

IgE-Mediated Allergen Presentation and Blocking Antibodies: Regulation of T-Cell Activation in Allergy

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Key Words

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Abstract

It is well established that both the production of IgE by B lymphocytes and the maturation and recruitment of eosinophils in late-phase reactions are dependent on the activation of allergen-specific type-2 T-helper cells. What is less well known is the fact that efficient activation of allergen-specific T cells upon low-dose exposure to allergens is critically dependent on IgE-mediated or -facilitated allergen presentation. In fact, changes in the level of IgE-mediated allergen presentation may account for many of the immunological effects described for specific immunotherapy or anti-IgE treatment. This review aims to summarize the current knowledge, and will discuss the clinical relevance of blocking IgG antibodies induced by specific immunotherapy and anti-IgE monoclonal antibodies that both interfere with IgE-mediated allergen presentation.

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Introduction

Atopic diseases, such as allergic rhinitis, asthma, and atopic eczema, are on the increase, and are currently among the most common causes of chronic diseases in the western world. Atopic individuals have a hereditary predisposition to produce IgE antibodies against common environmental allergens and are more susceptible to allergic diseases [1, 2]. Allergic patients respond strongly to innocuous proteins that should be ignored, as they pose no threat to the organism. Many of the immunological mechanisms that underlie atopic allergies have been elucidated in the last decade and have been reviewed extensively. Atopic disease is further characterized by the activation of allergen-specific T-helper type-2 cells (Th2). It is apparent that CD4+ allergen-specific T cells biased towards the production of Th2 cytokines play a crucial role in the induction of IgE and eosinophilia, factors involved in the immediate hypersensitivity reaction and late-phase responses, respectively. These Th2-like cells produce IL-4 and IL-13, which induce B lymphocytes to switch to the production of IgE, and IL-5, which induces the differentiation and maturation of eosinophilic granulocytes. Moreover, Th2 cell production of IL-9 may potentiate IgE responses and enhance airway inflammation in general [3]. Allergen-specific Th2 cells have been identified in the peripheral blood [4, 5], as well as in affected tissues of allergic patients [4, 6], further underlining the role that allergen-specific Th2 cells play in atopic allergies.

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Allergic Reaction

The classical type I IgE-mediated allergic response is composed of an immediate- and a late-phase response. Upon cross-linking of IgE bound to the high-affinity IgE receptor on mast cells and basophils by allergen, these cells release inflammatory mediators such as histamine, leukotrienes, and prostaglandins, resulting in an immediate hypersensitivity reaction within 5–30 min that will last for ~1 h. Subsequently, most patients develop a late-phase reaction that can manifest as nasal or airway obstruction. Generally, late-phase responses are maximal 6–12 h following the immediate reaction and resolve within 24 h. This late-phase reaction is characterized by the recruitment and persistence of eosinophils, basophils and activated CD4⁺ T cells at the sites of allergen exposure [1].

The immunopathologic changes in the mucosal tissues of subjects chronically exposed to inhalant allergens resemble those seen during the late response. The late-phase reaction and the allergic inflammation seen in chronic disease are dependent on the activation of tissue-residing allergen-specific T cells, followed by an influx of activated eosinophils and CD4⁺ T cells that can induce local tissue damage [1]. This leukocyte trafficking critically depends on the chemoattractant activity of chemokines and the presence of adhesion molecules on the vascular endothelium [1]. Late-phase allergic responses have been shown to be dependent on the presence and activation of CD4⁺ T lymphocytes [7–11], eosinophils [10, 12], and factors involved in eosinophil differentiation such as IL-5 [13–15]. A few recent findings have further underlined the important role of CD4⁺ T lymphocytes in allergic inflammation. Infusion of anti-IL-5 in humans strongly diminished eosinophils in blood as well as bronchoalveolar lavage of allergic asthma patients. However, airway inflammation was not affected, indicating that T cells are at least modulating the major part of the changes noted within the local tissue in allergic inflammation [16]. In another study setup, the group of Larche demonstrated that short overlapping peptides derived from the cat allergen Fel d 1, that did not cross-link IgE, elicited isolated late-phase reactions in the lung. In this study, the peptides were administered intradermally, but at the injection sites no early or late reactions were observed [17]. The latter study emphasizes that T lymphocytes, even without preceding mast cell activation, can induce allergic inflammation.

