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A Precised Data on Allergen Immunotherapy from the Past to the Future

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About the Study

Allergen Immunotherapy (AIT) is currently the only disease-modifying treatment for IgE-mediated Allergic Respiratory Diseases (ARDs; including Allergic Rhinitis (AR), Allergic Conjunctivitis (AC), and Atopic Asthma (AA)). Two routes of administration in AIT are Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SLIT) duration of 3 years. SCIT and SLIT are both effective treatments in reducing clinical symptoms elicited by aeroallegens, such grass pollens, trees and House Dust Mites (HDMs). Historically, the first empirical attempts of AIT were performed by Dr. Noon in 1911 with the aim of "vaccinating" against some hypothesized "aerogenic toxins." Despite the rationale was wrong, the subcutaneous administration of pollen extracts was effective for reducing hay fever symptoms. Thus, the use of SCIT gradually increased and was progressively extended to other allergens.

AIT confers its clinical effect through several mechanisms including innate immunity to modulate effector cells (mast cells and basophils), Dendritic Cells (DCs), and Innate Lymphoid Cells (ILCs) and adaptive immunity to deviate Th2 cell response toward a Th1 cell response, suppression or deletion of Th2 cells, induction of regulatory T and B cells, and induction of IgG-blocking antibodies, particularly IgG4 [1].

Recently, T follicular helper (Tfh) cells which mainly exist in germinal center of lymph nodes have a capacity to help B cells produce and maturate antigen-specific Igs. Furthermore, circulating Tfh (cTfh) cells also exist in peripheral blood and these cells are divided into three type cells, Tfh1 cells, Tfh2 cells and Tfh17 cells, by CXCR3 and CCR6 receptor expression on the cell surface corresponding to Th1, Th2 and Th17 cells. Especially, Tfh2 cells have the capacity to help B cells produce IgE [2]. For the first time, the expression profiles of Tfh cell subsets and Breg cells in Peripheral Blood Mononuclear Cells (PBMCs) from AR patients and AA with AR patients were analyzed. Interestingly, like the Th1/Th2 imbalance, we found a Tfh1/Tfh2 disproportion in both AR and AA with AR patients, showing predominance of Tfh2 cells. We also obtained evidence that the proportion of Breg ($CD19^+CD24^{hi}CD27^+$) cells was decreased during disease progression from AR to AA with AR. Moreover, in AA with AR cases, the ratio of cTfh/cBreg cells was significantly correlated with levels of Fractional exhaled Nitric Oxide (FeNO) and peripheral blood eosinophils, which are biomarkers of allergic airway inflammation [3].

The follicular regulatory T (Tfr) cells have been identified as a novel effector subset of regulatory T (Treg) cells with a specialized function in limiting Tfr cell mediated B-cell activation and antibody production in lymph nodes. Similar to Tfh cells, Tfr cells migrate into B cell follicles by upregulating CXCR5 and express Bcl-6. On the other hand, Tfr cells express the transcription factor Fork-head box P3 (Foxp3). Yao et al. showed that the percentages of circulating Tfr cells in blood positively correlated with the percentages of Tfr cells in tonsillar GCs in AR patients. They found that Tfr cells possessed the capacity to suppress Tfh cells-mediated antibody production from B cells and that patients after AIT showed increased numbers of Tfr cells with improved suppressive function [4].

Thus, AIT is effective and diseases modifying therapy and has been positioned as important therapy in Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Initiative for Asthma (GINA). However, there are a small number of patients showing an insufficient effect of AIT. To further examine the difference in the effectiveness of AIT in patients who received AIT, we compared Tfh subsets, Tfr, Treg and Breg cell, and HDM-specific Igs (IgE, IgG, IgG4 and IgA) of PBMC between responder and non-responder determined based on symptom and medication sores in AA with AR patients receiving House Dust Mite (HDM)-SLIT in two years. The percentage of cTfh2 cells and the ratio of cTfh2/cBreg cells and Der-p/f sIgEs greatly decreased in responders from 6 to 12 months. Also, the percentages of cTfr and cTreg cells showed significant negative correlations with the percentage of cTfh2 cells. The percentage of $IL\text{-}4^+$ cTfh cells were significantly decreased and the percentage of$IFN\text{-}\gamma^+$ cTfh cells were increased before treatment to 24 months. We performed multi plelogistic regression analysis based on these results, the ratios of cTfh2/cTfr cells and cTfh2/cBreg cells at the start of therapy were statistically effective biomarkers for predicting the response to HDM-SLIT in patients with AA with AR [5].

Severe asthma is often treated by usual medication in addition to biological agents, there is also progressing the novel AIT approach in combination with biological agents. Bożek and Hoshino reported better clinical efficacy in combination therapy than that of only AIT [6,

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7]. The mechanism leading to immune tolerance is caused by the unique administration with persistent and comparable high dose allergen. Although, there are not fully resolved its mechanism, administration method and clinical evidence in AIT, we are looking forward to better clinical effectiveness and expansion of AIT indications for allergic patients in the future.

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