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Allergy, IgG antibodies, inflammation and immunotherapy The impact of measuring IgG and IgG4 antibodies

Summary

Allergy is a systemic condition that leads into typical respiratory symptoms and several immunological effector cells are responsible for allergic inflammation. Understanding allergy as a systemic immunological condition should be the platform for the choice of diagnostic, treatment as well as monitoring options of the allergic patient. The allergic disease is driven by a subset of T helper lymphocytes (Th2), which are characterised by the production of cytokines like IL-4, IL-5. Allergic individuals have elevated allergen-specific IgE responsible for the early allergic reaction characterised by release of mediators from mast cells and basophils. Important mediator cells in the late phase inflammatory allergic response are activated Th2 cells, eosinophils and neutrophils. Non-atopics show mainly Th1 immunity characterised by production of interferon- γ , which also can inhibit the growth of Th2 cells.

Specific immunotherapy treatment interferes with the basic pathophysiological mechanisms of the allergic disease and suppresses the allergic response by several humoral and basic immunological mechanisms. Among these mechanisms an increase in the production of non-IgE (IgG) competitive antibodies, which in different ways reduces the pathological effects of IgE, is of importance. The different IgG related immunological effects relate to clinical outcome as reduction in symptoms and need for medication, and reduced inflammatory response. The size of induction of IgG following SIT is related to the dose used for treatment and to the clinical effects of SIT, and measurement of IgG during the course of SIT treatment could add information about the individual patient beneficial response to the treatment.

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Introduction

Symptoms of allergic rhinitis and asthma are caused by an exacerbation of continuously ongoing inflammation driven by natural immunological mechanisms. This reaction is causing an antigen mediated activation of mast cells, basophils and eosinophils.

Understanding the complexity of the allergic disease is crucial in order to offer the patient with allergy the optimal treatment which is interacting with the basic immunological condition as well as the symptoms. The optimum treatment of allergy increases the quality of life by reducing the primary symptoms and the need for medication, but the treatment should also influence the basic immunological allergic condition by changing the pathophysiological immunologic reactions.

The diagnostic tools available offer excellent possibilities for identification of the specific allergic trigger, treat the patient allergen specific and change the natural course of the systemic allergic diseases. Based on the diagnostic procedures, the treatment of inhalant allergy should together, with education of the patient, include avoidance of allergens, elimination treatment, treatment of symptoms and allergen specific immunotherapy as the treatment of the immunological cause of the allergic disease.

The immune system and allergic diseases

Many immunological effector cells are responsible for allergic inflammation and the allergic disease is driven by a subset of T helper lymphocytes (Th2), which are characterised by the production of cytokines like IL-4, IL-5. These cells and their cytokines are responsible for the effects on other cells involved in the allergic response. The most important effector cells in the allergic immunological response are eosinophils, mast cells and basophils. Th2 cells play an essential role in the promotion of allergen-specific IgE synthesis by B cells (Figure 1).

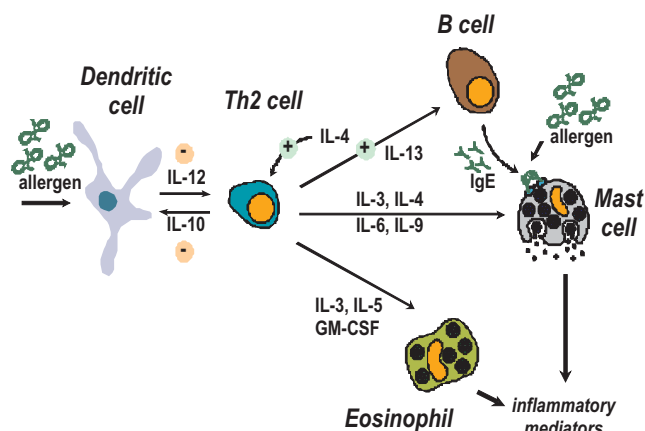


Figure 1. Overview of the typical Th2 driven allergic response.