Relevance of IgE-Mediated Allergen Presentation in Th2 Activation

One question that has not been addressed widely in the literature is the question how such efficient Th2 responses can occur in vivo. Exposure to aeroallergens is generally very low, with estimated inhalation levels in the range of a few micrograms per major allergen/year. In vitro experiments employ allergen doses of around 5 µg/ml to detect the activation of allergen-specific T cells. Whereas ordinary antigen uptake by antigen-presenting cells (APCs) via endocytosis or micropinocytosis requires relatively high antigen concentration, this suggests that a mechanism of specific, receptor-mediated allergen uptake is involved in the presentation of allergens to T cells in vivo. In allergy, IgE receptors or cell surface IgE would be ideal candidates for this role, using IgE to capture and subsequently focus the allergen-IgE complex to APC.

Both IgE Fc receptors, the low-affinity IgE receptor (CD23) and the high-affinity IgE receptor (FcεRI), are expressed on cells with antigen-presenting properties. CD23 can be expressed on B cells and macrophages [18, 19], and FcεRI on monocytes and dendritic cells [20, 21] of allergic patients.

CD23

CD23, which is expressed as both the CD23 a and b forms on B cells, can be internalized and transports IgE into the antigen-processing pathway, followed by presentation on MHC class II molecules. Notably, on macrophages CD23 is solely expressed as the CD23b form which does not internalize efficiently [22], suggesting that B cells are the primary APCs in CD23-dependent allergen presentation.

In 1989, a first paper appeared that showed that complexes of a 2,4,6-trinitrophenyl-specific IgE monoclonal antibody (mAb) could bind to CD23 on B cells, be internalized and activate 2,4,6-trinitrophenyl-specific T cells [23]. Similar experiments were performed by Pirron et al. [24] and Santamaria et al. [25], using an IgE-anti-(4-hydroxy-3-iodo-5-nitrophenyl)acetyl mAb bound to (4-hydroxy-3-iodo-5-nitrophenyl)acetyl-tetanus toxoid or (4-hydroxy-3-iodo-5-nitrophenyl)acetyl-Der p 1 conjugates, followed by activation of tetanus-toxoid-specific or Der-p-1-specific T cells. In 1993, van der Heijden et al. [26] were the first to demonstrate IgE-mediated allergen presentation via CD23 in an allergen-specific setting using unmodified serum IgE from allergic patients and allergens acti-

vating human allergen-specific Th2 cell clones. In this system, Epstein-Barr virus-transformed B cells with a high CD23 expression level were used as APCs. After capture of allergen by IgE, the Epstein-Barr virus-B cells are added to allow binding of the IgE-allergen complexes to the CD23. When these cells are used as APC, 100- to 1,000-fold lower allergen concentrations are required to fully activate allergen-specific T cells. This can be inhibited by anti-CD23 mAbs or polyclonal anti-IgE antisera. Van der Heijden et al. [27] further showed that the process is dependent on the level of allergen-specific serum IgE, which was confirmed later in another study [28]. These studies clearly demonstrated that allergen complexed to specific IgE can specifically bind to CD23 and can facilitate the presentation of allergens to T cells, resulting in extremely efficient T-cell activation. These studies demonstrate a functional cooperation between the humoral and the cellular allergen-specific immune response in allergic patients.

FcεRI

Around the same time the initial CD23 studies took place, Mudde et al. [29] had noted that IgE⁺ Langerhans cells from atopic dermatitis patients were very efficient APC for the activation of house-dust-mite-specific T cells, whilst IgE-Langerhans cells were not. This was followed by the elucidation that FcεRI is expressed by Langerhans cells [30]. In fact, it is now known that FcεRI is present on monocytes, dendritic cells and Langerhans cells of allergic patients [20, 31, 32]. In a classic study, Maurer et al. [33] showed that FcεRI expressed on monocytes of allergic patients is capable of IgE-mediated allergen presentation to specific T cells. In this study, antigen uptake and subsequent presentation was increased 100- to 1,000-fold in the presence of IgE. Later, the same group demonstrated that, quite surprisingly, the FcεRI on monocytes and dendritic cells exists of one α and two γ chains, but lacks the β chain present on mast cells and basophils [34]. This receptor is easily internalized and can deliver the allergen bound to IgE into a cathepsin-S-dependent pathway of MHC class II presentation [35]. In a slightly artificial model, Tkaczyk et al. [36] showed in 1998 that FcεRI expressed on cultured murine mast cells may also facilitate the presentation of allergens to allergen-specific T cells. Importantly, the expression of the αγ2 FcεRI is unique for human APC and has not been demonstrated to be present on APC in rodents, and may account for the fact that mouse models for inhalation allergy require high allergen doses.

