



Dossier : Allergy

Mechanisms of immunotherapy in allergic rhinitis

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Abstract

Allergic rhinitis is a common condition, but many people still experience suboptimal control of symptoms despite measures such as allergen avoidance, intra-nasal steroids and antihistamines. Specific immunotherapy (SIT) has been used for many years, but though many studies show clinical efficacy, its mechanism of action is still not clearly understood. Earlier studies showed changes in antibodies and it may be that SIT works through mechanisms that alter the ratio of 'protective' IgG4 to 'pro-allergenic' IgE. Other studies have shown a reduction in eosinophil migration to nasal mucosa as well as a reduction in inflammatory mediator release including basophil histamine release. More recent studies have proposed that SIT works through inhibition of T-helper 2 lymphocytes (Th2) which preferentially produce cytokines that promote allergic responses. SIT may cause a deviation from Th2 to Th1 (T-helper 1 lymphocytes) or may induce T-regulatory cells (T-regs) which inhibit Th2 responses directly or through inhibitory cytokines.

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1. Introduction

Allergic rhinitis is the most common allergic condition affecting over nine million people in the UK and the prevalence is increasing. It can affect people of all ages, sexes, social and ethnic groups and has an impact on their quality of life as well as healthcare utilisation. In a survey conducted by Allergy UK in 2005 [1], 49% of those who were surveyed reported that their rhinitic symptoms affect their school/work moderately to severely. Eighty percent of those also said that it affects how they spend their social time with 76% saying that it limits their choice of outdoor activities. Some patients had spent more than three hundred pounds in a year trying to make their home allergy free [1]. Therefore, there is a need to find more effective therapies for allergic rhinitis. Specific allergen immunotherapy (SIT) has been shown to be effective in patients who have

failed to respond to conventional therapies in allergic rhinitis. SIT has a long lasting benefit and has been shown to be cost-effective as well [2,3]. This article discusses the possible mechanism(s) of SIT based on the published literature evidence.

2. Mechanism of allergy

An allergen can induce both an immediate type I and a delayed type IV hypersensitivity reaction [4–6]. The immediate allergic response results in IgE dependent mast cell and blood basophil activation, preformed mediator release e.g. histamine and newly generated synthesis of mediators from the arachidonic acid pathway e.g. leukotrienes and prostaglandins. This can lead to acute clinical symptoms such as wheeze, urticaria, sneezing, rhinitis and conjunctivitis (Fig. 1).

Type IV hypersensitivity is a delayed phenomenon and can occur 6 to 24 h later. Allergen is taken up and processed by antigen presenting cells (APC) e.g. macrophages, dendritic cells and Langerhans cells which present the antigen to T lymphocytes. This can lead to production of Th2 CD4+ type T

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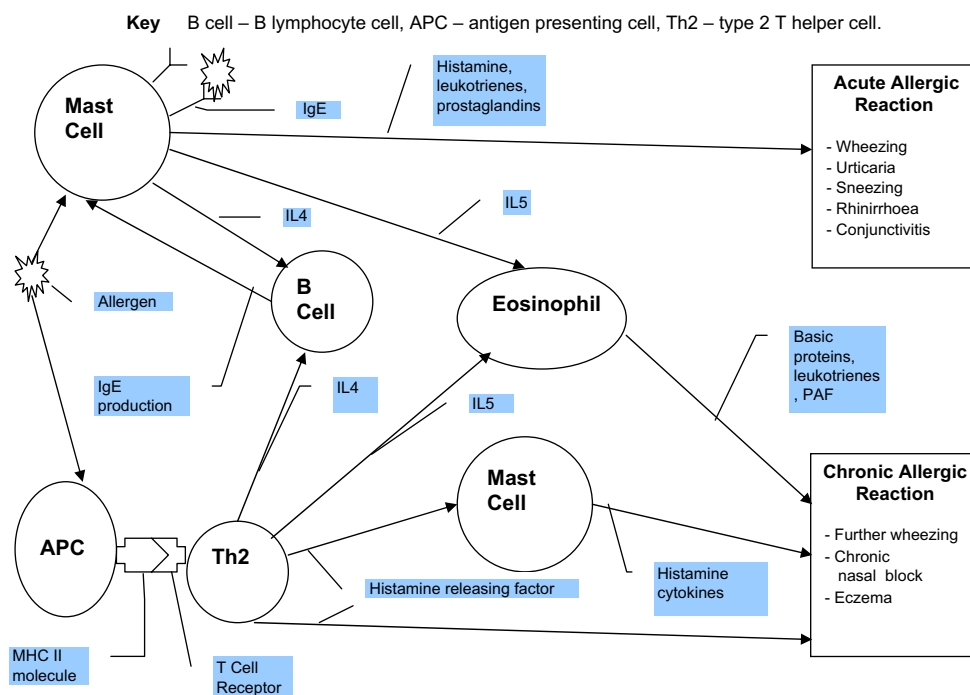


