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Immunotherapy in polysensitized patients: new chances for the allergists?

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Allergic rhinitis (AR) and asthma are the most frequent IgE-mediated diseases and may affect up to 40% of the general population, causing substantial social and economic burdens.¹ In fact, school or work performance (including school or work absences), daily activities, and quality of life (QoL) are significantly impaired in both children and adults with respiratory allergy.²

Moreover, the progressively increasing number of sensitizations (such as polysensitization) in the same allergic patient seems to characterize the natural history of allergy and represent a common feature of allergic patients. In addition, the component-resolved diagnostic techniques have documented that atopic infants usually start with monosensitization (sensitization to only one class of allergens) but soon tend to become sensitized to other allergens over time.³ Polysensitization is an immunologic phenomenon that is clinically and epidemiologically relevant. The presence of polysensitization has been well documented in both children and adults in general population surveys or allergic population-based studies.^{4–6} The increasing number of sensitizations seems to characterize the natural history of the allergic patient and may represent a typical evolution of allergy. In a patient survey study analyzing retrospectively 165 asthmatic patients, who were initially monosensitized, Silvestri and colleagues⁷ found that 43.6% of the patients became polysensitized at the second survey (after 10 years). The transition from monosensitization to polysensitization observed in the entire population was present also in preschool-aged and school-aged children when analyzed separately. In addition, the authors found that house dust mite sensitization and, at a lower degree, pollen sensitization appear to play a "triggering" role in the development of polysensitization because a high proportion of children initially monosensitized to house dust mites or pollens then became polysensitized.

The percentage of polysensitized patients ranges from 20% to 90%, with a great variability depending on the populations.^{4–6} Polysensitization may also be associated with different clinical pictures with respect to monosensitized patients, especially those with a more impaired QoL and more severe symptoms.⁶ In addition, allergic children seem to display a higher frequency of sensitizations than their parents, especially in families with polysensitization.⁷ In addition, a small proportion of patients remain monosensitized during their whole life.⁴ A recent preliminary study suggested that a functional defect of T-regulatory cells may explain the tendency to develop polysensitization.⁸ Children with persistent monosensitization produce higher amounts of interleukin 10 and interferon γ than children who develop polysensitization. This observation might envisage different immunologic phenotypes for monosensitized and polysensitized patients.

Allergen specific immunotherapy (SIT) is the only allergen-driven therapy for AR and asthma because it is able to reduce allergic symptoms and use of medications by inducing clinical and immunologic tolerance to the causal allergen. Subcutaneous immunotherapy (SCIT) is considered the standard modality of treatment, but sublingual immunotherapy (SLIT) is currently the most commonly prescribed form of SIT in many countries because of its efficacy, which has been confirmed by several meta-analyses.⁹ SLIT is currently recognized as a viable alternative to SCIT in the consensus documents.¹⁰

Polysensitization may have a profound influence in clinical practice. For instance, it may represent a crucial obstacle as far as the choice of the allergen extract to be used for immunotherapy is concerned. For this reason, many physicians are reluctant to prescribe SIT in polysensitized patients. In this regard, the evaluation of the efficacy of SIT in polysensitized patients still represents a partially unanswered question, and there are few studies on this issue.

Adkinson and colleagues¹¹ performed a controlled trial of SCIT in children with allergic asthma using different mixed (up to 7) allergens and found no discernible benefit. However, the trial had

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major methodologic problems, such as the use of mostly seasonal allergens in children with perennial asthma (the extract did not include cockroach and animal dander allergens, which may well have been the most important allergens in these mixed inner-city and suburban children). By contrast, Alvarez-Cuesta et al.¹² demonstrated in a placebo-controlled study that SCIT with both grass and olive pollen was able to significantly improve the QoL in patients with seasonal AR due to double sensitization. A recent open study investigated the efficacy of SLIT with grass pollen, birch pollen, or both in patients with double sensitization.¹³ Unexpectedly, SLIT with grass pollen only achieved some improvement in the birch pollen season and vice versa. The authors attributed this outcome to possible cross-reactivity of the 2 pollen allergens or to induction by SLIT of the production of interleukin 10, which exerts a nonallergen-specific immunologic effect. SLIT with both pollens provided the best clinical outcome. Finally, the efficacy of multiple allergen immunotherapy has been reported in 3 studies summarized by Nelson.¹⁴

