

EDITORIAL

Allergen-specific immunoprophylaxis: Toward secondary prevention of allergic rhinitis?

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25th year of PAI, 25th year of the MAS cohort

The year 1990 saw not only the birth of *Pediatric Allergy and Immunology*, but also that of the 1314 probands of the German Multicenter Allergy Study (MAS-90). Through 25 yrs, this scientific enterprise, conceived by Ulrich Wahn and the Bergmanns at the time of Berlin's 'Mauerfall' (1), has involved over 150 researchers and technicians, improving our understanding of food allergy, atopic eczema, allergic rhinitis, and asthma (2). Thanks to annual interviews, the natural history of allergic rhinitis in childhood could be carefully described (3); in parallel, blood samples were collected at 1, 2, 3, 5, 6, 7, 10, 13, and 20 yrs of age, so that the MAS bio-bank offers today the unique possibility of investigating—with microarrays requiring only a few drops of well-stored serum—the evolution of the antibody responses to allergenic molecules throughout childhood. Hence, by looking backward in the probands' life and blood, we can link immunological information to the clinical data. This mix may help us to design new strategies for prevention of allergic rhinitis(AR) in childhood.

The progressive trend of allergic rhinitis in childhood

An analysis of the follow-up data from 467 children of the MAS cohort has shown that the 12-month prevalence of AR quadrupled from 6% (at age 3 yr) to 24% (at age 13 yr) in children with non-allergic parents and more than tripled from 13% (3 yr) to 44% (13 yr) in children with at least one allergic parent (3). Half or more of the children with AR had 'severe persistent' symptoms. The impact of AR is substantial in childhood; the vast majority of affected children suffered persistently for periods of 2 months or more annually, and most of the children with persistent AR were impaired in their daily activities (3). Moreover, AR at pre-school age was found to be a predictor for developing wheezing at school age, with an adjusted relative risk of 3.82 ($p < 0.001$). In this group of children, 41.5% of all new cases of wheezing occurred among children with preceding AR

(4). Then, AR in preschool children is often a pre-morbid state of asthma development in the coming years, so that early assessment of allergic sensitization may be useful to identify the children at high risk of wheezing (4).

Allergen-specific or non-specific prevention?

The progressive characteristic of allergic diseases has inspired studies aimed at blocking their inception very early in infancy by immunological intervention rather than allergen avoidance (5). The target is to downgrade the overall propensity of the immune system to produce Th2-skewed responses to environmental and innocuous antigens (6). This prevention strategy is not allergen-specific as it is oriented to influence the overall innate immune response and, as a consequence, the polarization of the adaptive immune responses. Along the concepts developed with the hygiene hypothesis, probiotics (7) and bacterial lysates (8) have been tested and their beneficial impact, if any, seems to be restricted to certain subpopulations (7, 9). So far, recommendations to families for primary prevention of allergies and asthma are still limited to avoid active and passive tobacco smoke (10). By contrast, 'allergen-specific' approaches have been successful in 'tertiary' prevention. The so-called 'Preventive Allergy Treatment' (PAT) study has investigated the asthma-preventing capacity (tertiary prevention) of allergen-specific immunotherapy in children with allergic rhinitis. The onset of asthma was reduced by a factor of about 2.5 to 3.0 by treating with SIT (compared to placebo) children suffering from allergic rhinitis (11). This less ambitious prevention strategy, limited to prevent only the clinical consequences of sensitization to relevant allergens, has been therefore more useful than a broader, complex approach targeted to influence the whole immune response to environmental antigens. In a seminal review, Patrick Holt proposed 20 yrs ago the application of the allergen-specific approach to primary prevention of allergies and asthma (12). His vision was then translated in a proposal – within the framework of the

Immunotolerance Network (ITN), of a trial based on the sublingual administration of soluble allergens from timothy grass, dust mites and cat to at-risk children in their first year of life, i.e. before they developed any kind of atopic sensitization to airborne allergens. A report of the pilot phase of this trial has been recently published (13).

'Molecular spreading' of the pre-clinical IgE response to grass pollen

A complementary line of research has been generated by the analysis of the evolution of the IgE response performed at molecular level in the MAS cohort. It was shown that the IgE response against *Phleum pratense* very often evolves from a simple, monosensitization stage to an oligomolecular sensitization stage to end up in a polymolecular sensitization stage. This phenomenon has been defined as 'molecular spreading' (14, 15), that is, 'The sequential development of antibody (IgE) response to distinct non-cross-reacting molecules from the same antigenic (allergenic) source, starting with an "initiator" (allergenic) molecule' (Box 1). The terminology echoes the

BOX 1 – Molecular spreading

"The sequential development of antibody (IgE) response to distinct non-cross-reacting molecules from the same antigenic (allergenic) source, starting with an 'initiator' (allergenic) molecule".

so-called 'epitope spreading' phenomenon describing the evolution of the T-cell response during an autoimmune reaction and spreading from one single T-cell epitope to many T-cell epitopes within an individual molecule (16). Interestingly, Phl p 1 is the 'initiator' molecule (Box 2) in over 75% of the MAS

