

Biomarkers of airway inflammation and immunotherapy

Peanut allergy is the most common food-related trigger of anaphylactic reactions in the United States and some other countries.¹ Probiotic and Peanut Oral Immunotherapy (PPOIT) was shown to be effective at inducing desensitization and promoting sustained unresponsiveness (SU), however, there is an apparent lack of data on the long-term effectiveness and safety.² Hsiao and colleagues aimed to evaluate the mechanism by which PPOIT altered peanut-specific humoral immunity and how these mechanisms relate to SU induction.³⁻⁶ The study is a double-blinded placebo-controlled randomized trial that included 62 children with peanut allergy. Plasma levels of whole peanut and peanut components were measured, along with specific-IgE (sIgE) and specific-IgG4 (sIgG4) using ImmunoCAP, in addition to measuring salivary peanut-specific-IgA (sIgA) quantified

by ELISA. sIgE levels were significantly reduced post treatment, while sIgG4 levels, like sIgA levels, were significantly increased by end-of-treatment, but were lowered to placebo levels once treatment stopped. This study was the first to evaluate the long-term immunologic effects of PPOIT and resulted in two main novel findings. The first being that peanut and peanut component sIgG4 levels were directly proportional to the amount of peanut ingested post-treatment; increased peanut sIgG4 levels being reflective of an active allergen exposure. The second observation was that peanut and peanut component sIgG4 levels were significantly lower in subjects with persistent SU compared to those without. The study also provides evidence on the important role that allergen specific-IgE plays in the attainment and persistence of SU. The authors highlighted