Fig. 1. Mechanism of early and chronic allergic symptoms.

cells which express interleukin (IL)-4 and IL-5 which in turn have a direct effect on IgE producing B lymphocytes and a variety of inflammatory cells e.g. mast cells, basophils and eosinophils, thus causing a delayed inflammatory response and chronic symptoms in cases of persistent exposure (Fig. 1).

3. Management

Currently, patients with allergic rhinitis are treated symptomatically with anti-histamines, topical steroids and leukotriene receptor antagonists together with measures to avoid allergens [2,3]. Some patients may experience side effects while on going prescriptions and allergy avoidance can be costly as well as impractical. Symptom control may still be suboptimal with less than 40% of patients with seasonal allergic rhinitis reporting good symptom control in UK general practice [7].

Specific allergen immunotherapy involves weekly administration of gradually increasing subcutaneous, sublingual or intranasal doses of allergen to which the patient is sensitive to in order to improve symptoms associated with subsequent exposure. It is the only therapy to date that can affect the natural course of allergic disease and has been shown to be effective in the treatment of allergic rhinitis/conjunctivitis, allergic reactions to stinging insects and allergic asthma in many double blind randomized studies [2,3,7]. It may also prevent the development of asthma in patients with allergic rhinitis as well as further allergen sensitisations [2,3,8]. Currently it is licensed in the UK for allergic rhinitis and allergic reactions to insect venom.

4. Mechanism of immunotherapy

Although it is generally accepted that SIT reduces symptoms of allergic reactions, the precise molecular mechanism behind this improvement is not clearly understood. Various studies have observed changes in antibodies, cellular events and cytokines before and after treatment which may explain how SIT works.

4.1. Changes in antibodies

Earlier studies by Cooke et al. [9] and Loveless [10] showed that patients with allergy receiving SIT had a rise in IgG antibody levels. A study by Lichtenstein et al. [11] demonstrated that an immunotherapeutic dose that fails to induce an increase in IgG antibody is unlikely to result in a significant improvement in symptoms. IgG antibody titres however do not necessarily predict clinical success in individual patients and a causal relationship has not been proven. In a number of studies, subsets of patients with good clinical relief had no significant IgG antibody production and some patients with increased IgG antibody titres showed no clinical response [12].

Peng et al. showed that IgG1 is the dominant immunoglobulin response during the early course of immunotherapy and IgG4 begins to appear in significant quantities after prolonged immunization [13]. It has been suggested that IgG4 antibodies are associated with protection by binding to the allergen, thereby preventing its interaction with allergen specific IgE attached to effector cells or by forming an IgG4–allergen–IgE complex which inhibits IgE triggering. However some studies have failed to confirm these findings and the increase in

allergen specific IgG4 levels has not been shown to be closely linked to the clinical response [14]. On the other hand, a more recent study by Nanda et al. demonstrated the early predictive value of SIT-induced specific IgG4 increase in the case of SIT for cat allergy rhinitis [15]. Indeed, in this study a statistically significant rise of cat allergen-specific IgG4 levels (but not the increase in total IgG) measured after 5 weeks of SIT was correlated with the decrease of clinical symptoms scores measured after one year of SIT.

