

Is there a role for anti-IgE in combination with specific allergen immunotherapy?

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Purpose of review

A line of novel therapeutic approaches that try to interfere more specifically with the immunological mechanisms underlying allergen-induced pathology are currently undergoing clinical evaluation. The most advanced of these is anti-IgE, which directly targets IgE serum antibodies, thus inhibiting the central mechanism of immediate type hypersensitivity reactions. In addition, a lot of interest has recently been focused on allergen-specific immunotherapy due to its potential to cure allergic diseases. In the present review, state-of-the-art treatment of allergic diseases with anti-IgE and allergen-specific immunotherapy is summarized, and the potential of combination therapy with both treatment options is discussed.

Recent findings

Application of anti-IgE antibodies effectively reduces IgE serum levels regardless of allergen specificity. This treatment has been successfully tested in patients with allergic rhinitis, asthma and food allergy, showing significant efficacy in reducing symptom scores and rescue medication use. Anti-IgE therapy is limited by high costs and the necessity for permanent or every-season treatment. The strongest argument in favor of allergen-specific immunotherapy is the potential to cure allergic diseases, which has been demonstrated in patients with allergic rhinitis, insect venom allergy and, to a lesser degree, asthma. The broader application of allergen-specific immunotherapy is restricted by sometimes life-threatening side effects. A combination of anti-IgE and allergen-specific immunotherapy was shown to be superior to each single treatment protocol in children and adolescents with allergic rhinitis, as demonstrated by efficacy of symptom scores and rescue medication use.

Summary

There are strong arguments for a combination of anti-IgE plus allergen-specific immunotherapy for treatment of allergic diseases: improved efficacy, limited side effects, and potential curative effects.

Keywords

antiallergic treatment, allergen-specific immune therapy, anti-IgE therapy

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Abbreviations

ICS	inhaled corticosteroid
QOL	quality of life
SAR	seasonal allergic rhinitis
SIT	allergen-specific immunotherapy
Th1	T helper 1
Th2	T helper 2

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Introduction

The prevalence of asthma, hay fever and other IgE-mediated diseases [1] has significantly increased in industrialized countries over the last few decades, making allergies a very serious public health problem [2,3]. This is especially true for children in whom asthma is already the most common chronic illness overall [4].

Despite the growing understanding of the pathophysiology of allergic diseases, current treatment is unspecific and intervenes at a late stage of the allergic cascade (e.g. antihistamines, β -2-agonists, topical and systemic corticosteroids and chromones) [5,6]. New treatment options are therefore required that target the pathophysiological cascade of allergen-mediated immune reactions at an earlier stage or in a more general way [7,8]. Due to the pivotal role of IgE, antagonizing or inhibiting IgE responses directly by anti-IgE antibodies provides such a novel and promising approach to treat allergic diseases [9]. In this review, the effects and mechanisms of anti-IgE therapy for treatment of allergic diseases are highlighted, and the possibilities of using a combination of anti-IgE with allergen-specific immunotherapy (SIT) are discussed in view of the available clinical data.

Anti-IgE for the treatment of allergic diseases

Application of monoclonal antibodies directed against IgE is one of the first available options in a line of novel treatment strategies directly targeting specific immunological events in the development of allergic diseases.

Mechanism of Anti-IgE

Key cells for the development of the IgE-mediated allergic immune reactions are T and B lymphocytes. Upon allergen sensitization and activation, T lymphocytes produce cytokines, predominantly T helper 2 (Th2), including IL-4, IL-5, IL-9 and IL-13, inducing IgE isotype switch in B lymphocytes. IgE attaches to specific receptors expressed by tissue mast cells and

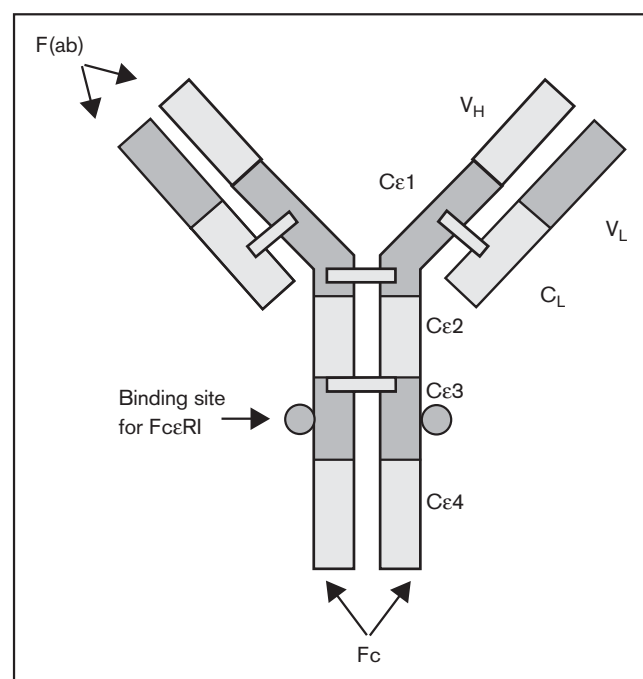
blood basophils that, after subsequent allergen contact, release preformed and newly synthesized mediators such as leukotrienes, prostaglandins, cytokines and chemokines, thus initiating the early allergic reaction [10•]. Sustained Th2 cytokine production recruits and activates other effector cells, such as eosinophils, thus triggering the development of the late allergic reaction [11].

