

EXPERT
REVIEWSManagement of
polysensitized patient: from
molecular diagnostics to
biomolecular immunotherapy

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A panel of Italian allergists gathered to discuss the issue concerning the management of polysensitized patients. The main conclusions were as follows: polysensitization is a relevant clinical characteristic as it affects about 70–80% of the global allergic population; the diagnostic pathway needs the use of an adequate and thorough methodology, based on the demonstration of consistency between history and documented sensitization; polysensitization and polyallergy are not synonymous: true allergy should always be demonstrated; polysensitization does not constitute a limitation to allergen immunotherapy prescription, as 1–2 allergen extracts could be effective in polysensitized patients; the allergen immunotherapy product characteristics should include the following: high efficacy and optimal safety profile, standardized production, and documented presence and titration of the major allergen.

KEYWORDS: allergy • immunotherapy • management • molecular allergens • polysensitization

Respiratory allergy, such as allergic rhinitis and asthma, has an impressive prevalence, as it may affect up to 40% of the general population and has an important impact on pharmacoeconomy, with worsening school and work performance as well as daily activities and quality of life (QoL) [1,2]. The hallmark of allergic reaction is the ongoing production of allergen-specific IgE, such as sensitization. Sensitization may be considered the *condicio sine qua non* to define allergy. On the other hand, the natural history of allergy is frequently characterized by an increasing number of sensitizations (such as the polysensitization phenomenon). In fact, it has been reported that younger children are more frequently monosensitized than older ones, and monosensitized children can frequently develop polysensitization over time [3–6].

Polysensitization is an immunological event that is relevant from an epidemiological and clinical point of view. The polysensitization prevalence ranges from 20 to 90%, with a great variability depending on the analyzed populations [7–9]. However, it is important to

differentiate between true cosensitization to different allergen sources and corecognition due to sensitization to one or more pan-allergens. Also, in the former case, it has to be established whether each of the sensitizations is clinically relevant, such as is it true allergy, or not.

It has been reported that polyallergic patients usually have a clinical picture different from monoallergic ones, such as they have more severe symptoms and impaired QoL than monoallergic ones [10,11]. The immunological basis of this phenomenon might be a functional defect of allergen-specific T-regulatory cells (Treg), such as a defective production of IL-10 and IFN- γ [12]. Treg-dependent cytokines exert an antiallergic role, probably preventing polysensitization.

Allergen immunotherapy (AIT) is the only specific cure for allergic rhinitis and asthma, as it is able to induce clinical and immunological tolerance toward the causal allergen, reducing allergic symptoms and medications' use [13,14]. As AIT consists of administration of the causal allergen, the detection, during the workup, of

a polysensitization may have a profound influence in the clinical practice. In this regards, many doctors believe that polysensitization may represent a crucial obstacle for choosing the allergen extract(s) for AIT composition. The practical consequence is the frequent reluctance to prescribe AIT in polysensitized patients. In this context, few studies investigated the AIT efficacy in polysensitized patients. A first study provided negative findings, but a mixture of different allergens (up to seven) was used in children with allergic asthma [15]. By contrast, there are some positive reports in polysensitized patients using only one or two allergen extracts [16–19]. Moreover, a series of real-life multicenter observational studies (poly-sensitization impact on immunotherapy [POLISMAIL]) has been performed to investigate the clinical impact of polysensitizations on AIT prescription behavior and immunotherapy efficacy in polysensitized patients [20]. POLISMAIL studies provided evidence that polysensitization does not represent an obstacle to AIT prescription, as only one or two allergens were used and AIT efficacy was observed in most patients [20].

On the other hand, molecular-based allergy diagnostics have recently become available in the clinical practice; it allows to precisely defining and characterizing the sensitization profile [21]. In particular, molecular diagnostics can change allergen-specific immunotherapy prescription [22]. In fact, positivity to major allergens excludes false reactivity to pan-allergens. [22]. In this regard, a large study (conducted on 651 children) provided evidence that molecular diagnostics changed the skin prick test-based decision on AIT prescription in >40% of children [23].

Nevertheless, a fundamental concept has to be pointed out: the production of allergen-specific IgE does not ever correspond to true allergy, such as symptom occurrence after exposure to the sensitizing allergen. Thus laboratory findings should always be interpreted. In other words, a patient may be sensitized to many allergens, but allergic only to few (or to nothing!). The role of the allergist is indeed to define true allergy in polysensitized patients.