Does IgE-Mediated Allergen Presentation also Occur in vivo?

The fact that both IgE receptors, CD23 and FcεRI, strongly decrease the amount of allergen needed to efficiently activate allergen-specific T cells in vitro suggests that allergen-specific IgE may be a key regulator of T-cell activation in vivo as well. This implies that allergen-specific T cells can be activated in vivo upon exposure to extremely low allergen doses.

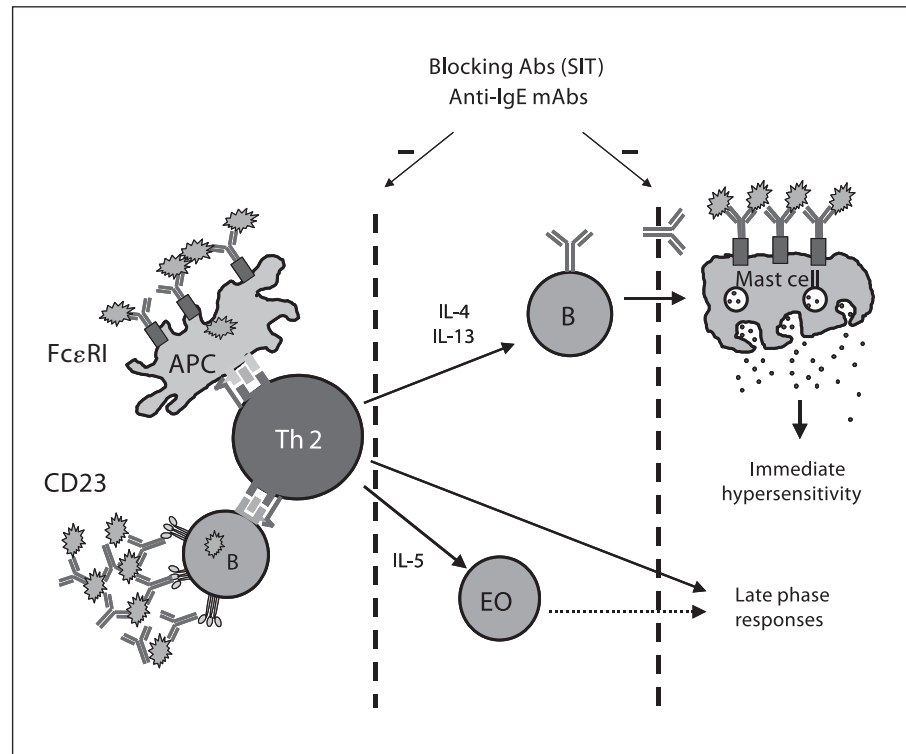
In atopic dermatitis patients, FcεRI-bearing Langerhans cells are important for the allergen-induced lesions [37–39]. The expression of allergen-specific IgE on the epidermal Langerhans cells makes these cells also about 1,000-fold more sensitive for allergens [29]. In this way, the minute amounts of aeroallergens that can penetrate the upper layers of the skin can be picked up by the IgE-bearing Langerhans cells and can subsequently be presented to allergen-specific T cells in the tissue.

In addition, the role of IgE and IgE receptors in T-cell activation in vivo has been addressed in several animal models. The first in vivo studies to address this question showed that antigen-specific IgG and IgE production is enhanced >100-fold after the administration of allergen-IgE complexes in mice [40–42], or by allergen-anti-CD23 mAb conjugates [43]. These data strongly suggest a role for IgE and CD23 in T-cell-dependent allergen-specific antibody responses. Interestingly, CD23 knockout mice lack this ability [44]. Similarly, the production of IL-4 and IL-5 and the recruitment of eosinophils to the lungs of mice sensitized with house dust mite can be inhibited by treatment with an anti-CD23 or anti-IgE mAb [45]. Direct demonstration of IgE-dependent T-cell activation in vivo comes from a recent paper by Getahun et al. [46], who demonstrated that the administration of specific IgE + antigen induces a 10-fold stronger antigen-specific T-cell response in vivo than administration of antigen alone. Interestingly, these results also indicate that CD23+ B cells in particular are crucial for T-cell activation and antibody production in vivo.

