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Commentary

One more step towards a deeper understanding of the mechanisms of allergen immunotherapy

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Allergen immunotherapy (AIT) has a long history of evolution starting from its empirical introduction in the 1900s, when the pathophysiology of allergy was unknown, up to the high evidence of efficacy and safety provided by several meta-analyses [1]. Two routes of administration are available, subcutaneous and sublingual. For allergic rhinitis, a recent systematic review, promoted by the European Academy of Allergy and Clinical Immunology in the process of developing Guidelines for AIT, included 160 studies performed by subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), with no mention of superiority of a route over the other [2]. The progressive improvement in quality of products for AIT was driven by the increasing knowledge of mechanisms of action of this treatment, which is aimed at inducing tolerance to the administered allergen through modifications of the immunologic response. In fact, starting from the initial hypothesis on a role for IgG blocking antibodies, with time a complex network of immunological responses to AIT was revealed [3,4] In particular, regulatory T cells (Treg) and regulatory B (Breg) are of critical importance in governing key mechanisms of immunological changes associated to peripheral tolerance to allergens. Allergen-specific Treg, with a major role for FoxP3(+) CD4(+)CD25(+) Treg cells, inducible type 1 Treg (Tr1), and Breg cells, orchestrate a broad immunoregulatory activity, which includes the suppression of inflammatory cytokines elicited by dendritic cells, as well as of effector TH1, TH2, and TH17 cells and of allergen-specific IgE, with induction of IgG4 instead [4]. The modulation of T- and B-cell responses finally results in inhibiting the migration to tissues and the mediator release of the effector cells, such as eosinophils, basophils and mast cells.

The study by Zissler et al. in *EBioMedicine* followed-up a group of patients with grass pollen induced moderate-severe allergic rhinitis treated with SCIT for over three years, one group of grass pollen allergic patients not SCIT treated and one group of non-allergic subjects serving as controls. The immunotherapy product was an alum absorbed allergoid consisting of a mixture of six grass species chemically modified with formaldehyde [5]. A number of laboratory techniques were used to investigate the effects of AIT, as assessed in blood and tissues. Among them, the local T cell subsets of $CD3^+CD4^+IL17^+$ (Th17), $CD3^+CD4^+$ FoxP3$^+$IL17 (Tr17), $CD3^+CD4^+FoxP3^+$ (Tregs), and $CD3^+CD4^+$-FoxP3$^+$IL10$^+$ (IL10$^+$ Tregs) were evaluated by nasal flow cytometric analysis of nasal samples taken during the peak pollination season. Local B cell subsets, including $CD19^+$ (B cells) and $CD19^+IL10^+$ (IL10$^+$ B cells), were also studied. The immunological changes observed in AIT treated patients were characterized by an increase in IL-10$^+$B-cells and a decrease in Th1/Th17 and $CCR6^+$IL17+ FoxP3$^+$ T cells in the up-dosing phase, followed by a conversion phase with Th17 regaining in absence of Th2 cells, and a tolerance-mounting phase after 3 years of AIT characterized by generation of Tregs and allergen-specific Th17 and suppression of Th2 responses. Of interest, a relationship between the ratio of circulating Breg/IL-10+ B cells to Th17 after the up-dosing phase and the tolerance mounting phase was found, as suggested by the strong statistical correlation detected with the clinical symptoms after 3 years of AIT. The authors hypothesized that the clinical effects in the early phase of treatment are due to desensitization of the innate immune system in presence of a maintained allergen responsiveness of the specific immune system, while the late tolerance is based on the suppression of Th2 responses. Such hypothesis is supported by the correlation between IgG4 antibodies measured in the early phase and the clinical outcome after 8 months of grass pollen AIT, the Breg/Th17 ratio being suitable as an early predictor of efficacy.

The reliability of this mechanism increases when judged against previous studies, that have gradually increased the knowledge on humoral and cellular effects of AIT [6–8]. Indeed, the novel finding from the present study is that the Breg/IL-10+ B cells to Th17 ratio that was detected after the initial phase of AIT predicted the clinical efficacy after 3 years of treatment. Such indicator could have a significant impact on the management of allergic patients undergoing AIT, based on their early identification as responders or not with clear advantage in terms of personalized medicine [9]. However, further studies are needed to confirm the predictive value of the Breg/IL-10+ B cells to Th17 ratio that was found with a grass pollen allergoid, also in AIT with natural grass allergens as well as with other inhalant allergens and other forms of AIT such as SLIT.

Disclosure

The author declared no conflicts of interest.

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