Allergic individuals have elevated allergen-specific IgE to one or more common inhalant allergens and exposure to allergen triggers results in an immediate IgE-mediated mast-cell driven response (Type 1 hypersensitivity). Mast cells reside within tissue and increased numbers have been demonstrated in patients with allergic disease. Mast cells express the high-affinity IgE receptor, FcεRI, and have IgE bound to their membrane surface. Cross linking of adjacent, specific IgE molecules by allergen results in receptor aggregation which activates the mast cells. In turn, mast cell activation results in granule exocytose, releasing histamine, serine proteases and proteoglycans. These events occur within seconds to minutes of allergen exposure; giving rise to immediate allergic symptoms that peak 15-30 minutes following exposure. Activated mast cells also synthesize lipid mediators that include prostaglandins and leukotrienes. The release of pro-inflammatory mediators and cytokines by mast cells increases vascular permeability and promotes the subsequent recruitment of other effector cells. Like mast cells, basophils have histamine-containing granules and express the high-affinity IgE receptor, FcεRI.

The allergic late-phase which is characterised by an inflammatory response usually occurs up to 24 h after allergen exposure. The late allergic responses are accompanied by changes in blood eosinophils that precede and predict the typical clinical symptoms of inflammation and associated hyperresponsiveness. The most important mediator cells in the late phase allergic response are activated Th2 cells, eosinophils, neutrophils and basophils. These cells are represented systemically and reside within the blood and can infiltrate local tissue upon allergen exposure (1).

Allergy – a systemic condition

Allergy is a systemic disease often resulting in a local response following allergen exposure. Rhinitis, asthma and BHR are closely related and a systemic pathway, involving bloodstream and bone marrow, contributes to the cross-talk between upper and lower airways (2).

A close relation between allergic rhinitis and allergic asthma exists (3-4) and the co-morbidity of upper and lower airway diseases is carefully described (5). A European survey covering 7000 allergy patients showed that 80 % of the patients with typical asthma symptoms also reported nasal symptoms, and 40% of rhinitis patients reported coexisting asthma (6). Allergic rhinitis is a major risk factor for later development of asthma (4, 7) and more than 20% of all rhinitis patients develop asthma later on in life (8). Up to 50% of the rhinitis patients have increased bronchial hyperresponsiveness during and as well as outside the pollen season (9) and an ongoing subclinical level of inflammation (10). Allergic sensitivities usually increase with age from childhood to adulthood and monosensitised children are likely to become polysensitised with time (11). Being sensitised to one allergen source also increases the risk for appearance of more allergic sensitivities over time (12). The understanding of allergy as a systemic immunological condition should be the platform for the choice of diagnostic, treatment as well as monitoring options of the allergic patient (13).

Natural development of the immune system and development of allergy

Early life events appear to have a critical influence on maturation of and the natural development of the acquired immune response.

The understanding of the T-cell immunology underlying the allergic sensitisation is being investigated. Allergy in adults is associated with the long-term expression of allergen-specific immunity, characterised by production of Th2 cytokines such as Interleukin-4 and Interleukin-5, responsible for promoting IgE production and eosinophilia respectively. By contrast, non-atopic individuals show mainly Th1 immunity characterised by production of interferon-γ, which also can inhibit the growth of Th2 cells. Usually a rapid suppression of Th2 responses during the first year of life is seen in normal non-atopic children, while a long term consolidation of the Th2 response is characteristic for atopics, associated with reduced interferon-γ production. The continuation of allergen-specific Th2 responses during infancy is a defining feature of the inductive phase of atopic disease, and is associated with decreased capacity for production of the Th1 cytokine interferon-γ by atopic newborns. Many groups have observed that newborns at high risk of allergy have a greater relative deficiency of interferon-γ responses than infants at low risk of allergy (14-15).

Specific immunotherapy

When the allergen responsible for the unwanted reaction of the immune system is identified, it is possible to manipulate the response by use of the antigen (allergen) directly. The way the antigen is presented to the immune system affects the nature of the response and the induction of one type of response to an antigen can inhibit a pathogenic response to the same antigen. This principle is being used in the treatment of IgE mediated allergies, the symptoms of which are caused

by exposure to very low doses of antigen. Repeated treatment of allergic individuals with high doses of allergen seems to divert the allergic response to one dominated by T-cells that favour the production of IgG and IgA antibodies. These antibodies are thought to desensitise the patients by competing with the IgE mediated allergic response.

Specific immunotherapy (SIT) is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease (16). Intensive research has led to important knowledge about clinical efficacy, safety, influence on specific as well as non-specific objective parameters, basic immunological mechanisms and inflammation which have then again resulted in recommended dosing of allergens (17).

