

Editorial

Systemic and specific treatment for a global disease: allergen immunotherapy revisited

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Over the last few years, allergy journals have been overwhelmed with original reports and reviews addressing different aspects of traditional and novel forms of allergen-specific immunotherapy (SIT) and reflecting the revival of interest in this mode of treatment.

Although authors usually refer to almost a century of tradition of allergen immunotherapy (1), it should be remembered that less than 20 years ago, our community was not so certain as to the real value of this treatment modality in allergic disease.

In April 1988, allergen-SIT was put on trial during an international meeting held in one of the leading world allergy centres (2). The 'jury' consisted of 100 doctors attending an international allergy course. Three major issues were on trial: (i) Does immunotherapy work? (ii) Is it safe? (iii) How does it compare with other forms of treatment? The official verdict was 47 *for* and 50 *against* immunotherapy... I wonder how the vote would go today?

This month's issue of *Allergy* presents a series of articles discussing important aspects of classical allergen-SIT as well as novel approaches to immunomodulation of allergic diseases.

Between pharmacotherapy and causative treatments of allergy

There is no doubt that SIT is effective in venom allergy (3). However, from the patients' perspective, the major breakthrough in our fight against respiratory allergies

such as allergic rhinitis and bronchial asthma was the understanding by doctors (in the mid-1980s) of the significance of underlying chronic inflammation of the airway mucosa for the pathogenesis of allergic disease. Subsequent improvements in anti-inflammatory treatments including more effective topical steroids and the development of new medicines (e.g. antileukotrienes) resulted in dramatic changes in the effectiveness of treatment and, as a consequence, in an improvement in patients' well-being. Early reports indicated certain 'anti-inflammatory' effects when using allergen-SIT, but the paucity of well-controlled clinical trials together with a wave of reports of lethal events associated with specific subcutaneous immunotherapy (SCIT) marked the last few decades of the 20th century as a golden era for anti-inflammatory treatment. At the same time, a retreat from allergen immunotherapy became evident.

However, the expectations of allergy patients go far beyond controlling the symptoms of rhinitis, conjunctivitis or bronchial asthma achieved by an anti-inflammatory treatment. From qualified specialists, patients expect not only the relief of symptoms but also effective prevention, hope for a long-lasting remission and even a cure of the disease. These expectations could not and cannot be met with pharmacotherapy. They turn out to be achievable by 'old fashioned' and, for some of us, a neglected form of SIT. Moreover, a better understanding of the nature of immunoglobulin-E (IgE)-mediated allergies has led to an increased recognition by the scientific community that our ultimate goal should be

the treatment of the systemic nature of allergic disease rather than the fighting of local organ symptoms.

Benefits of classical immunotherapy

Although the clinical benefits from immunotherapy in allergic rhinitis/conjunctivitis patients have not been questioned, the efficacy of SCIT in patients with allergic asthma was the subject of serious controversy for years. The benefits and side effects were discussed at great length. Since the 1990s, a series of well-controlled studies followed by meta-analyses and a WHO consensus paper (4–7) have all reported the fact that immunotherapy with pollens and mites was clinically effective in selected patients with asthma and had wide-ranging anti-inflammatory effects. Despite such clinical evidence, the usefulness of SCIT in patients with allergic asthma has to be gauged against standard anti-inflammatory therapy with inhaled corticosteroids (ICS). Current asthma treatment recommendations consider SCIT as a rather secondary treatment modality with an unproven efficacy. The most recent Global Initiative for Asthma (GINA) guideline positions immunotherapy as a second or third-line treatment:

‘Given the current state of information, SIT should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient’s asthma. There are no studies that compare SIT with pharmacologic therapy for asthma.’ (8)

The Blumberg et al. study (9) published in this issue of *Allergy* provides scientific arguments for a significant extension of indication of SIT in bronchial asthma beyond GINA indications. In a double-blind, placebo-controlled study, the efficacy of subcutaneous SIT was assessed in patients with moderate and severe bronchial asthma requiring ICS doses equivalent to at least 500 µg of fluticasone propionate daily. The addition of SIT to standard anti-inflammatory treatment resulted in an impressive 82% reduction in median ICS doses when compared with a 42% decrease in the placebo group after 3 years of treatment. The effect was better in moderate than in severe asthmatics, and the reduction in ICS was achieved despite the fact that most patients (72%) were also sensitized to other seasonal and perennial allergens. This indicated a potential value of immunotherapy also in polysensitized patients with asthma. If these observations are confirmed by other studies, one can expect that SCIT may be recommended in future as a valuable addition to therapy in asthmatic patients taking moderate/high doses of ICS.