The binding site of IgE for the high-affinity receptor FcεRI is located within the third domain of the heavy chain, Cε3 (Fig. 1) [12]. A murine antibody, MAE1, is generated that recognizes the same residues in the Cε3 domain of IgE that are responsible for binding to FcεRI [13]. To avoid sensitization with foreign proteins, a humanized version, containing 95% of a human IgG1 antibody and only 5% of the murine IgE-specific epitope, was constructed and referred to as recombinant humanized monoclonal antibody-E25 or omalizumab (Novartis) [14]. A similarly acting mAb is available from a different company and termed TNX-901 (Tannox) [15•].

The main features of anti-IgE are as follows [16•].

- (1) It recognizes and binds IgE, but not IgG or IgA.
- (2) It inhibits the binding of IgE to FcεRI.

Figure 1. Structure of IgE and position of binding site for FcεRI



IgE contains two identical heavy (H) and two identical light (L) polypeptide chains connected by disulfide bridges. The variable domains (V_H and V_L) contain the binding site for specific allergen (Fab), the constant domains (Cε) contain the binding site for the high-affinity IgE receptor, FcεRI. Reproduced from Hamelmann *et al.* [16•] with permission.

- (3) It does not bind to IgE bound to mast cells or basophils and thus does not cause degranulation ('non-anaphylactic antibody').
- (4) It blocks mast-cell degranulation following passive sensitization *in vitro* or challenge with allergen *in vivo*.
- (5) It is unspecific for the allergen specificity of the IgE antibody, that is it binds to any IgE molecules.

Safety, tolerability, route of administration

A series of preclinical and phase I studies were conducted to test safety and efficacy of anti-IgE. Studies in cynomolgus monkeys showed that anti-IgE binds IgE resulting in the formation of small (~1000 kDa), nonprecipitating and noncomplement-activating immune complexes that are no longer able to bind IgE receptors. E25 was found to be most concentrated in the serum compartment, however no specific organ deposition was observed and immune complexes were eliminated by urinary excretion [17]. In addition to the effect on circulating IgE, treatment with anti-IgE also suppresses IgE-receptor expression on basophils *in vitro* [18], supporting the current understanding that IgE receptor expression is regulated by and associated with IgE serum levels.

Single and multi-dose trials in adults with and without allergic disease showed that anti-IgE was well tolerated and caused a decrease in IgE serum levels in a dose-dependent manner as soon as 5 min after intravenous injection and within 24 h of subcutaneous injections [19,20]. The decrease in IgE lasted, depending on the antibody dose, for about 4–6 weeks after a single injection with anti-IgE. Whereas the subcutaneous and intravenous routes of administration were similarly effective [21] (Fig. 2), application of aerosolized anti-IgE did not significantly suppress serum IgE levels and did not affect early asthmatic responses to allergen, despite detectable levels of omalizumab [22].

Anti-IgE for the treatment of asthma

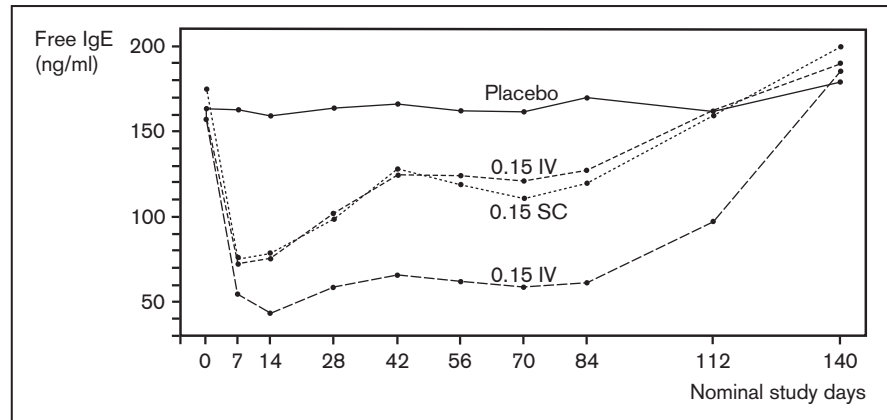
Asthma treatment has substantially improved over the last few decades. Inhaled corticosteroids (ICSs) have become the standard antiinflammatory medication and normally effectively control symptoms of mild to moderate asthma. Some patients with moderate to severe asthma, however, remain symptomatic even under persistent ICS treatment, or constantly require high doses of ICSs or systemic steroids to control the condition. This patient group would greatly benefit from new treatment options targeting the pathophysiological events in a more specific way.