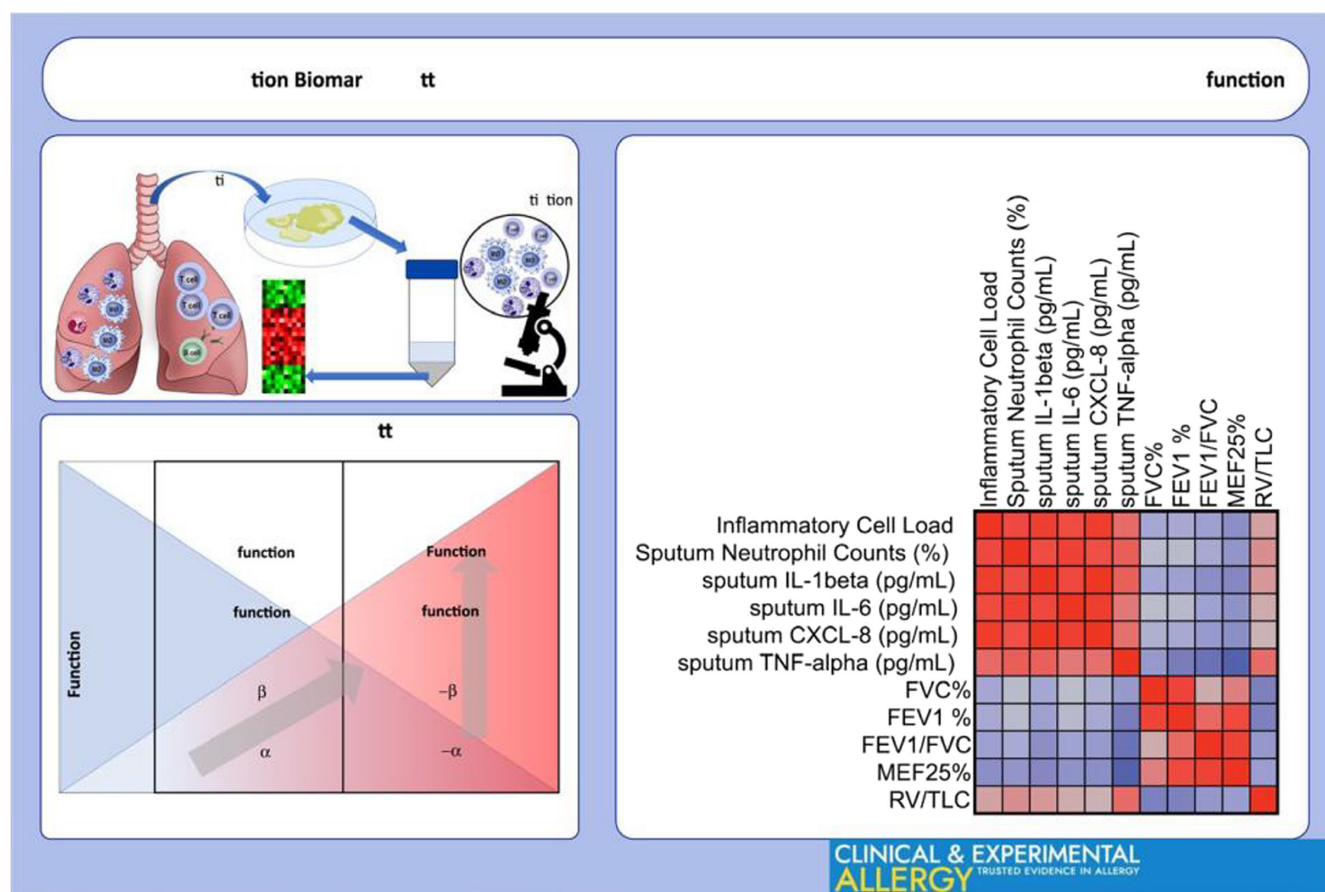


FIGURE 1 The minimally invasive technique of induced sputum can reveal the intrapulmonary cellular and humoral inflammatory pattern in patients with humoral immunodeficiency associated with lung function parameters. This is mirrored by gene regulation and secretion of proinflammatory secreted mediators IL-1 β , IL-6, CXCL-8 and TNF- α , which were induced in lower airway cells along with local neutrophil counts. In addition, bronchiectasis-related airway dysfunction was associated with higher levels of proinflammatory cell load and increased levels of proinflammatory-secreted mediators IL-1 β , IL-6, CXCL-8 and TNF- α .



FIGURE 2 Immunotherapy with three monthly injections with extracts containing each 1000 SQ-U of birch pollen and 1000 SQ-U of grass pollen, or either and placebo, in bilateral inguinal lymph nodes was safe and effective. One or two allergens rendered similar clinical response in patients with allergic rhinitis due to birch and grass pollen. Symptoms, medication and quality of life were all improved in all treatment groups. An increase in the proportion of activated Treg cells may explain the results

one are for future work that might increase the impact of this study, which is to evaluate antigen-specific IgE memory B cells. This would give invaluable insight into the mechanism of tolerance induction following PPOIT and provide a more comprehensive overview of the immunologic effects of PPOIT.

Severe humoral immunodeficiencies include common variable immunodeficiency (CVID) which is the most common form of symptomatic primary antibody deficiency syndrome. People with CVID suffer from recurrent bacterial respiratory tract infections and around half of people with CVID develop obstructive pulmonary disease. Unfortunately, immune deficiencies are generally underdiagnosed, leading to advanced lung damage prior to diagnosis and treatment in some cases. Zissler et al. aimed to assess the grade of chronic lower airway inflammation with small airway dysfunction using induced sputum samples.⁷ The study included 22 patients with different types of immune deficiency (14 CVID, 3 X-linked agammaglobulinaemia, 3 hyper-IgM syndrome, 1 hyper-IgE syndrome along with low IgG levels due to rituximab treatment and 1 severe combined immune deficiency following bone marrow transplant and persistent humoral defect), along with 21 healthy controls. Comparison of pro-inflammatory cytokine levels showed increased levels of secreted IL-1 β , IL-6, CXCL-8 and TNF- α in bronchiectasis-related

airway dysfunction mirroring the bronchial inflammation. The study identified TNF- α as a specific biomarker to detect the development of bronchiectasis in patients with immune deficiency (Figure 1). Additionally, induced sputum showed a significant increase in total cell count and severe neutrophilic inflammation in such patients when compared to healthy controls. The study also explored that the context-dependent cytokine pattern could be helpful in identifying different patient subgroups; however, further studies are needed to validate the results.

Allergic Rhinitis (AR) is a major cause of morbidity and affects more than 20% of the population in the United Kingdom and western countries.⁸ Intralymphatic immunotherapy (ILIT) was investigated as an alternative allergen immunotherapy method to overcome the limitations of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In order to evaluate the safety and efficacy of ILIT, Ahlbeck et al. conducted a study of ILIT using birch, grass pollen or both allergens in a 3-year double-blind randomized trial with 72 severe AR patients.⁹ The patients were randomized into receiving both birch and grass allergen extracts, birch and placebo, or grass and placebo. The rhinoconjunctivitis total symptom scores, medication score and rhinoconjunctivitis quality of life questionnaire were

assessed before treatment and post each birch and grass pollen season in the 3 subsequent years. Furthermore, circulating T helper subsets and allergen-induced cytokine and chemokine production were measured. Fewer symptoms and lower medication use were reported in all three groups. In addition, the quality of life during the birch and grass pollen season was improved each year after treatment regardless of using one or two allergens. The most common adverse event was mild local pain at the injection site, however, on 3 occasions, patients recorded severe pain from ILIT. It was observed that IgE levels to birch decreased, while IL-10 secretion increased in all three arms of the study. Regulatory T cell frequencies were increased in all three groups, 3 years following treatment. The study concluded that ILIT with one or two allergens in grass and birch pollen allergy patients was safe and effective (Figure 2). However, more studies are still needed to validate the optimal dose required for efficacy and minimal side effects.

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