Lichtenstein et al. demonstrated that there was a fall in the usual seasonal rise in IgE antibody which has been shown to be inversely correlated with the rise in IgG [16]. There is also, after an initial rise, a slow decline in the level of specific IgE in patients with allergy during the course of SIT [16]. Another reported effect of SIT is reduced levels of the soluble low affinity receptor for IgE, CD23, known to be of importance in the regulation of IgE antibody production [17,18].

Platts-Mills et al. have shown that patients with ragweed and grass allergy had a seasonal increase in specific IgA and IgG antibodies in nasal secretions. SIT with ragweed in these patients is associated with a further increase in IgG and IgA antibodies. However, no relationship has been demonstrated between these findings and clinical improvement [19].

A provisional explanation for these apparently contradictory data regarding the role and predictive value of allergen-specific IgG4 in SIT can be proposed when considering the findings of Akdis et al. [20] and those by Michils et al. [21] for bee venom immunotherapy. In the study by Akdis et al. it was shown that successful SIT initially increases both the 'pro-allergenic' IgE and the 'protective' IgG4, but the overall bee venom-specific IgE/IgG4 ratio is decreased as a consequence of SIT. Michils et al. found that ultra-rush SIT induces early alterations of allergen binding by specific IgG antibodies as early as 12 and 24 h after its initiation [21]. As

a consequence, even though the overall levels of allergen-specific IgG may not be significantly modified, the set of bee venom allergen epitopes that are recognized by IgG is changed. Thus it appears that SIT success may be better correlated with changes in IgG4/IgE ratios and the more subtle alterations in antibody binding specificities rather than with overall IgG titres that can be measured in the serum.

4.2. Changes in effector cells

The late phase reaction is dependent on the recruitment of various cells including eosinophils, neutrophils and basophils into the inflammatory site where they release inflammatory mediators that perpetuate the inflammatory response. Studies have demonstrated that after exposure to allergen, eosinophil migration into nasal secretions is significant by 2 to 4 h and continues to increase up to 8–10 h. A similar though not significant increase is seen with basophils. SIT has been shown to reduce allergen induced eosinophil migration and blunt the typical seasonal influx of eosinophils into the nasal mucosa [22]. Majchel et al. showed that SIT prevented the increased responsiveness of the nasal mucosa to histamine that is usually seen in allergic patients challenged during the ragweed-pollen season [23].

Studies have shown that in most allergic patients undergoing SIT, there was a decrease in basophil histamine release [24,25]. This was associated with a marked reduction in clinical symptoms. However, there were some exceptions with some patients experiencing improvement in symptoms but with high basophil reactivity [24,25]. A study by Creticos et al. showed that after nasal provocation with ragweed in ragweed allergic patients, significantly fewer patients in the immunized group experienced clinical symptoms or demonstrated inflammatory mediator release in their nasal secretions