Effects of anti-IgE on early and late-phase allergic responses (phase I/II studies)

Two double-blind, placebo-controlled studies were performed on a small number of patients with mild

Figure 2. Anti-IgE reduces free IgE serum levels

Intravenous (IV) and subcutaneous (SC) application of anti-IgE similarly reduces total IgE serum levels rapidly and for up to 12 weeks. Reproduced from Casale *et al.* [21].



asthma to test the ability of anti-IgE to inhibit early and late-phase allergic responses after bronchial challenge with allergen [23,24]. Anti-IgE was administered intravenously at a dose of 2 mg/kg body weight on day 0 and at a dose of 1 mg/kg on days 7, 14, 28, 42, 56 and 70. Anti-IgE treatment significantly decreased IgE serum levels and reduced the early allergic response, as demonstrated by a significantly smaller reduction in forced expiratory volume in 1 s and a significant increase in median allergen PC15 after allergen challenge on days 27, 55 and 77 [23]. A similar effect was observed for the late-phase response to allergen, assessed 2–7 h after allergen provocation [24]. No improvement in unspecific hyperresponsiveness, asthma symptom score and overall lung function was shown after treatment with anti-IgE compared with placebo.

Effects of anti-IgE on asthma symptom scores (phase II study)

The somewhat promising results of the early studies had to be confirmed in a large-scale multi-center, randomized, double-blind, placebo-controlled study investigating the efficacy of anti-IgE for treatment of asthma. Application of anti-IgE was by intravenous route and was adapted to individual body weight and serum IgE levels to ensure a constant ratio of IgE to anti-IgE antibody [25]. Patients were under stable steroid medication for the first 12 weeks, and steroid dosages were tapered during the last 8 weeks. Treatment with anti-IgE led to a fast decrease in serum IgE levels, which remained stable and less than 5% of mean baseline values for 20 weeks. Following treatment with the low or high dose of anti-IgE, the proportion of patients at 12 weeks with at least a 50% reduction in asthma symptom scores was significantly higher than in the placebo group. The mean reduction in symptom scores from baseline values was significantly higher in the two groups receiving high or low dose anti-IgE compared to placebo, although

placebo-treated patients also enhanced during the course of the study [25]. Importantly, the requirements for inhaled or oral steroids were reduced in patients treated with anti-IgE, associated with a decrease in β -2-agonist use [25].

In summary, improvements in patients on anti-IgE therapy were modest, but significantly better than in the placebo group, and occurred despite reductions in steroid and β -2 agonist therapy. These promising results led to larger scale studies using anti-IgE but with modified settings.

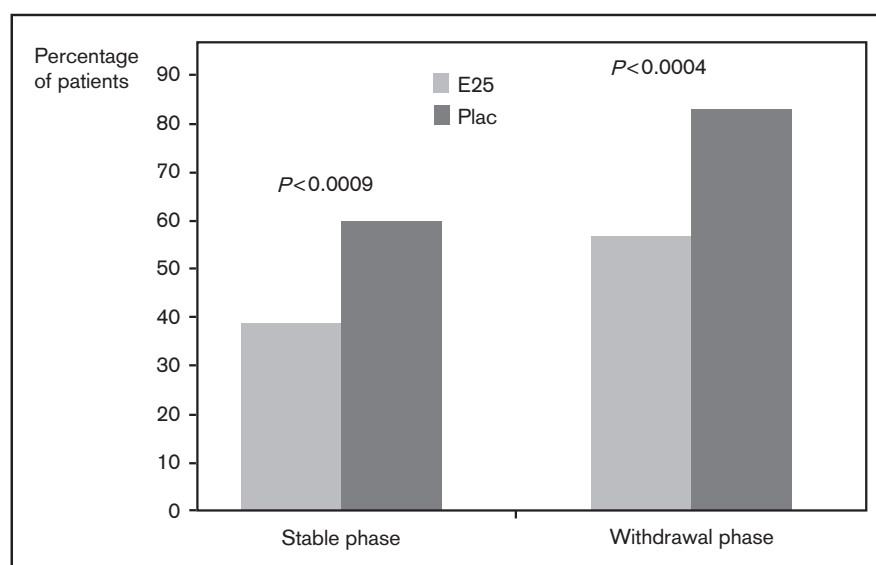
Effects of anti-IgE on asthma exacerbation (phase III studies)