The monitoring of airway inflammation has become increasingly important in assessing the effects of allergy treatment (10–13). Noninvasive methods of monitoring (e.g. nitric oxide measurement in exhaled breath) were shown to improve the effectiveness of pharmacological control of asthma compared with symptom-based asthma

management (14). An attempt to use a noninvasive method for monitoring airway inflammation [in this case, exhaled breath condensate (EBC) nitrite levels] in order to assess inflammation during SCIT in children with asthma and mite allergy has been reported by Inci et al. (15). Surprisingly, an improvement in symptoms and a decrease in medication use after 1 year of SCIT was accompanied by an increase in EBC nitrite levels indicating that symptom control is not the same as proper control of underlying inflammation. An increase in the concentration of an inflammatory marker in exhaled air reflecting uncontrolled inflammation was probably due to a decrease in dose and/or a termination of inhaled glucocorticosteroids in patients receiving immunotherapy. These observations point to the importance of continuous anti-inflammatory treatment during SIT. Further studies should however be carried out to determine the effect of long-term SCIT on airway inflammation both with and without pharmacotherapy.

Preventive effects of SCIT

The beneficial effects of allergen-SIT may be long lasting and go beyond symptomatic improvement, e.g. a decrease in the development of new sensitizations (16–18). In a ground-breaking multicentre study published in 2002, Moller et al. (19) demonstrated that in children with birch or grass pollen allergies, SIT slowed down the allergic march in children with allergic rhinitis. After 3 years of treatment, significantly fewer children on SCIT developed bronchial asthma when compared with children receiving symptomatic treatment [odds ratio (OR) 2.52, $P < 0.05$]. In this issue of *Allergy*, the same authors present a 5-year follow-up of this group of children (20). At 5 years from the beginning of the study and 2 years after SIT was discontinued, the preventive effect of immunotherapy was still evident. Among 142 patients without asthma before the start of the study, those on SIT had significantly less asthma than those in the control group [OR 2.68 (0.3–5.7; $P < 0.05$)]. The conjunctival reactivity to a specific allergen was lower in patients on SIT documenting a persistence of specific nonresponsiveness for up to 2 years after cessation of treatment. However, nonspecific bronchial hyperactivity to metacholine was not decreased in the SIT group. Such discrepancy between the persistence of specific hyperresponsiveness to allergens and the lack of a continuous effect of SIT on the underlying inflammatory process in the lower airways, as reflected by nonspecific bronchial reactivity, may indicate the need for a local anti-inflammatory treatment with inhaled steroids.

In contrast to SIT of respiratory allergies, clinical benefits from desensitization to food allergens have not been well documented. This may be surprising as food-induced reactions often develop into severe anaphylactic and life-threatening events. Effective prevention by strict avoidance of the incriminated food is not practical, is

troublesome and, in most instances, not feasible. As reviewed by Niggemann et al. (20), the clinical effectiveness of the induction of specific oral tolerance for the management of food allergy has not been well documented and placebo-controlled studies have not as yet been published. The authors point at unresolved questions indicating a need for extensive new research into food allergy immunotherapy.

Alternative routes of allergen-specific immunotherapy

In many but not all countries, the traditional subcutaneous route of immunotherapy is still predominant in allergy practice. However, the possible risk of severe and even fatal side effects raises increasing interest in alternative, noninjectable routes of allergen delivery (21–26). Oral and bronchial routes did not show satisfactory clinical efficacy but sublingual immunotherapy (SLIT) has increasingly been the focus of both allergists and allergen manufacturers (27). Numerous studies of SLIT were published confirming a lack of important severe adverse reactions and documenting symptom relief in patients with respiratory allergy due to both seasonal and perennial allergens (28–31). Additionally, SLIT and SCIT turn out to have similar preventive effects: they both significantly decrease the onset of new sensitizations and affect the natural history of allergy by reducing the chance of asthma development in patients with rhinitis (32–34). However, not all studies demonstrated the clinical benefit of SLIT and several aspects remain unanswered, e.g. the effective duration of SLIT in achieving improvement, the efficacy on rhinitis with various degrees of severity, the effect on quality of life or the cost-effectiveness of the sublingual, when compared with the classical, injectable route of administration (35, 36). Passalacqua et al. (37) carried out a double-blind, controlled study of SLIT with carbamylated allergoid tablets in mite-sensitive patients with allergic rhinitis. Immunotherapy with mite allergoid tablets was shown to be effective in relieving the symptoms of rhinitis in patients with mild disease. An improvement in symptoms was observed after only 1 year of treatment. It is important to note the positive effects on nasal obstruction, a leading symptom in perennial rhinitis, as well as an excellent tolerance of the vaccine. The carbamylated allergoids used in this study as well as a reassuring safety profile demonstrated an increased bioavailability at the gastrointestinal level due to a higher resistance to enzymatic degradation. These features are particularly relevant if SLIT is to be used in younger children (38).