Anti-IgE Therapy

Non-anaphylactogenic anti-IgE antibody is used as a novel treatment for IgE-mediated allergies. Its rationale is based on the fact that functional neutralization of IgE will prevent IgE from binding to its receptors and hence from exerting clinical effects. It has been known for several decades that serum IgE levels and IgE receptor ex-

Fig. 1. IgE-mediated T-cell activation and the allergic immune response. After entering the body, an allergen will bind to FcεRI-bound IgE on an APC (dendritic cell or monocyte) or form complexes that bind to CD23 on a B cell. Following this binding, the allergen is internalized, processed and presented to an allergen-specific T(h2) cell. The production of Th2 cytokines by this T cell induces as well as perpetuates the production of allergen-specific IgE by B cells. In addition, the allergen binds to FcεRI-bound IgE on basophils or mast cells, thus triggering the release of histamine and other inflammatory mediators. Finally, the activation of the allergen-specific T cells results in the occurrence of late-phase allergic responses. Blocking antibodies induced by SIT, as well as anti-IgE treatment shift the amount of allergen needed for T-cell activation by preventing the binding to IgE (SIT) or the internalization (anti-IgE) of the allergen. Likewise, the release of histamine and other inflammatory mediators is inhibited by SIT-induced blocking antibodies or anti-IgE. EO = Eosinophil.



pression on mast cells and basophils are positively correlated [47]. Several publications have elucidated that high-level expression of FcεRI on basophils and mast cells indeed critically depends on the presence of IgE molecules [48–50]. Serum IgE levels, as well as the levels of FcεRI expressed on peripheral blood basophils, are dramatically decreased after treatment with anti-IgE mAb [51, 52]. This decreased FcεRI expression is reversible, and expression levels are restored upon discontinuation of anti-IgE treatment [53]. Next to the effect on basophils and mast cells, FcεRI expression on dendritic cells is also decreased after anti-IgE treatment [54].

These findings strongly suggest that the clinical effect of anti-IgE treatment is not only the result of decreasing peripheral blood IgE levels, but also indirectly the result of downregulation of FcεRI surface expression.

Further, anti-IgE mAb inhibits bronchial late-phase responses and the number of eosinophils in sputum of allergic asthma patients [55], and data on the anti-inflammatory activity of anti-IgE are accumulating [56–58]. The fact that anti-IgE has anti-inflammatory activity and inhibits the development of (T-cell-dependent) late-phase responses suggests that IgE may also be necessary for T-cell activation in vivo. In vitro inhibition of the IgE-mediated activation of allergen-specific T cells by anti-

IgE has been demonstrated, which hints towards an additional mechanism of anti-IgE next to decreasing mast cell and basophil activation [59] (fig. 1).

Specific Immunotherapy

Specific allergen immunotherapy (SIT) with allergen extracts has been practiced ever since its introduction by Noon [60] in 1911. However, even though the clinical efficacy of SIT is well documented by the clear reductions in symptom/medication scores, early and late-phase skin responses, and strongly increased allergen threshold levels in provocation tests [61], the mechanisms behind these effects are only now emerging from studies using unmodified allergen extracts for SIT [62].

So far SIT is the only causal allergy treatment as evidenced by the sustained clinical effects several years after treatment discontinuation [62–65], and it can be seen as a vaccination regime aimed to induce clinical tolerance to an antigen against which there is an excessive, unwanted immune response [66]. In addition, SIT has been shown to reduce the risk of developing new sensitizations, and has been suggested to inhibit the progression from rhinitis to asthma [67, 68].

Immunological Effects of SIT

The immunological changes leading to these clinical effects of immunotherapy include a reduction in eosinophil infiltration and activation levels [69, 70], as well as enhanced Th1 activation and IL-12 production by APC [71, 72] at the site of allergen exposure. Moreover, changes in the activation threshold for basophils and reduced numbers of mast cells and basophils in the mucosa have also been described after SIT [70, 73]. Apart from a shift from Th2 to Th1 responses [74, 75], recent reports have described a general reduction in allergen-specific T-cell activation as a result of the production of the inhibitory cytokines IL-10 and TGF- β by regulatory T cells (Treg) [76, 77]. This increased IL-10 (and TGF- β) production has been suggested by Akdis and Blaser [78] to be the hallmark of successful immunotherapy, and the induction of T-cell regulation has been investigated intensively during the last number of years. In addition, increases in CD4CD25⁺ Tregs have also been used as an indication of enhanced T-cell regulation induced by SIT [79].