Recently, a series of real-life, multicenter, observational studies, named POLISMAIL (Polysensitization Impact on Immunotherapy), was conducted to elucidate the clinical relevance of polysensitizations.¹⁵ These studies also aimed to evaluate the characteristics of polysensitized AR patients and the behavior of the allergists treating them. The effectiveness and the safety of a 2-year SLIT treatment in such patients were also evaluated at different times. The rationale of the POLISMAIL studies was based on several issues: (1) polysensitization usually starts from childhood, (2) polysensitization progresses with aging, (3) up to 80% of allergic adults are polysensitized, (4) polysensitization may depend on a T-regulatory cell defect, (5) polysensitization may significantly affect QoL, (6) polysensitization may be associated with more severe symptoms, and (7) polysensitization may discourage immunotherapy prescription. These studies were conducted in 11 allergy centers that were homogeneously distributed in Italy to include samples representative of the general population. The POLISMAIL studies clearly indicated that polysensitization should not constitute an obstacle to SLIT prescription. In fact, only the clinically relevant allergens (such as the sensitizing allergens able of inducing symptoms when inhaled) were chosen for SIT. The suitability of this allergen choice was confirmed by SLIT effectiveness on the reported improvement of AR and asthma classifications and severity. In fact, the restricted choice to limit SLIT to 1 to 2 allergen extracts, preferably separated and at high dosages, was sufficient and effective in improving symptoms and QoL in those polysensitized patients.¹⁵

However, the clinical efficacy of immunotherapy, either SCIT or SLIT, has been supported by numerous clinical trials and meta-analyses, recently reviewed by Compalati¹⁶ and generally conducted in qualified settings. Typically, an immunotherapy trial includes patients sensitized to a single allergen or to other allergens unable to bias the observation. For example, a trial on SCIT or SLIT with a grass pollen extract may include patients sensitized to cypress pollen, which has totally separate seasons. However, in real life, and especially in adults, most patients are sensitized to multiple allergens, which have exposure overlap. In the Mediterranean area, characterized by a complex pollen pattern, molecular diagnosis can change SIT prescription.¹⁷ In the United States, this is not perceived as an obstacle because patients are treated with allergen mixtures,¹⁸ including all the allergens eliciting a positive response to allergy skin tests. In Europe, the usual practice involves the administration of few relevant allergens. Such an attitude is influenced by the awareness that the enzymatic activity of some allergens might degrade some other ones. In addition, in the case of adverse events it is not possible to discriminate the allergen extract causing the untoward effects.

The dose dependence of efficacy of immunotherapy has been sufficiently confirmed for both SCIT and SLIT.¹⁹ However, the fact

Table 1

The possible added values provided by molecular diagnosis for a correct immunotherapy in polysensitized patients

- Quick and thorough information on sensitization profile
- Explanation for symptoms or diagnostic results due to cross-reactivity
- Intelligibility of complex results (ie, pan-allergens)
- More precise identification of candidate to immunotherapy
- Potential reduction of specific immunotherapy costs

that polysensitized patients cannot be treated at all with immunotherapy is not supported by scientific data. The POLISMAIL series was performed in a real-life setting. On the other hand, observational, real-life studies are less methodologically rigorous than randomized controlled trials but are possibly more respectful of the daily practice. Therefore, the conclusions of this study should be considered in a broader perspective. The POLISMAIL studies should convince the allergists, as well as other specialists who treat allergic patients, that polysensitization should no longer represent an obstacle in prescribing SLIT because a treatment limited to 1 to 2 allergen extracts might be effective in improving the clinical symptoms and QoL of patients, while maintaining the well-known safety of this therapy. These observations further underline that the discrepancy between diagnosed sensitizations and immunotherapy prescription should be more carefully considered and evaluated in future studies as recently outlined.²⁰