The clinical as well as the immunological response is directly related to the dose of allergen used for maintenance immunotherapy treatment as well as the time course of treatment. Different applications as subcutaneous respective sublingual application may influence the immunological activity of the allergen and induction of the relevant immunological mediator cells. Several studies have documented the dose-response on clinical as well as immunological parameters during immunotherapy treatment (18-21).

The documented clinical effect of immunotherapy is divided into four levels:

- **Early effect** (appears 8-12 weeks after initiation of treatment)
 - Reduction of symptoms/need for medication
- **Progressive effect** (appears during continuation of treatment up to 3 years)
 - Further reduction in symptoms/need for medication
 - Reduction in hyperresponsiveness/late phase response
- **Persistent effect** (appears as continuous effect after termination of treatment)
 - Long-term reduced symptoms/need for medication
 - Long-term reduced hyperresponsiveness/late phase response
- **Preventive effect** (secondary prevention of asthma and new allergies)
 - Prevention of new sensitivities and exacerbation of disease (rhinitis into asthma)

Immunological mechanisms of immunotherapy

The immunological response to immunotherapy is related to a basic change in the immunological inflammatory cascade of immunological active cells and mediators. SIT is acting by influencing basic immunological mechanisms (22) thus resulting in the suppression of the seasonal increase in eosinophilia (23), late-phase reactivity is reduced (24-25) and a shift from Th2 to Th1 like response is initiated and maintained (26-29).

Role of blocking antibodies

One mechanism by which immunotherapy suppresses the allergic response is by an increase in the production of IgG antibodies, primarily of the IgG4 subtype and assays for detection of specific IgG/IgG4 antibodies can be used to follow

changes in antibody production during immunotherapy (ImmunoCAP)(30-31). Because the production of IgE against harmless antigens is the hallmark of allergic responses, the production of antigen specific IgG antibodies, can antagonize and block the allergic inflammatory cascade resulting from antigen recognition by IgE. Therefore, the shift in balance between IgE and IgG4 is a phenomenon crucial for successful allergen specific immunotherapy. In successful immunotherapy despite optimal clinical effect it has been shown that the specific IgE response over time does not change neither in peripheral blood nor estimated as skin test reactivity (24, 32-33), while a specific dose related IgG response primarily characterised by specific IgG4 is initiated and persisting (34-36). Although the serum level of IgG always seems to increase during successful immunotherapy and some studies have shown a direct relation to clinical outcome (37), an estimate of direct correlation to clinical efficacy is resulting in conflicting results. One important reason is that the patient to patient variability in total IgG/IgG4 should be integrated in the calculations. On the other hand, for individual patients an increase in specific IgG/IgG4 compared to baseline is usually seen. Another reason for variability is that IgG induced towards irrelevant protein molecules from the allergen source could reduce the effect of blocking antibody induction. Estimation of the induction of non-IgE competitive specific antibodies (which primarily would be represented by specific IgG/IgG4) has been made to confirm that the production of competitive antibodies is dependent on the dose of allergen used for immunotherapy (36,38) and always seems to go hand in hand with the clinical benefits.

Mechanisms of blocking antibodies

Induction of specific IgG has the capacity to influence the allergic response in different ways, and is related to immunological effector mechanisms, also responsible for the reduced late phase hyperreactivity and ongoing allergic inflammation. These immunological responses to allergen specific immunotherapy are illustrated in figure 2. The figure illustrates the clinical benefits and induction of IgG antibodies initiated by immunotherapy (middle). On the right side is illustrated the different ways that induced specific IgG/IgG4 antibodies can influence the immunological cascade which otherwise would lead into allergic symptoms.

Inhibition of mediator release

The inhibition of mediator release could be caused by a direct inhibition of the allergen-IgE interaction or through co-aggregation of the inhibitory FcγRIIB and FcγRI as demonstrated in an artificial system (39) and it has also been demonstrated that SIT-induced IgG inhibited histamine release from basophils (40).

Blocking antibody

Another mechanism of competing specific IgG antibodies is by a “dilution” of the antigen exposure to specific IgE antibodies by binding to epitopes on the surface of the allergen, and thereby directly reduce the antigen presenting capacity by the relevant cell types (41-42).