At the level of antibody production, the most consistent finding related to SIT is an increase in allergen-specific non-IgE antibodies and an initial rise in the allergen-specific IgE production followed by a return to pretreatment levels combined with a blunting of the seasonal increase in the IgE production [80, 81]. The changes in antibody titers will be further discussed below, but the production of regulatory cytokines by Tregs are probably causally related to the production of blocking antibodies via the induction of isotype switching to IgG4 or IgA induced by IL-10 or TGF- β , respectively. This has led to a model proposed by Robinson et al. [66] for the combined effects of Treg and blocking antibodies that explains most of the recently published findings regarding mechanisms of SIT. However, as the role of T-cell regulation in SIT is not demonstrated in all studies [82], additional mechanisms may yet be involved.

The mechanisms induced by SIT might be related to changes induced by exposure to high allergen levels, as is hypothesized in the 'modified Th2 response' theory [83]. Consequently, if exposure to high allergen concentrations by itself leads to the production of allergen-specific non-IgE antibodies, the immunological changes observed after SIT may be primarily related to the induction of these blocking antibodies. Through inhibition of IgE-mediated allergen presentation this could lead to the cellular changes observed via a change in the activation threshold for the allergen-specific Th2 cells. The blocking of IgE-mediated allergen presentation will reduce the

involvement of B cells as APC, which in turn leads to T-cell activation through the presentation of the allergen by professional APC such as dendritic cells or macrophages. This will primarily take place in a non-receptor-mediated fashion that requires higher allergen concentrations, favoring Th1 development [84]. Also, application of anti-IgE treatment during SIT will potentially inhibit the IgE-mediated allergen presentation and change the sensitivity of the immune system for the allergens [85, 86].

Mechanisms and Immunological Changes following SIT: Antibody Responses

In 1935, Cooke et al. [87] demonstrated that serum from patients treated with SIT contained a 'protective substance' that inhibited the early-phase reaction in the skin. The thermo-stable protective antibodies in serum were found to mainly reside in the IgG fraction [88, 89], and are now also known as 'blocking antibodies' because of their ability to inhibit the interaction between allergen and IgE. Other studies have shown that IgA antibodies are also blocking [90]. However, only low levels of IgA are present in serum.

The first investigations of the serum IgG subclasses induced by SIT showed that the increase in allergen-specific IgG was mainly in the IgG4 subclass [91, 92]. Other studies have shown that in addition to IgG4, SIT also induces increases in IgG1 whereas only minor changes are found in IgG2 and IgG3 [93, 94].

Many studies have compared quantitative changes in serum IgG and IgG4 levels during SIT with clinical improvement, but the results have been conflicting [95–97]. In rush venom SIT, clinical improvement was even found before the appearance of allergen-specific antibodies [98].

To date, serum levels of blocking IgG4 antibodies have been measured against allergen extracts, which may make it harder to directly link the IgG levels to clinical benefit. Flicker and Valenta [99] have pointed out that the effect of blocking antibodies should ideally be studied using single major allergens rather than extracts to exclude the effects of irrelevant IgG antibodies. This is especially relevant when correlations between IgG4 levels and clinical efficacy are studied, as IgG induced to irrelevant proteins in the extracts will cloud the real effect of the blocking antibodies directed to major allergens to which the IgE is directed [99].

It has further been suggested that functional properties such as affinity and epitope specificities of the in-

duced IgG, especially IgG4, should be investigated, as changes in these properties may be more relevant for the clinical effect of the antibodies [100, 101]. Only minor differences were found when measuring the avidities of IgG to different allergens, and SIT did not induce any appreciable avidity changes [102]. Likewise, in birch pollen SIT no or minor changes were found in the $Bet\ v\ 1$ K_d values of polyclonal IgG [103]. Furthermore it has been demonstrated that the blocking effect of specific IgG4 is not superior to that of other IgG subclasses [104]. Even though it is highly relevant, only few studies have addressed the presence of antibodies in the affected organs. In one study, SIT induced increases in IgG but not in IgA in nasal secretions; the changes in IgG were, however, small compared to the changes in serum [105]. In another study, increases in both IgA and IgG were found in nasal secretions following SIT, the antibodies inhibited peripheral blood basophil histamine release, and there was a correlation between antibody levels and inhibition of histamine release [106]. In a recent clinical study on birch SIT, Reisinger et al. [107] showed that apart from the induction of serum IgG specific for birch, IgG was also induced topically in nasal secretions. This presence of IgG4 in the nasal secretions was significantly associated with reduced nasal sensitivity to birch allergen determined by nasal allergen provocations.