Experts' agreement

On the basis of these topics, it is clear that the management of polysensitized patients represents an intriguing challenge for the allergist. For this reason, a workshop was conducted involving a group of Italian allergists (Italian Study Group on polysensitizations), particularly expert in AIT as together they managed thousands of allergic patients. Two main topics were discussed: the diagnostic and therapeutic approach in polysensitized patients and the characteristics of a high-quality allergen extract.

Here we report the main conclusions.

The therapeutic approach to the polysensitized patients

The common experience rates a prevalence of polysensitization in up to 80% of allergic patients. It has been agreed that polyallergic subjects usually complain of more severe symptoms and impaired QoL than monoallergic ones, confirming previous

studies [24,25]. Experts retained that it is fundamental for the allergist to identify a correct and thorough diagnostic pathway, mainly concerning the differentiation between simple polysensitization, such as mere production of IgE without symptoms occurrence, after sensitizing allergen exposure and true polyallergy, to prescribe the best therapeutic option.

The allergy diagnosis presumes a pragmatic method, based on symptom history (duration, frequency, severity and period), knowledge of local allergen exposure characteristics and assessment of patient's supply.

Molecular allergy diagnostics should always (where available) be performed to exclude false allergy by investigating the major allergen molecules. However, a restricted panel of allergens (based on geographical peculiarity) should be used to optimize financial resources.

In true polyallergic patients, the number of allergen extracts should be restricted to 1–2 major allergens: 80% of experts prefer limiting the choice to a single allergen, also considering the objective of improving the AIT adherence [26].

Experts conclude that: molecular diagnostics surely will improve upon a correct and sure definition of the causal allergen; traditional diagnosis (in the absence of molecular diagnosis) allows reaching an adequate therapeutic option in most patients; and the AIT with 1–2 allergens is the most efficient therapeutic strategy in polyallergic patients.

The characteristics of a high-quality allergen extract for AIT

Experts recognize that a high-quality AIT product should have the following properties: efficacy; safety; certified material (composition and quantity); titration (allergenic potency expressed in µg); molecular profile characterization, such as to be the real cause of symptoms (i.e., the causal allergen); definition of the ideal maximal therapeutic dose [27]; and optimal quality/price ratio. It is noteworthy to ascertain that these proposed requirements correspond well to those that emerged in a recent survey [28].

Another relevant unmet need was the possibility of guaranteeing the presence of the major allergen in AIT products. It is desirable that major allergen quantity be guaranteed in AIT products. However, major allergen depends on geographic characteristics; in this regard, the phenotype of patients enrolled for Phase III clinical trials should be detected. AIT products with biomolecular profile, such as the declaration of the contents expressed in microgram of major allergen, have been very recently introduced in the marketplace.

Therefore, experts stated that: AIT products with biomolecular profile meet the requirements of regulatory agencies, scientific societies and allergists; as patients inhale allergenic molecules, including major allergens, that cause allergic symptoms, it is mandatory to know whether AIT products contain these antigens and their quantity; and mass spectrophotometry is the most advanced technique to quantify major allergen during the productive process.

Conclusions

Polysensitization is a common feature in allergic patients, but it should be carefully assessed and managed. In particular, sensitization does not ever correspond to true allergy, and AIT should always be prescribed (when indicated) in polysensitized patients.

Expert commentary

The management of polysensitized patients should be based on a thorough allergy workup based mainly on molecular diagnostics. In effect, defining the major and genuine causal allergen is crucial in selecting the allergen extract for AIT prescription. Another relevant issue is to use AIT products that are well standardized and contain the major allergens. Some products are presently available, but more will be soon become available.

Five-year view

It should be desirable to define in the next years a restricted panel of allergen molecules able to cheaply screen polysensitized patients and easily define the causal allergens and relevance in individual patients, mainly concerning the specific geographical area. In this regard, cutoff IgE levels could be very fruitful in detecting true allergy: some ongoing studies are investigating this issue.

Financial & competing interests disclosure

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Key issues

- Polysensitization is a relevant clinical characteristic as it affects about 70–80% of the global allergic population.
- Diagnostic pathway needs the use of an adequate and thorough methodology, based on the demonstration of consistency between history and documented sensitization by skin prick test and/or serum allergen-specific IgE measurement. In selected patients, molecular diagnostics should be performed.
- Polysensitization and polyallergy are not synonymous: true allergy should always be demonstrated.
- Polysensitization does not constitute a limitation to AIT prescription. There is convincing evidence-based medicine literature supporting the concept that 1–2 allergen extracts could be effective in polysensitized patients.
- The AIT product characteristics should be: high efficacy and optimal safety profile (validated by evidence-based medicine trials for single allergen), standardized production, and documented presence and titration of major allergen.

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