Three identically designed large-scale phase III studies were performed to evaluate the efficacy of anti-IgE in the treatment of asthma: protocol 008 in the US [26], protocol 009 in the EU, US, South Africa and Australia [27] and protocol 010 in children with asthma in the US [28]. In contrast to the phase II study [25], anti-IgE was administered subcutaneously rather than intravenously and only once every 4 weeks for patients with low and intermediate IgE baseline serum levels. In addition, the duration of the trial was extended, the age range of the adult patients was increased, and the primary endpoints were frequency of asthma exacerbations. In contrast to the studies in adults, asthma was well controlled (not symptomatic) on entry to the study on children [28]. Differences between anti-IgE and placebo-treated patients therefore were only obvious during the steroid-withdrawal phase.

The main findings of the phase III trials were similar and confirmed the results of the phase II trial [25]. Treatment with anti-IgE was significantly more effective than placebo in reducing the number of exacerbations, the primary endpoint of the trials, in both the stable-steroid and the steroid-withdrawal phase (Fig. 3). This

Figure 3. Percentage of patients with exacerbations during stable-steroid and steroid-withdrawal phases

Patients were under therapy with either anti-IgE (E25) or placebo (Plac). Reproduced from Busse *et al.* [26].



reduction in asthma exacerbations in the anti-IgE treatment group was obvious despite significantly lower ICS use or complete withdrawal of beclomethasone dipropionate during the steroid-withdrawal phase.

Symptom scores improved in both the placebo-treated and the anti-IgE-treated patients, but the improvement was significantly higher in the latter group, despite the lower use of corticosteroids. Similarly, β -2-agonist use was significantly lower in the anti-IgE group than in the placebo group during the stable-steroid phase (Fig. 4). Lung function improved significantly more in patients receiving anti-IgE compared with placebo, as indicated by increases in peak expiratory flow and a small, but significant, improvement in forced expiratory volume in 1 s. Two recent studies have shown that symptom control and reduction of medication use is paralleled by improvements in asthma-related quality of life (QOL) [29,30].

Similarly, asthmatic children treated with anti-IgE showed significantly better results than those receiving placebo during the steroid-withdrawal phase for frequency and incidence of exacerbation, median reduction of beclomethasone dipropionate doses, complete discontinuation of steroids, and requirements for rescue medication. No statistical differences occurred for symptom scores or spirometry measurements (peak expiratory flow) between the two groups in either the stable-steroid or the steroid-withdrawal phase [28].

Taken together, the phase III studies show that treatment of adults and children with moderate to

severe asthma with anti-IgE is safe, statistically lowers the number of disease exacerbations, reduces the requirements for ICS use and reduces the need for unscheduled outpatient interventions and hospitalization [31].