Facilitated Antigen Presentation (FAP)

In the allergic patient high local levels of allergen-specific IgE result in the formation of allergen-IgE complexes at mucosal surfaces. The process whereby these allergen-IgE complexes are efficiently captured on the antigen-presenting cell and also on the surface of B-cells, by binding to IgE receptors, is called IgE-facilitated antigen presentation. IgE-facilitated antigen presentation results in the activation and subsequent proliferation of allergen-specific T cells at extremely low concentrations of allergen and activates Th2 cells which will then produce important cytokines (IL-4, IL-13) inducing further IgE synthesis (40). Immunotherapy-induced specific IgG antibodies can also affect and inhibit IgE-facilitated antigen presentation and activation of Th2 cells and thereby significantly reduce the allergic response (1, 43-44).

These different IgG related immunological effects acting as a competitive response to that of specific IgE, results in clinical effects as reduction in symptoms and a need for medication, and reduced inflammatory response to allergen presentation.

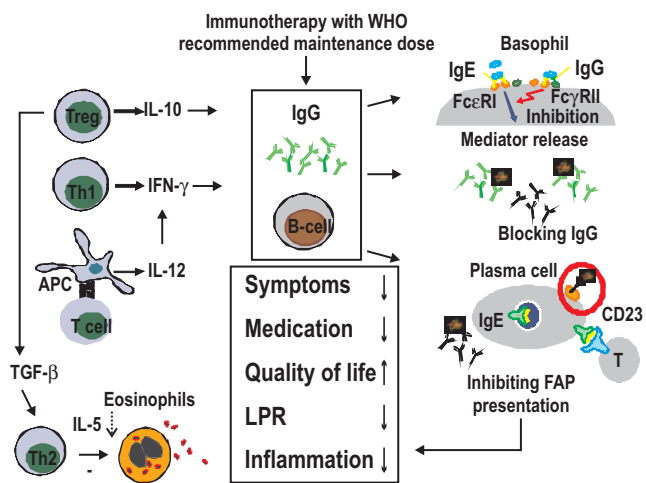


Figure 2. The immunological response to allergen specific immunotherapy.

Basic immunological changes

The left side of figure 2 summarises the basic immunological changes during immunotherapy.

Studies have shown that symptomatic improvement correlates with reductions in eosinophils and IL-5 expression in the nasal mucosa (45) during the pollen season as well as increases in IFN- γ production (46). Immunotherapy induces an IL-12 response shown to inversely relate to IL-4 production and to promote a Th1 response estimated as Interferon- γ which promotes B-cells into IgG production (26). Several studies have shown that immunotherapy induces a new regulatory T-cell response characterised by induction of IL-10 (21, 37) that precedes the inhibitory IgG4 antibody activity (47). TGF- β is another regulatory T-cell mediator induced by immunotherapy(48) which is responsible for a downregulation of the Th2 response – reducing IL-5 production (29) and prevention of allergen exposure induced eosinophilia and inflammation (45). The importance of T regulatory cells in allergy and relation to immunotherapy has been carefully reviewed (49). The immunological mechanisms described above illustrate the close connection between the basic immunological response

to immunotherapy and the humoral response, characterised by induction of competitive specific antibodies.

These basic immunological changes depend not only on the dose of antigen that is used for immunotherapy but also the time course of the treatment. In order to achieve a basic shift in the Th2 to Th1 and regulatory T-cell response and initiate the basic inflammatory long term response, a certain treatment period is needed. It has been shown that despite good clinical tolerance to allergen after 3 months of immunotherapy treatment in grass pollen allergic patients, the basic change in the immune response was seen only after 12 months of treatment (27). In HDM allergic asthmatics it was found that challenge to HDM after 6 months of SIT was significantly better tolerated although response to challenge with methacholine test was improved only after 12-18 months of treatment (50). As mentioned above, the clinical benefits and the induction of specific IgG response are also dependent on the dose of allergen used for immunotherapy (35-36).

Non-IgE competitive antibodies and relation to dose used for SIT and the clinical outcome

One study published at the AAAAI meeting (51) illustrates the relation between induction of non-IgE competitive IgG antibodies and the clinical response.

This study was a double-blind, randomized, placebo controlled study of 410 subjects randomized to a high dose immunotherapy (100,000 SQ-U, 20 μ g of major allergen Phl p 5), a low dose immunotherapy (10,000 SQ-U, 2 μ g of major allergen Phl p 5), and placebo. Standardized depot preparations of grass pollen extract (Alutard SQ, ALK-Abello, Denmark) were administered by subcutaneous injection. Mean symptom and medication scores were 29% and 32% lower, respectively, in the 100,000-SQ-U group compared to placebo (both $P < 0.001$). The 10,000-SQ-U group had 22% less symptoms than the placebo group ($P < 0.01$), and medication scores reduced by 16% ($P = 0.16$).

