

EDITORIAL

Clinical & Experimental Allergy

Bypassing T cells using a B cell mimotope allergy vaccine

This editorial discusses the findings of the paper in this issue by Wallman et al. [19]

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Allergen-specific immunotherapy (ASIT), or allergy vaccination, is the only treatment able to change the natural course of allergic disease [1, 2]. It comprises repeated administration of allergen in order to induce allergen-specific unresponsiveness, usually during a time span of several years. The treatment was first introduced by Noon in 1911 [3]. It has thus been practiced for almost 100 years but still the immunological mechanisms by which symptom relief is achieved are poorly understood. One main hypothesis is that T cells are the preferential targets of successful ASIT. The proposed mechanism may either involve an induction of a state of anergy/deletion of allergen-specific T cells or immune deviation, i.e. a shift from a predominantly T-helper type 2 (Th2) -like to a more Th1-like phenotype [4–6]. Induction of regulatory T cells, in particular IL-10-producing regulatory T cells, has also been reported and proposed as a mechanism of action for ASIT [7–9]. Another main hypothesis stresses the importance of the humoral immune response to resolve the allergic symptoms. It has been shown in several studies that allergen-specific IgG is induced during ASIT [10–13]. This has led to the suggestion that ASIT acts through blocking antibodies, i.e. allergen-specific IgG preventing allergen–IgE interactions. Even though evidence for both mechanisms has been documented, it is not settled whether both T and B cells have to be targeted to achieve the desired effect of ASIT, or if it would suffice to target either T or B cells alone.

Several attempts have been made to create allergy vaccines that solely targets allergen-specific T cells. The rationale has been to create safe vaccines by excluding B cell epitopes able to bind to allergen-specific IgE. In this way, it would be possible to decrease the risk of severe

treatment-associated side-effects that is caused by allergen-triggered cross linking of high-affinity FcεRI receptors on effector cells, leading to degranulation and release of anaphylactogenic mediators. This may be achieved by creating so-called hypoallergens, i.e. chemically or genetically modified allergens with reduced IgE binding capacity [14]. The most striking example of T cell-targeting allergy vaccines is, however, peptide vaccines. These consist of T cell epitope bearing peptides, which due to their short linear structures have strongly reduced B cell reactivity. A couple of peptide vaccines have been applied both in experimental allergy models and in humans [15]. For example, treatment efficacy has been reported for cat-allergic asthmatic patients treated with a peptide vaccine consisting of 12 shorter (16–17 residues) overlapping T cell epitope-containing synthetic peptides derived from the major cat allergen Fel d 1 [16]. The mechanism involves induction of allergen-specific IL-10+ T cells and linked suppression to epitopes not included in the vaccine [17]. The concept was recently pushed even further with the construction of an allergy vaccine exclusively targeting T cells. This vaccine consists of virus-like particles engineered to display the immunodominant T cell epitope of the mugwort pollen allergen Art v 1 in the context of HLA-DR and costimulatory molecules [18]. It is thus possible to affect the allergen-specific immune response, as well as the allergic symptoms, with T cell targeting vaccines. A concern with this approach is, however, that the vaccines may cause late-phase asthmatic reactions independent of IgE, as a result of activation of allergen-specific effector T cells.

Is it then possible to create an allergy vaccine that solely targets the allergen-specific B cells? Such a vaccine would hypothetically act through the induction of allergen-specific blocking antibodies. However, a vaccine with intact B cell epitopes would suffer from the same safety issues as common allergen extracts used for ASIT today, i.e. the risk for activating effector cells through cross linking of FcεRI receptors, which in the worst-case

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scenario may cause anaphylaxis. On the other hand, the risk of late-phase reactions would be reduced compared with allergen extracts containing the intact allergens. Certainly, it is challenging to test the principle of a B cell-targeting allergy vaccine. It might open a possibility to treat patients where late-phase reactions are of special concern, e.g. patients with asthma. In addition, it would provide a means to study the mechanism of ASIT in a system where only B cells are targeted.