Anti-IgE for the treatment of allergic rhinitis

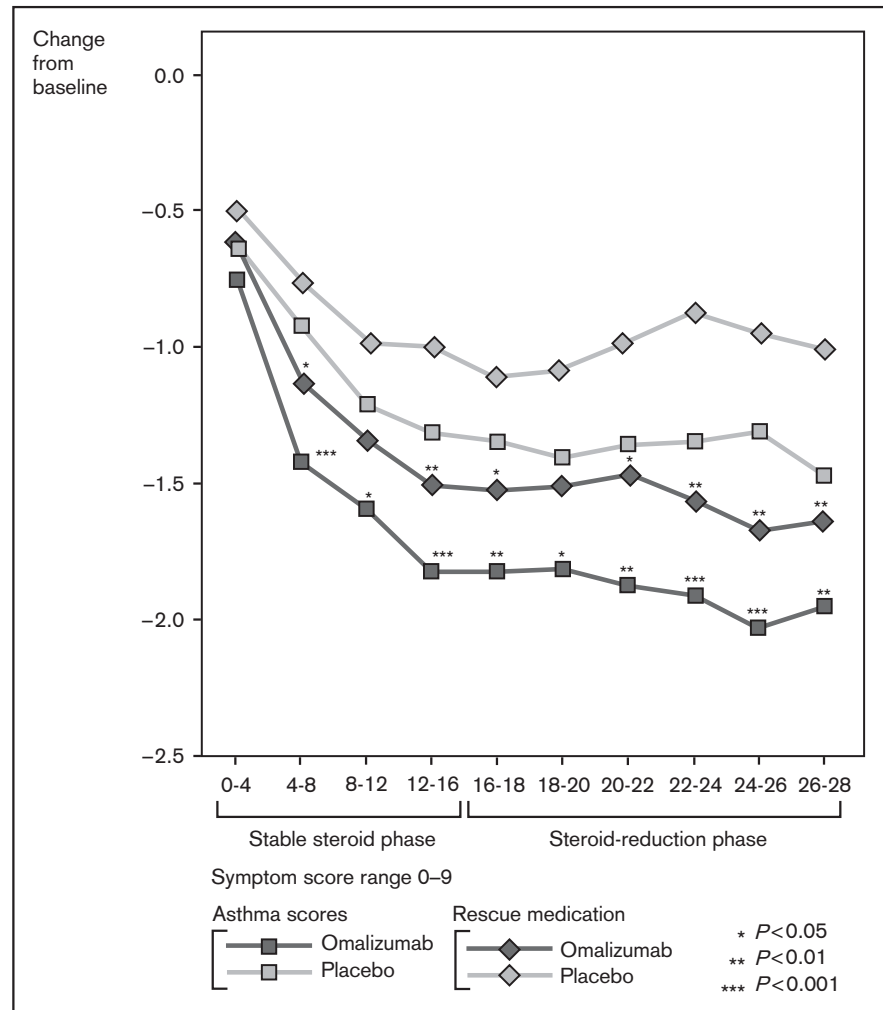
Seasonal allergic rhinitis (SAR) is a frequently underestimated disease, affecting the QOL of patients who experience a significant level of morbidity. Allergen avoidance as a means of secondary intervention is difficult to achieve in patients with SAR who are often sensitized to multiple outdoor allergens. SIT, the only available curative approach [32], is restricted in polysensitized patients, who require therapy for several months of the year and suffer most from decreased QOL [33] and reduced productivity [34]. Despite optimized treatment regimens, including antihistamines, corticosteroids or mast-cell stabilizers, many patients with SAR still have suboptimal symptom control [32]. Therefore, new treatment options targeting more specifically and earlier in the allergic cascade are desirable.

Efficacy of anti-IgE in treatment of seasonal allergic rhinitis in adults (phase II study)

A large-scale double-blind, placebo-controlled, multicenter trial was performed to assess optimal dosing regimens and test the efficacy of anti-IgE for the treatment of SAR [21]. Patients in the active arms received different intravenous doses of anti-IgE once every second week for 12 weeks, followed by a 6-week observation period. Anti-IgE decreased serum IgE levels

Figure 4. Symptom scores and rescue medication use during stable-steroid and steroid-withdrawal phases

Reproduced from Soler et al. [27] with permission.



in a dose and baseline IgE-dependent fashion (Fig. 2), but IgE levels did not consistently decrease to less than 25 IU/ml in any of the treatment groups. Moreover, the average symptom score before and during the peak of the season was only small and use of rescue medication was similar between the groups.

Despite these limitations, the data showed that (1) clinical efficacy is only achieved in patients with significantly reduced IgE levels, and (2) for significant suppression of IgE levels, higher doses of anti-IgE are required. These findings resulted in a dosing regimen taking individual body weight and baseline IgE levels into account: 0.005 mg anti-IgE/kg bodyweight/week for each IU baseline IgE /ml serum, doses between 150 and 375 mg per interval of 2–4 weeks. As equivalent results were seen with intravenous and subcutaneous dosing regimens, the latter route was preferred in subsequent trials for practical ease of administration.

Effects of anti-IgE on symptom scores in seasonal allergic rhinitis in adults (phase III study)

The results of the previous study [21] warranted further evaluation of the efficacy of anti-IgE therapy in SAR in two multi-center studies [35,36]. In the Swedish study higher anti-IgE doses were used [35]. Serum IgE levels at weeks 3/4 were decreased to less than 25 IU/ml, a critical threshold level for clinical efficacy, in 113 (69%) of patients treated with anti-IgE, and levels exceeded 50 IU/ml in only three of these patients. Average daily nasal and ocular symptom severity did not change or even decreased during the course of the study in the anti-IgE group, but significantly increased in the placebo group. Importantly, the average use of rescue medication was significantly lower in the anti-IgE group compared with the placebo group, and the proportion of days without any requirements for SAR medication was almost twice as high. Statistically significant differences in favor of anti-IgE were similarly observed for

estimation of QOL [35]. The clinical benefit was associated with an antiinflammatory effect on cellular markers in blood and nasal tissue [37]. The US SAR study confirmed the significant association of nasal symptom scores and rescue antihistamine use with IgE reduction using three differing doses of omalizumab [36]. Conclusively, anti-IgE was safe and effective in controlling birch pollen-induced SAR compared with placebo, with less use of rescue medication and improved QOL.