BOX 2 – Initiator molecule

"The allergenic molecule, within an allergenic source, responsible for the induction of the first IgE antibody response to that allergenic source".

probands developing grass pollen allergy. This may imply that Phl p 1 is a valuable target for early intervention (14, 15). Then, the response involves usually Phl p 4 or Phl p 5; thereafter also Phl p 2 and Phl p 11 and only in a later-stage Phl p 12 or Phl p 7. A cross-sectional study in Italian children has shown that a not negligible proportion of children remain sensitized only to Phl p 1, while only very few develop a full-blown response with involvement of all the eight allergenic molecules of *Phleum pratense* examined in these studies (17). The immunological basis of the expansion of the IgE response has been thoroughly discussed elsewhere (18).

Clearly, in most children, the IgE response evolves over time and becomes more and more complex. In parallel, the serum concentration of IgE antibodies against grass pollen extracts grows progressively both for an increase in the number of interested molecules, and for a rising concentration of IgE antibodies directed against any individual allergenic molecule (14). Interestingly, a specific IgE response to Phl p 1 can be observed already years before (up to 5 yrs before) in many children who will develop seasonal allergic rhinitis (Fig. 1). This 'pre-clinical' IgE sensitization, characterized by weak and simple IgE responses, is progressively increasing in concentration (geometric mean values from 1–2 to 30–40 kU/l) and molecular complexity (from 1 molecule to over 4 allergenic molecules involved). In the first years, after the onset of allergic rhinitis, a slower increasing trend in the number of molecules recognized by IgE is observed, while the overall serum concentration of IgE antibodies against *Phleum pratense* still grows at a consistent pace (14).

Toward 'secondary' allergen-specific immunoprophylaxis (SIP) of allergic rhinitis?

The evidence of a molecular-spreading process in allergic rhinitis calls for an earlier immunological intervention targeted to prevent its clinical consequences. In this perspective, Holt's proposal of an 'immunoprophylaxis of atopy' can be expanded to be applied not only at 'primary' prevention, i.e. to not-sensitized children (12, 13), but also at 'secondary' allergen-specific immunoprophylaxis (SIP) (Box 3), targeted to children already sensitized to grass pollen but still healthy (14, 15). The PAT study proved the disease-modifying

BOX 3 – Secondary, allergen-specific immunoprophylaxis (SIP)

"The administration of an allergen preparation to prevent the onset of allergic symptoms in healthy children with IgE antibodies against the corresponding allergenic source".

potential of allergen immunotherapy when applied early enough (11). However, we can also postulate that the immune response is more susceptible to be corrected and re-addressed in the first, weaker, *pre-clinical monomolecular* stages, rather than in the advanced, stronger and polymolecular, clinical stages. Early monitoring of the IgE response may be therefore helpful to start as soon as possible an allergen-specific intervention. Moreover, given the higher simplicity of the pre-clinical IgE response (mono- or oligomolecular stage), a prophylactic intervention tailored on the child's molecular sensitization profile (often only Phl p 1) would be more feasible (15, 19) than at later stages (20). Such intervention could be defined as 'component-resolved prophylaxis' (CRP) (Box 4), analogous to the concept of component-resolved therapy proposed by Rudolf Valenta (21). Similarly, it is