Inhibition of Basophil/Mast Cell Degranulation by Blocking Antibodies

It has been demonstrated by several investigators that SIT-induced IgG inhibited histamine release from basophils [89, 94]. Blocking of histamine release has been shown with monoclonal human $Bet\ v\ 1$ -specific IgG1, and with both polyclonal IgG1 and IgG4 [108, 109]. The inhibition could be caused by a direct inhibition of the allergen-IgE interaction or through coaggregation of the inhibitory $Fc\gamma RIIB$ and $Fc\epsilon RI$ as demonstrated in an artificial system by Kepley et al. [110]. However using sera from SIT-treated patients, we were not able to demonstrate a contribution of $Fc\gamma RIIB$ activation to the inhibitory effect of SIT-induced IgG [111].

In conclusion, the induction of allergen-specific blocking antibodies during SIT and the blocking effect in vitro is well documented, although a clear-cut correlation between the serum level of blocking antibodies and clinical the effect of SIT remains to be established. Therefore, functional tests pinpointing the inhibitory effects

of these blocking IgG1/IgG4 antibodies in the context of allergen-specific IgE-induced immune responses are important.

Blocking Antibodies Induced by SIT Inhibit IgE-Mediated Allergen Presentation

Blocking antibodies do not only have an effect on the immediate allergic reaction via inhibiting basophil/mast cell release, but can also interfere with T-cell activation. As described above, T-cell activation is crucial for the development and perpetuation of the allergic immune response, and is also directly linked to the late-phase response as well as chronic inflammation of the airways. The low annual exposure to aeroallergens suggests that IgE-mediated allergen presentation via CD23 or $Fc\epsilon RI$ is the most likely in vivo mechanism for T-cell activation in allergic patients. In 1999, we demonstrated that IgE-mediated allergen presentation to birch-allergen-specific T cells was inhibited by sera of birch SIT patients, but not of grass SIT patients, suggesting that an allergen-specific factor in their sera inhibited the IgE-mediated allergen presentation [28]. The inhibitory effect was shown to be present in the IgG fraction of the birch SIT sera. In fact, this study and a follow-up study of sera from a placebo-controlled birch SIT study [112] demonstrated that 100- to 1,000-fold higher allergen doses are needed to activate birch-allergen-specific T cells after SIT. This may be a good explanation for the finding that the T-cell-dependent late-phase response is also decreased after SIT.

In grass-allergic patients undergoing SIT, inhibition of binding of IgE-allergen complexes to CD23 was also shown, confirming the findings in birch pollen SIT [113, 114]. It seems therefore that the inhibition of IgE-mediated allergen presentation via CD23 is a general effect of blocking antibodies induced by SIT. The effect of SIT on T-cell activation may be even more pronounced if IgE-mediated allergen presentation through $Fc\epsilon RI$ is also inhibited by blocking antibodies as seen for $Fc\epsilon RI$ -induced basophil histamine release.

IgE-mediated allergen presentation measures the biologically relevant fraction of allergen-specific IgE in patient serum by measuring the effect of IgE in the presence of blocking antibodies. As such, it may be developed into a functional assay for the ex vivo evaluation of SIT success.

However, it was not possible to strongly correlate the inhibition of IgE-mediated T-cell activation to clinical efficacy in single patients after birch SIT [112], and it has

not been attempted in studies on grass SIT [113, 114]. This may be related to several technical aspects of the experimental setup for IgE-mediated allergen presentation analyses including the low dynamic range of the assays used.

Originally, the assay used to study IgE-mediated allergen presentation was based on a highly sensitive T-cell readout [28, 112], but recent publications have shown that it is possible to measure the level of IgE-allergen complexes bound to CD23 on the surface of B cells by FACS analysis [59, 113, 114]. Moreover, two different systems are used for grass and birch allergy. In grass IgE-mediated allergen presentation, an indicator serum and grass allergen extract are used to generate allergen-IgE complexes, and the effect of SIT is investigated indirectly by adding post-SIT sera and determining the reduction in IgE binding to the B cell. In birch SIT, the complex formation was measured directly in sera before and after immunotherapy using purified Bet v 1 [112]. In addition to this, the complexity of the mechanism behind allergic disease and the symptoms experienced by the patients may make direct correlations difficult to establish. Therefore, statistical evaluations based on ranking of the patients may be more useful, but this calls for IgE-mediated allergen presentation data on larger patient groups than the ones investigated to date.

