis is providing new diagnostic tools that may lead to the identification of an accurate patient sensitization profile. Moreover, it is noteworthy to underline the clinical importance of serum IgE assessment in the management of allergic patients. In this regard, a series of evidence was produced highlighting the clinical relevance of serum allergen-specific IgE measurement, mainly in polysensitized patients:

- Allergen-specific IgE, IgG, IgG4 and IgA serum levels are significantly different for each tested allergen; there is also significant relationship between IgE levels and allergy severity. Thus, the immunoglobulin production pattern depends on the specificity of the allergenic response [6].
- Polysensitized children (494), with SPT unable to define causal allergen, showed significant difference among serum-specific IgE (sIgE) levels: this study evidenced that IgE measurement is more appropriate in polysensitized children [7].
- Polysensitized adult patients (610), with the same SPT result (such as ++++), had significantly different serum-specific-IgE values. Also, this study supported the concept that specific IgE measurement is more appropriate in managing polysensitized patients [8].
- Furthermore, it was also evidenced that serum IgE discriminates allergy from sensitization better than skin testing in polysensitized patients: 122 allergic patients were enrolled, skin testing was compared with sIgE, the demonstration of symptom occurrence after exposure to sensitizing allergen

was considered the gold standard for defining true allergy. Results showed for sIgE that the positive and negative predictive values were 72 and 80%; area under the curve was 0.83. Therefore, this study evidenced that serum IgE measurement is a reliable tool for identifying true allergic patients and choosing the allergen extract for immunotherapy in polysensitized patients [9]. On the other hand, a recent review reported some studies that have compared skin prick testing, provocation testing and serum IgE levels with allergen components [10]. Some of these studies showed conflicting findings, for example, that skin prick testing and not serum IgE levels seem to give a better reflection of clinical sensitivity. In particular, Niederberger *et al.* evaluated 24 patients with pollen allergy and 8 healthy non-allergic subjects, performing skin testing, serum IgE measurement and nasal challenge [11]. These authors demonstrated on a molecular level that skin testing provides a better reflection of immediate-type respiratory sensitivity than serologic measurements.

All these considerations highlight the concept that the allergist should perform an accurate work-up to correctly define the causal allergen, such as the clinical relevance of skin and/or serum testing findings, mainly in polysensitized patients [12]. This pathway is important to individuate the allergen extract for AIT.

Serum IgE, a biomarker for AIT efficacy?

This topic is surely intriguing as to have available a biomarker able to predict AIT response is clinically relevant. However, very few studies addressed this issue and the outcomes were conflicting.

A first study reported some years ago that the serum-specific IgE/total IgE ratio may predict the clinical response to AIT in monosensitized patients to grass, *Parietaria judaica*, *Olea europaea* and house dust mites (HDM) [13]. In fact, high ratios (>16.2) were associated with an effective response [13]. This study was well conducted, but the allergic population was particularly selected as only monoallergic patients were recruited, whereas it is well known that polysensitization is more prevalent than monosensitization. On the contrary, Fujimura *et al.* reported opposite findings: patients with low serum-specific IgE/total IgE ratio (<0.19) achieved better AIT benefit than patients with higher ratio [14]. However, this study reported the start of clinical improvement only after the second AIT treatment year. These data seem to be conflicting with the concepts that the response to AIT is usually prompt, higher specific IgE means more likely to be clinically allergic and the better response is achieved by patients with severe symptoms [15].

A possible criticism to both studies may be that authors resorted to investigate the ratio between specific and total IgE. We believe that to consider only the specific IgE level instead the ratio between specific and total IgE levels may be easier and may allow avoiding confounding factors depending on high total IgE values due to extra-allergic causes, such as genetic predisposition, infestation, smoking, cutaneous disorders, malignancy, etc.

Anyway, it seems to be important to emphasize the surprising paucity of data in this area and to highlight the need to look at the relationship between specific and total IgE and response to AIT in the recently published large trials of AIT.

New evidence

A recent real-life experience reported that high sIgE levels could predict response to AIT in 75 adults with allergic rhinitis [16]. AIT effectiveness was calculated considering both clinical improvement and drug use (prescribed on demand) reduction. Patients globally evaluated both parameters, reporting their perception by visual analog scale (VAS). After 3-year sublingual immunotherapy (SLIT), 63 patients (84%) were AIT responder. Serum-specific IgE levels were significantly higher in responder patients than in non-responder ones. More recently, a retrospective study was performed to confirm these preliminary findings [17]. It was conducted on 174 allergic patients treated with SLIT for 3 years. Responder patient was defined on the basis of a VAS (both for symptom and drug assessing) reduction of at least 30% compared with the baseline value. Response to SLIT was considered effective in 145 (83.3%) patients. A cut-off value (such as >9.74 kU/l) for serum-specific IgE was able to discriminate effective from ineffective AIT [17]. Thus, this study concluded that specific IgE level assessment before AIT starting might predict its efficacy in adult patients with allergic rhinitis. A further proof of this hypothesis has been provided by a pediatric study [18]. This study investigated whether a cut-off sIgE level >10 kU/l could be associated with perception of effective AIT also in children with allergic asthma and/or rhinitis due to HDM. Thirty-one allergic children with serum HDM-specific IgE levels >10 kU/l were evaluated. Eight allergic children with levels of sIgE to HDM <10 kU/l were considered as control. All patients were treated with SLIT for 3 years with HDM allergen extract. Children perception of AIT efficacy was assessed by VAS, considering both symptom severity and drug use. Responder patient was defined with >6 VAS. Severity of nasal symptoms was assessed by nasal VAS, asthma control was evaluated by Asthma Control Test; both were considered before and after AIT. All children (but one) with sIgE >10 kU/l perceived AIT efficacy, whereas only one child with sIgE <10 kU/l perceived AIT benefit. There was a strong relationship between perception of AIT efficacy by

VAS and sIgE levels ($r = 0.615$). Also nasal VAS and Asthma Control Test significantly improved only in children with sIgE >10 kU/l. Therefore, allergen-specific IgE assessment before AIT prescription might represent a useful tool to individuate potential responder. On the other hand, the small numbers studied and the discrepancy between the numbers of non-responders compared with responders in the three studies cited should be considered as limitation of these experiences. In fact, the first study reported that there are 12 non-responders out of 75 AIT-treated subjects. The second study reported 33 non-responders out of 178 and the third study only 8 out of 39 AIT-treated subjects. Therefore, one cannot draw firm conclusions of response rates in individual subjects and larger studies are needed.

Conclusion

The availability of a biomarker predicting the AIT outcome would be extremely useful in the clinical practice, but it should be reliable and easily achievable. sIgE assay is a popular test, commonly used by the allergist. Moreover, IgE is a typical marker for the allergic phenotype, and high levels of serum sIgE well correlate with most severe symptoms [19]. The recent studies confirm that the serum allergen-specific IgE levels may be associated with positive AIT response. In other words, sIgE level more than 10 kU/l before AIT prescription could be an indication to the allergist that AIT might have good chance of efficacy. However, there is the need to obtain more robust support to confirm this preliminary finding. In fact, randomized controlled studies should be conducted for confirming this view, mainly in polysensitized patients, as it has been reported that polysensitized subjects could also benefit from AIT [20].

In conclusion, allergen-specific IgE assessment before AIT prescription might in the future represent a useful tool to individuate potential responder.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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