Anti-IgE for the treatment of other allergic diseases

More recently, the potent antiallergic effect of anti-IgE therapy has been demonstrated in patients with food allergies [15]. In this study, the threshold amount of peanuts leading to allergic symptoms after oral intake was significantly increased after injection of anti-IgE antibody (Fig. 5), showing the powerful consequences of a treatment directly targeting IgE-mediated immediate type hypersensitivity reactions.

Allergen-specific immunotherapy for the treatment of allergic diseases

Specific allergen immunotherapy implies the application of specific allergen in order to impair or inhibit allergen-mediated diseases. According to the standard procedures of SIT, patients receive weekly injections with increasing doses of allergen until a maintenance dose is reached, which is repeatedly given at monthly intervals for 3–5 years. Alternative protocols have been estab-

lished with more or less rapid dose-escalating regimes (so-called semi-rush and rush protocols), with the advantage of earlier protection, but the disadvantage of increased risk of serious adverse reactions. Although SIT has been employed for more than 100 years, its efficacy for the treatment of allergic diseases has only recently been established by double-blind clinical trials.

Mechanisms of allergen-specific immunotherapy

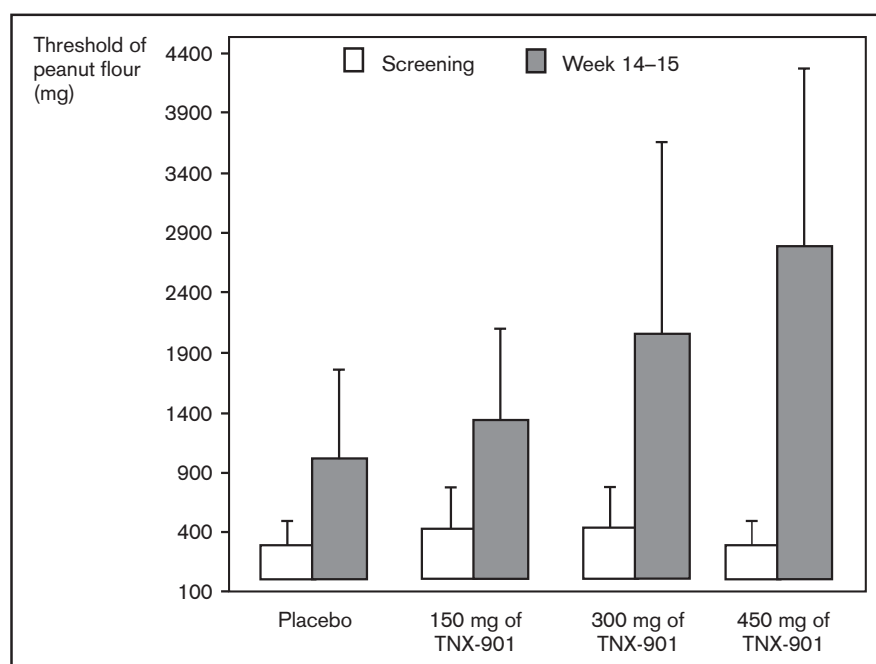
The clinical effects obtained with SIT may be explained by several mechanisms [38].

- (1) Reduction in specific IgE antibodies.
- (2) Induction of blocking IgG antibodies.
- (3) Alteration of T-cell cytokine production (increase in T helper 1 (Th1) cytokines).
- (4) Induction of specific T-cell tolerance (T-cell anergy, regulatory T cells).

Until recently the effects of SIT were explained by modifications in the level of Ig production. Decreases in allergen-specific IgE levels were observed at late stages of SIT and were associated with increased allergen-specific IgG antibodies that were thought to 'block' allergic responses by binding to a specific allergen. The dissociation between the timing and the degree of the rise in allergen-specific IgG levels on the one hand, and the onset and the magnitude of the clinical advantage on the other hand, however, makes this mechanism rather unlikely.