A clear dose dependent induction of competitive antibodies was found (Figure 3). The treatment related induction of competitive specific non-IgE antibody was estimated by use of an experimental inhibition immuno-assay. A two-step assay procedure measures the grass specific non-IgE antibodies which mainly consist of specific IgG/IgG4 and some IgA antibodies.

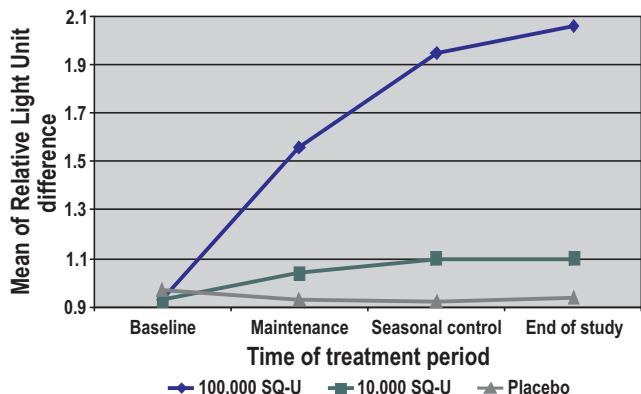


Figure 3. Dose response of competitive specific antibody production following immunotherapy.

Based on the level of competitive specific non-IgE antibody (IgG/IgA) at the time of the first maintenance injection, subjects were classified into 3 equal size groups. The mean symptom score values for each group were calculated. The difference between means was tested and a statistical significant difference in mean symptom score in favour of a high IgG response in clinical successful immunotherapy was found.

It was shown that 98% of the subjects with the highest induction of competitive specific non-IgE antibody response belonged to the 100,000 SQ group, and 85% of the placebo group belonged to the lowest induction group (Figure 4).

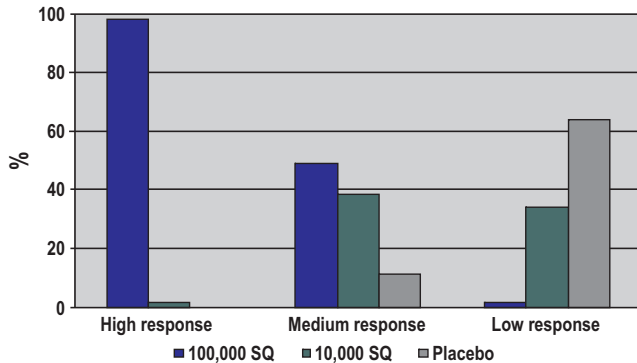


Figure 4. Percentage of competitive antibody responders related to dose of immunotherapy.

Clinical efficacy in this study was shown to be related to the dose used for allergen specific immunotherapy and the study has shown a relationship between induction of competitive allergen specific non-IgE antibodies, mainly consisting of IgG/IgG4 and clinical efficacy and dosage used for allergen specific injection immunotherapy.

Salient points:

- Induction of specific IgE competitive antibodies (IgG/IgG4) is related to the clinical effect of immunotherapy
- Induction of specific IgG/IgG4 antibodies is an integrated parameter of the mechanism of immunotherapy
- In effective immunotherapy specific IgG/IgG4 is induced
- The level of induction of competitive antibodies is individual and should be monitored on single patient basis.
- Due to the biological variability in a patient's sensitivity, biological exposure and individual organ hyperreactivity, a statistical correlation between clinical effect and IgG/IgG4 induction should focus on qualitative methods.

Conclusion

Allergy is a systemic immunological condition and immunotherapy treatment interferes with the basic pathophysiological mechanisms of the allergic disease. The treatment associated different IgG related immunological effects acting as competitive response to that of specific IgE, results in clinical effects. In effective immunotherapy specific IgG/IgG4 is induced and the size of induction of IgG following SIT is related to the dose used for treatment and to the clinical effects of SIT. Measurement of IgG/IgG4 during the course of SIT treatment could add information about the individual patient beneficial response to the treatment and if a patient should not respond with an induction of competitive antibodies during immunotherapy a careful re-evaluation of the treatment options could be useful.

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