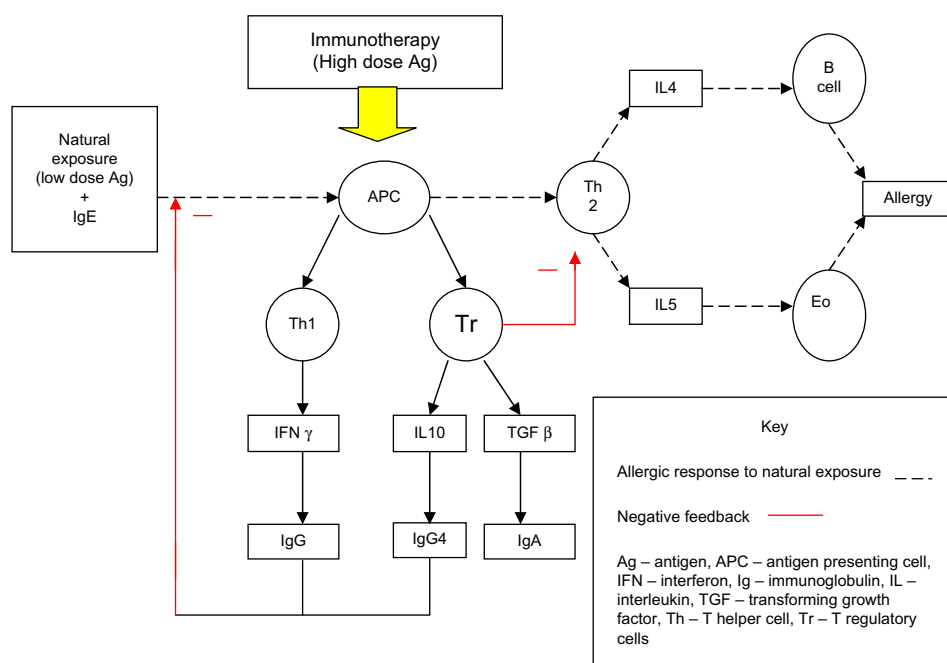


Fig. 2. Schematic diagram of mechanism of immunotherapy by altering T cells and cytokine profile.

Table 1
Major immunological changes during immunotherapy

↑ in IgG—initially IgG1 then IgG4
Initial ↑ in IgE followed by slow decline
Blunting of usual ↑ of seasonal IgE
↑ IgG and IgA in nasal secretions
↓ effector cells and mediator release
↓ of Th2:Th1 activity
Induction of T regulatory cells

including histamine, TAME-esterase, prostaglandins and leukotrienes [26].

4.3. T-cell changes

More recent studies have focused on the effects of SIT on allergen specific T-cell responses and cytokine production [2] (Fig. 2). Thus it has been proposed that SIT acts by altering the 'balance' between the allergic T-cell responses (generated by the T-helper type 2 (Th2) lymphocyte subset) and the subsets that inhibit Th2 (i.e. Th1 and/or 'regulatory' T cells). Th2 cells are responsible for allergic immune responses because they preferentially produce the cytokines IL-4 (that promotes IgE production and inhibits Th1), IL-5 (a growth and differentiation factor for eosinophils) and IL-13 (involved amongst other pro-allergenic processes in the bronchial tissue remodulation that occurs in asthma).

The mechanisms involved in Th2 inhibition by other T-lymphocyte subsets are as yet unclear. Th1 cells produce interferon- γ and IL-2, which inhibit Th2 lymphocytes in experimental models such as in vitro cell cultures. These findings led to the development of SIT adjuvants that boost Th1 responses (such as monophosphoryl lipid A or nucleotide immuno-stimulatory sequences derived from bacteria) [27]. However, Th1 responses are responsible for inflammatory processes (such as diabetes mellitus and other autoimmune diseases) so it is unclear whether a simple immune deviation of allergic responses from Th2 to Th1 underlies SIT and whether such a change would be beneficial.

A more likely immune mechanism for SIT is the induction of regulatory T cells (T-regs) (Fig. 2). T-regs are defined as a subset of CD4⁺ CD25⁺ T cells that express the Fox p3 transcription factor and are able to suppress both Th1 autoimmune [28] and Th2 allergic responses [29]. It is now clear that there are several T-reg subsets involved in the limitation and inhibition of potentially auto-aggressive immune responses and that these subsets may use different suppressive mechanisms [30]. Thus, T-regs may act directly upon Th2 cells to suppress allergen specific Th2 responses. Alternatively they may act indirectly by producing the inhibitory cytokines IL10 and transforming growth factor (TGF- β). IL-10 promotes production of IgG4 and TGF- β promotes IgA production. Finally, it has also been proposed that T-regs may inhibit allergic responses indirectly by acting upon the dendritic cells that present the allergens to Th2 cells [24].

In conclusion, although there are many clinical trials which show SIT to be an effective treatment in the management of

allergy including allergic rhinitis, its mechanism of action is not clear. Studies so far have helped us to appreciate that SIT probably modulates and affects many different immunological and non-immunological processes (Table 1) and that clinical improvement is a consequence of different mechanisms over time which may vary in different groups or individuals. Further research into the mechanism of action may lead not only to more efficacious therapies with minimal side effects, but also to a better understanding of airways disease in general.

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