New developments in allergy vaccines

In parallel to the improvements in both SCID and SLIT, intensive work is underway with new approaches to

immunomodulation of allergic diseases. Studies of the mechanisms of effective allergen-SIT have led to a better insight into the critical mechanisms responsible for the development and progression of chronic allergies. These studies have also paved the way for new improvements in allergen immunotherapy. Peripheral T-cell tolerance resulting from interactions between allergen-specific T-regulatory cells and Th2 and/or Th1 cells has turned out to be a crucial mechanism of immunotherapy (39). Current understanding of the mechanisms of immunotherapy has been reviewed by Jutel et al. (40) in a review article in this issue of the journal. The authors also present a vision of how the immunological manipulation – either by the stimulation or by an adoptive transfer of T reg cells – may lead to a future change in the natural course of allergic disease and eventually to the prevention of development of respiratory allergy.

Additional improvement in the effectiveness of allergy vaccines can be achieved if adjuvants (e.g. probiotics, CpG) inducing allergen-specific Th1 responses and enhancing the development of immune tolerance are delivered together with an allergen (41). In this issue of *Allergy*, two experimental studies address the possibility of enhancing allergen immunotherapy using innovative but different approaches. A study reported by Grüber et al. (42) demonstrated that the vaccination of mice with diphtheria and tetanus toxoid prior to sensitization with ovalbumin allergen significantly suppressed the development of IgE production and IgE-mediated immune response and that co-vaccination with a whole cell pertussis vaccine inhibited allergen sensitization and bronchial hyperreactivity. An alternative approach to the enhancement of immunosuppressive effects of allergy vaccine has been presented by Daniel et al. (43) who developed recombinant lactic acid bacteria (*Lactobacillus plantarum* and *Lactococcus lactis*) capable of expressing major birch pollen allergen Bet v1. A mucosal vaccination with live recombinant lactic acid bacteria of Bet v1-immunized mice resulted in the modulation of allergic immune responses induced by birch pollen allergen (reduced allergen-specific IgE production and enhanced IgG2 generation concomitant with reduced IL-5 production). Although earlier attempts at employing mucosal allergy vaccines in humans were not successful, the local delivery of recombinant allergens expressed in recombinant probiotic bacteria combining a more effective delivery by live carriers with intrinsic immunomodulatory capacity is worthy of further exploration.

The most advanced, although still experimental, strategy aimed at the downregulation of the allergic response is based on the development of DNA vaccines. These vaccines are composed of plasmid DNA which encode allergen molecules directly in the transfected cells of a target organism resulting in the production of antigens in the host, e.g. within the airway epithelial cells (43). When plasmid vectors containing genes that encode allergens

were injected into animals, either before or after allergen challenge, it resulted in decreased Th2-mediated responses, enhanced Th1-mediated responses, and suppressed the allergic response.

However, DNA vaccines are still far from the bedside (44). So-called conventional DNA vaccines, although showing high immunogenicity in mice and other rodents, are not so effective in primates and humans and, usually, relatively high amounts of DNA are necessary to elicit a strong immune response. DNA vectors could be enhanced by optimizing promoters, introns and polyadenylation signals. A new approach has been to create a 'self-replicating' nucleic acid vaccine that utilizes a viral replicase protein derived from RNA viruses that amplify the viral genome after infection of the host cells. DNA vectors that contain replicons derived from the prototype alphavirus when transfected into cells or injected directly into animal muscle launch a self-replicating RNA vector (replicon) which in turn directs the expression of a model antigen (45). When the organism detects this process, it responds with a strong antiviral immune response. In animal models of infectious disease, these plasmid DNA replicons are substantially more efficient at stimulating antigen-specific immune responses, particularly cellular responses, when compared with conventional plasmid DNA expression vectors (46). This approach was applied for the first time by Scheibelhofer et al. (47) to deliver allergen in DNA vaccines. In a mouse model of allergy, it was demonstrated that nanogram amounts of replicon-based DNA vaccines triggered a protective Th1 response

in animals immunized to allergen β -galactosidase, also alleviating established allergic reaction. When compared with classical DNA vaccines, 20 000 fewer replicase-based DNA plasmids were sufficient to evoke comparable induction of Th1 memory, the suppression of allergen-specific IgE generation and IL-5 production in animals sensitized to *Escherichia coli* β Gal protein. To date, because of their safety and efficacy, plasmid DNA replicons have been proposed for the development of recombinant vaccines for infectious diseases and cancer. This study demonstrated for the first time that a replicase-based approach can be usefully introduced for the construction of a new generation of effective DNA vaccines for allergic diseases.

The symptomatic treatment of allergic diseases, although clinically effective, is costly and is not able to offer long-lasting effects without mentioning the prevention or cure of allergies. Respiratory allergy is a systemic disease and requires systemic treatment addressing basic pathophysiological mechanisms in a more specific way. In this setting, allergen immunotherapy, after almost 100 years of success and disappointment, emerges yet again as a major strategy for an effective therapy and prevention of allergic disease. I am convinced that ongoing clinical research on both subcutaneous and noninjectable allergen immunotherapy as well as on the development of innovative approaches to the modulation of allergic immune response is paving the way for an improved life for allergy patients marking the future of our discipline.

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