Figure 5. Mean threshold doses of peanut flour eliciting allergic symptoms after oral food challenge in peanut allergic patients

Mean threshold doses at time of screening or after subcutaneous treatment with either anti-IgE (TNX-901: 150, 300 or 450 mg) or placebo every 4 weeks for four doses. Reproduced from Leung *et al.* [15].



There is increasing evidence that SIT mainly works through an effect on allergen-specific T-cell responses. SIT is accompanied by a shift in the balance of Th1 and Th2 cells, with increased production of Th1 cytokines IL-2, IFN- γ and IL-12 [39,40]. Moreover, successful SIT has been shown to induce so-called regulatory T cells, producing increased amounts of IL-10 and thus suppressing ongoing allergen-specific T-cell responses [41]. This may explain why SIT is effective even in patients with sustained high IgE serum levels.

Safety of allergen-specific immunotherapy

The broader application of SIT for the treatment of allergic diseases, especially asthma, is limited by the considerable risk of serious, potentially fatal adverse reactions. Therefore, SIT is currently restricted to patients with a high probability of clinical response and at no or low risk of serious side effects. Additional means that may lower the risk of side effects as a consequence of specific allergen application are thus required to allow more extensive use of this possibly curative approach.

Allergen-specific immunotherapy for the treatment of asthma

Asthma is a common indication for SIT in the US and continental Europe [42,43^{••}]. In contrast to other treatment options, SIT offers the chance of modulating the immune response against allergens, thus inhibiting the 'allergic march', that is the development of asthma from a less serious phenotype. A Cochrane analysis from 2003 of all studies on SIT published in the last 35 years demonstrated that SIT is beneficial for the treatment of adult asthma [43^{••}]. Compared with placebo, patients treated with SIT experienced significant improvements in symptom scores, asthma medication use and allergen-induced airway responses, but had no signs of overall enhanced lung function. This analysis was supported by double-blind placebo-controlled studies on SIT for patients with grass pollen-mediated asthma. SIT patients showed increased asthma symptom and treatment scores, enhanced peak flow rates during the pollen season, and reduced asthma medication use compared with placebo-treated patients [44]. Disadvantages limiting a more general use of SIT for treatment of asthma still include the relatively high costs compared with symptomatic medications and the potential for serious side effects.

Allergen-specific immunotherapy for the treatment of allergic rhinitis

SIT is considered as the only curative treatment for allergic rhinitis as long as its prerequisites are fulfilled: a small number of sensitizations, and administration of adequate doses of standardized allergens [42,45^{••}]. The effectiveness of SIT for the treatment of SAR has been confirmed in several studies with grass, ragweed and

birch pollen sensitized patients. Moreover, SIT was successful even in patients with severe SAR, where conventional drug therapy had failed [46]. In contrast, treatment of patients with perennial rhinitis by SIT is less effective, possibly reflecting the fact that causes other than allergy add to this disease [47]. This shows once more that a clear selection of patients with proven allergen-mediated disease is a prerequisite for treatment with SIT.

One of the main differences between SIT and symptomatic therapy is that the beneficial effects of SIT can be observed even years after discontinuation of treatment [48,49[•]]. In addition, SIT may prevent the occurrence of new sensitizations [50,51^{••}]. Furthermore, it was established that SIT is able to prevent the extension of upper airway disease to the lower airways [51^{••}].

Allergen-specific immunotherapy for the treatment of other allergic diseases

SIT with insect venom preparations is very effective in decreasing the risk for severe anaphylactic reactions after insect stings, providing fast protection for venom allergic patients. Especially in the up-dosing phase or during rush and ultra-rush SIT protocols, the risk of severe side effects by the delivery of specific venom allergen is considerable. Therefore, additional antiallergic medication such as anti-IgE antibodies may greatly facilitate increasing the allergen dose or the pace of the protocol.

Anti-IgE in combination with allergen-specific immunotherapy (phase III study in children with seasonal allergic rhinitis)

Since anti-IgE reduces the serum concentration of IgE and thereby reduces IgE-mediated reactions, it was hypothesized that concomitant treatment with anti-IgE and SIT could improve the risk/benefit ratio of SIT in polysensitized patients during consecutive pollen seasons, therefore proving to be clinically superior to treatment with SIT alone. A randomized, double-blind, parallel-group, multi-center study in children with SAR was initiated to investigate whether combined therapy with SIT and anti-IgE is superior to single treatment [52^{••}]. A total of 221 patients (6–17 years) with moderate to severe SAR and sensitization to birch and grass pollen were started on SIT-birch (two groups) or SIT-grass (two groups) for at least 14 weeks prior to the start of the birch pollen season. After SIT titration (12 weeks), placebo or anti-IgE was added for 24 weeks to either one of the two groups of the respective SIT arms. When analyzed separately by season, the two groups receiving unrelated SIT were considered as placebo controls. Anti-IgE was administered subcutaneously at 2 or 4-week intervals at a dose equivalent to a minimum of 0.016 mg/kg/IU IgE/ml serum in 4