Therapeutic Use of Blocking Antibodies: Can Polyclonal Blocking Antibodies Be Used for Seasonal Allergy Treatment?

Even though it is hard to directly link blocking IgG antibodies to clinical improvement on a single patient level, induction of allergen-specific serum IgG is generally linked to clinical improvement on the level of treated versus untreated patient groups. In vivo evidence from several animal models also suggests that blocking antibodies may suppress allergic symptoms. Behrens et al. [115] showed in 1984 that administration of allergen-specific IgG in the lungs abrogates late-phase responses. In addition, two more recent studies have shown the effect of blocking antibodies in the airways. First, when allergen-specific IgG was administered to sensitized mice intranasally, followed by allergen challenge, eosinophilic inflammation was strongly reduced as was goblet cell metaplasia [116]. This was in part dependent on the presence of IFN- γ and Fc γ R, suggesting that apart from the effect on IgE-mediated allergen presentation, IgG antibodies may also have an effect by skewing the T-cell re-

sponse to a more IFN- γ -dominant type of response. Likewise, IgA was also shown to have an inhibitory effect on the development of airway hyperresponsiveness and eosinophilia [117].

Allergen-specific blocking IgG antibodies may simply neutralize the allergen before it can be bound by Fc ϵ RI-bound or circulating IgE, thus making the allergen incapable of inducing effector mechanisms via triggering of IgE receptors on basophils/mast cells or on APC. In patients with severe chronic inflammation and airway remodeling, the clinical relevance of blocking antibodies is probably less pronounced as is the role of allergen exposure per se than in patients with relatively mild seasonal allergies [118, 119].

However, as was discussed earlier, the administration of polyclonal allergen-specific IgG or IgA has been shown to be beneficial in several animal models. Would it be possible to establish this as a novel method to treat inhalant allergy? Several clinical studies performed in the 70s and 80s have in fact addressed this question.

The effect of blocking antibodies in the target organs has been studied by experiments with local passive administration of allergen-specific IgG. Purified IgG from a patient with a high titer of specific IgG was administered by nasal spray, and the patients were then observed during challenge or during the pollen season. One study showed an effect of passive administration of IgG, the results of which could, however, not be reproduced in another study [120, 121]. In bee-venom-allergic patients, intravenous or intramuscular administration of plasma from hyperimmune beekeepers with high levels of specific IgG had a protective effect in a following allergen challenge [122, 123]. Other studies have combined active and passive immunotherapy in venom SIT in order to prevent side effects by pretreating allergic patients with IgG from hyperimmune beekeepers. Pretreatment with IgG resulted in an increase in the tolerated dose of bee venom [124, 125]. In a similar study on ragweed SIT, higher doses were tolerated in patients receiving combined passive and active immunotherapy [126].

Isolation of blocking IgGs from patients or healthy controls has however never been a realistic way of treating allergy because of the low amounts of IgG that can be obtained in this way, and because of the human origin of the IgG. Because of the polyclonal nature of the allergen-specific IgE, mAbs are of no use either. However, with the advent of novel antibody engineering technologies, this form of allergy treatment may become possible in the near future. It is now technically possible to make polyclonal human IgG antibodies in mice (and theoretically

also in larger mammals), and oligoclonal antibodies can now be produced by recombinant means in a single cell line, opening up possibilities to apply antigen-specific polyclonal human (or humanized) IgG for treatment purposes.

Clearly, this mode of treatment may not be as effective as SIT because it will, for example, not result in the induction of altered cytokine profiles in T cells, and its effect will cease upon discontinuation of treatment. However, as human IgG has a long half-life, two to three injections may be enough to obtain enough clinical effect to get through the pollen season.

It may however be similar or more efficient than anti-IgE treatment because instead of neutralizing 95% of serum IgE, which still leaves allergen-specific IgE on (few-

er) FcεRI molecules on the mast cells and basophils, one could now neutralize 100% of all allergen molecules entering the body.

Conclusions

Much progress has been made in our understanding of the role and functional effects of blocking antibodies in allergy. Using this information, new diagnostic methods as well as new therapies may be developed in the future that will enable a better monitoring of the clinical status of allergic patients and even further increase the efficacy of SIT.

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