In the current issue of *Clinical & Experimental Allergy*, Wallmann et al. [19] present data on an allergen vaccine based on a single B cell epitope of the grass pollen allergen Phl p 5. To create the vaccine, an earlier identified IgE-binding epitope of Phl p 5 was targeted [20]. The epitope had been identified by phage display technology as a mimotope, i.e. a peptide that mimics a three-dimensional B cell epitope. In the present report, the Phl p 5 mimotope (termed Phl mim 5) was coupled to the carrier keyhole limpet haemocyanin (KHL). The supposed function of the carrier was to allow the mimotope to be displayed at high density on the surface of KHL, and to provide T cell bystander help to guarantee the immunogenicity of the mimotope. Indeed, when mice were immunized with the mimotope vaccine (Phl mim 5-KLH), IgG antibodies specifically recognizing Phl p 5 were formed. It was also shown that Phl mim 5 was unable to stimulate T cell proliferation and IL-5 production in splenocyte cultures from Phl p 5-sensitized mice, confirming that the mimotope was not recognized by allergen-specific T cells. The mimotope vaccine was tested in a mouse model of acute allergic asthma. Mice sensitized and subsequently aerosol challenged with recombinant Phl p 5, were treated with Phl mim 5-KLH, rPhl p 5 or KHL. The treated mice were then rechallenged with allergen and the outcome of the treatment evaluated in terms of ability to affect allergen-specific IgE and impact on airway inflammation and mucous production. Interestingly, a clear reduction of the eosinophilic airway inflammation, as well as of mucous hypersecretion, was observed in mice treated with Phl mim 5-KLH compared with control (KLH-treated) mice. No airway function tests were performed in the present study. Thus, it is not possible to say if the Phl mim 5-KLH treatment will also have a beneficial effect on allergen-induced airway hyperreactivity. Moreover, IgG in treated mice was not characterized. Although, Phl mim 5 had the capacity to induce IgG cross-reactive to Phl p 5 in immunized naïve mice, it was neither shown that these antibodies had blocking capacity nor was it possible to conclude that treatment-induced IgG would have that ability. Therefore, a mechanism involving blocking antibodies could not be confirmed in the present study. The treatment did not affect the elevated levels of Phl p 5-specific serum IgE in sensitized mice. One could thus fear that treatment with Phl mim 5-KLH would cause IgE-mediated reactions due to the high density of Phl mim 5

exposed on the vaccine. This was, however, not the case; neither local nor systemic side-effects were observed during treatment. Possibly the structure of the Phl mim 5-KLH vaccine did not allow cross binding of IgE in spite of high density of exposed mimotope. Alternatively, the fact that the mimotope represents only one B cell epitope, probably with decreased binding capacity compared with the original epitope on the allergen, might limit the ability to activate effector cells. Finally, the induced IgG antibodies could bind to inhibitory FcγRIIB on mast cells preventing IgE-induced mast cell activation. Taken together, the mimotope vaccine treatment resulted in a reduction of allergen-induced airway inflammation, without affecting the levels of allergen-specific serum IgE [19]. It remains to be shown if the positive effect on allergic inflammation will be linked to symptom relief and to elucidate the mechanism behind the treatment.

If the B cell targeting vaccine approach proves to be effective, by applying the mimotope concept or by any other strategy, it would be specifically attractive for the treatment of allergic asthma. When asthmatic patients receive ASIT, the allergic inflammation may be worsened by treatment-induced activation of allergen-specific Th2 cells. T cell-mediated reactions have indeed been observed in patients treated with T cell epitope containing peptide vaccines [16, 21]. Thus, despite many attempts to bypass B cells by constructing T cell-targeting allergy vaccines, these vaccines may not be well suited to treat asthma patients. On the other hand by bypassing T cells with B cell targeting vaccines, some problems with treatment-associated late-phase reactions may be solved but instead it will be a challenge to achieve an effective immune modulation leading to long-lasting symptom relief. The development of allergy vaccines that selectively target different disease mechanisms linked to the manifestation of certain symptoms may be a first step towards a more symptom-adjusted treatment. The tools acquired may also be used to shed new light on the basic mechanisms of successful immunotherapy.

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