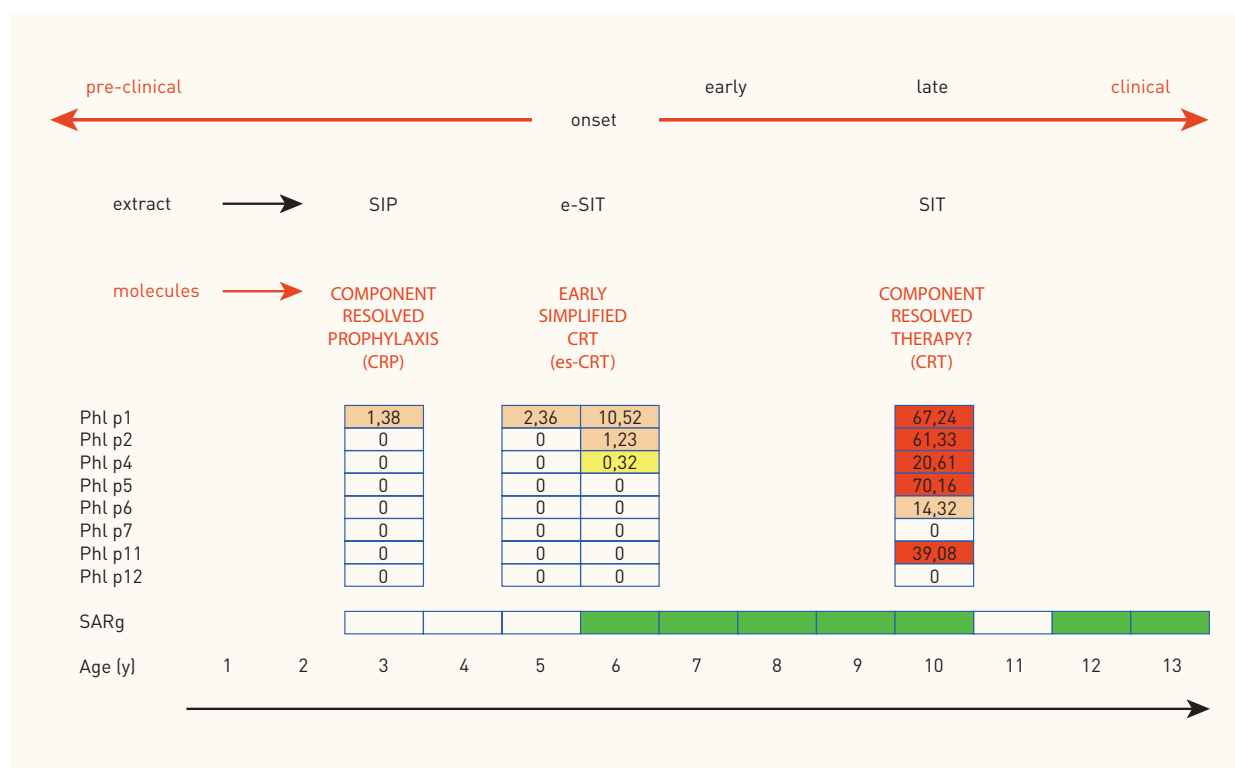


Figure 1 Molecular spreading of the IgE response to Timothy grass and potential implications for allergen-specific immunologic intervention in a child with seasonal allergic rhinitis to grass pollen (SARg). Molecular spreading of the IgE response to Phleum pratense and implications for allergen-specific immunological intervention in one child with hay fever (case from the MAS birth cohort). This child started suffering from hay fever symptoms at the age of 6 years. IgE response against Phleum pratense started 3 years before with a weak, monomolecular sensitization to Phl p 1. This IgE response was stronger and directed also to Phl p 2 and Phl p 4 at disease onset. After disease onset, the IgE response was much stronger and directed also to Phl p 5, Phl p 6, and Phl p 11. In clinical practice, allergen-specific immunotherapy (SIT) would be 'normally' prescribed at this advanced stage, after some years of symptoms (age 10 yrs). An interesting hypothesis is that SIT would be more efficient if started much earlier, ideally 'at' disease onset (age 6 yrs) (early SIT). Moreover, it could be investigated whether an immune intervention at the earliest, preclinical stages (age 3 yrs) of disease could even better change the natural history of the sensitization and prevent or delay diseases onset (allergen-specific immunoprophylaxis, SIP). The use of recombinant allergens would be easier at this stage, as less molecules should be used (component-resolved immune prophylaxis (CRP)). Reprinted with the permission of Wolters Kluwer Health License, first published in P.M. Matricardi: Molecular profile clustering and potential implications for specific immunotherapy *Curr Opin Allergy Clin Immunol* 2013 Aug;13(4): 438–45.

BOX 4 – Component Resolved Prophylaxis (CRP)

"The administration of allergenic molecules, tailored to the individual molecular IgE sensitization profile, to prevent the onset of allergic symptoms in healthy but already sensitized children".

conceivable that allergen-specific immunotherapy would have a bigger efficacy if started immediately after disease onset than, as usual, years afterwards. This concept of 'early specific immunotherapy' (e-SIT) (Fig. 1) (Box 5) deserves to be tested in properly designed clinical trials.

BOX 5 – Early specific immunotherapy (e-SIT)

"Specific immunotherapy started within 12 months after the onset of allergic symptoms".

SIP: whom? which target?

Healthy pre-school children with IgE to grass pollen are likely to develop at school age a classical seasonal allergic rhinitis triggered by grass pollen, especially if their parents are also affected by hay fever (14). Then, children with these two determinants may be a target for prevention. This is a pre-clinical 'window of opportunity' for SIP (Fig. 1). The target of

the intervention with grass pollen extract would be first of all to prevent the onset of seasonal allergic rhinoconjunctivitis, thus to keep the IgE response to grass pollen at a subclinical level. Even if the disease were not prevented, its onset could be delayed and its symptoms milder and not progressing to asthma. From a biologic perspective, it could be important to prevent the molecular spreading and the increase in the concentration of IgE to grass pollen. Given the breeding role of IgE-driven inflammation on the IgE responses (22), a secondary outcome would also be the prevention of new sensitizations to additional pollens or other airborne allergenic sources. An interesting perspective is to expand this research to other pollen sources, to mite allergy, and to other airborne

allergens in general. The concept of SIP, whose deep roots are planted in previous thinking (1, 12, 18), let us hope will be implemented before our MAS cohort participants turn 50, and provide a beneficial impact on their genetically predisposed grandchildren.

Acknowledgments and Conflicts of Interest

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