The recently available component-resolved diagnostic tools (either recombinant or purified allergens for skin prick test or CAP assay or microarray systems) have been reported to represent a significant advance in the accurate identification of the sensitizing allergen(s)²¹ with potential advantages in the management of the vaccination programs (Table 1). For instance, a positive skin prick test result to grasses and birch may be related to a true sensitization to the major allergens (Phl p 1 and Bet v 1) or simply due to a cross-reacting response to Bet v 2 and Phl p 12, which are profilins present with small conformational change in both species of pollens. Thus, not only the detection of IgE against genuine allergenic components but also the demonstration of a sensitization to pan-allergens (eg, profilins and PR-10) and/or cross-reacting allergens (eg, lipid transfer proteins, cupins, and tropomiosins)^{5,21} may at least in part modify the vaccination strategies in the near future. In addition, an advantage of the component-resolved diagnosis compared with the skin prick test is the quality of allergen extracts used for the diagnosis that could invalidate the findings.

Unfortunately, a patient's tailored vaccination program based on recombinant allergens will not be available in the next few years. Nevertheless, a comprehensive description of the IgE profiling even now allows allergists to identify relevant allergens, to disregard "positive" allergens because of the presence of a sensitization to pan-allergens, to be alert for the presence of potentially dangerous cross-reacting allergens, and, finally, to instruct the patient to accurately avoid the relevant allergen(s) potentially in different environments and foods. In conclusion, the challenge continues for allergists, whose focus on polysensitized patients will be more and more clinically relevant and demand updated skills.

References

- [1] Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160.
- [2] Pawankar R, Canonica GW, Holgate ST, Lockey RF, eds. *WAO White Book on Allergy*. Milwaukee, WI: World Allergy Organization; 2011.
- [3] Melioli G, Marcomini L, Agazzi A, Bazzuro G, Tosca Rossi GA, et al. The IgE repertoire in children and adolescents resolved at component level: a cross-sectional study. *Pediatr Allergy Immunol*. 2012;23:433–440.
- [4] Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the

- third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116:377–383.
- [5] Baatenburg de Jong A, Dikkeschel LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, mono-sensitized, and polysensitized children. *Pediatr Allergy Immunol*. 2011;22:166–171.
 - [6] Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy*. 2007;62(suppl 85):17–25.
 - [7] Silvestri M, Oddera S, Crimi P, Rossi GA. Frequency and specific sensitization to inhalant allergens within nuclear families of children with asthma and/or rhinitis. *Ann Allergy Asthma Immunol*. 1997;79:512–516.
 - [8] Prigione I, Morandi F, Tosca MA, et al. Interferon-gamma and IL-10 may protect from allergic polysensitization in children: preliminary evidence. *Allergy*. 2010;65:740–742.
 - [9] Radulovic S, Calderon M, Wilson DR, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2010;12:CD002893.
 - [10] Canonica GW, Bousquet J, Casale T, et al. Sublingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy*. 2009;64(suppl 91):1–59.
 - [11] Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med*. 1997;336:324–331.
 - [12] Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, et al. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy*. 2005;35:572–578.
 - [13] Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol*. 2007;98:274–280.
 - [14] Nelson HS. Multiple allergen immunotherapy for allergic rhinitis and asthma. *J Allergy Asthma Immunol*. 2009;123:763–769.
 - [15] Ciprandi G, Incorvaia C, Puccinelli P, et al. The POLISMAIL lesson: sublingual immunotherapy may be prescribed also in polysensitized patients. *Int J Immunopathol Pharmacol*. 2010;23:637–640.
 - [16] Compalati E, Penagos M, Tarantini D, et al. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol*. 2009;102:22–28.
 - [17] Sastre J, Landivar ME, Ruiz-Garcia M, Andregnette-Rosign MV, Mahillo I. How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area. *Allergy*. 2012;67:709–711.
 - [18] Cox L, Jacobsson L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103:451–459.
 - [19] Calderón MA, Larenas D, Kleine-Tebbe J, et al. EAACI Task Force Report on “dose-response relationship in allergen-specific immunotherapy.” *Allergy*. 2011;66:1345–1359.
 - [20] Calderon MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol*. 2012;129:929–934.
 - [21] Melioli G, Compalati E, Bonini S, Canonica GW. The added value of allergen microarray technique to the management of poly-sensitized allergic patients. *Curr Opin Allergy Clin Immunol*. 2012;12:23.