weeks. Combination therapy of anti-IgE and SIT reduced symptom load (sum of mean daily symptom severity score plus mean daily rescue medication use) over the entire pollen seasons (birch and grass) by 48% compared with SIT alone ($P < 0.001$). Reduction was highly significant for both analyses: SIT-birch + anti-IgE versus SIT-birch + placebo and SIT-grass + anti-IgE versus SIT-grass + placebo (Fig. 6).

Differentiating the two components adding to symptom load revealed that rescue medication reduction was a major contributing factor to the observed improvements. Over both pollen seasons, addition of omalizumab resulted in a reduction in the median rescue medication score of about 80% compared with the two SIT groups. Oral corticosteroids, the last rescue medication to be used, was reported by 15 patients receiving SIT + placebo compared with five patients on SIT + anti-IgE. Symptom severity, the second component of symptom load, was significantly reduced by the anti-IgE and SIT combination in the separate groups. Moreover, the decline in serum IgE levels accomplished by anti-IgE treatment correlated with the decreased leukotriene release after in-vitro stimulation of mast cells with allergen [53•].

Thus the results strongly support the primary hypothesis that combined treatment with SIT and anti-IgE is more effective than SIT alone. Patients receiving anti-IgE required almost no additional rhinitis medication.

Conclusion

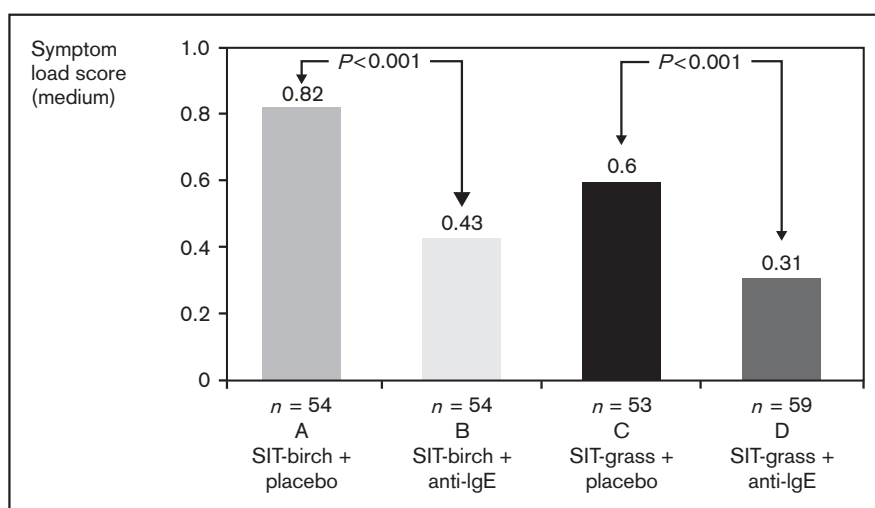
Anti-IgE therapy and SIT are two powerful and effective yet very different approaches for the treatment of allergic

diseases. Anti-IgE is one of the first of several new immunological methods for antiallergic therapy with a disease-specific approach. Targeting IgE is aimed at the common and most distinct phenotype obvious in all patients suffering from allergic diseases: increased IgE serum levels. Anti-IgE therapy is a very sensible approach as many studies demonstrate a pivotal role for IgE in the development of bronchial asthma and other allergic diseases [2,54]. Indeed, the findings of clinical phase II and III trials showed that anti-IgE is an effective therapy for pediatric and adult patients with allergic rhinitis and moderate to severe allergic asthma: it successfully reduces serum IgE levels and allergen-related symptoms, increases QOL of rhinitis patients, reduces frequency of asthma exacerbations, and reduces the requirements for steroid medication in both groups of patients. Importantly, it was found to be safe and well tolerated.

These considerable benefits of anti-IgE therapy are counterbalanced by some disadvantages. Anti-IgE is not a curative approach since it does not aim to inhibit the induction phase of an allergic immune reaction or to induce allergen-specific (immune) tolerance. Therefore, treatment with anti-IgE has to be repeated or sustained whenever allergen-mediated responses may be elicited, for example during the pollen season or prior to consumption of food allergens. Moreover, anti-IgE targets just one of many mediators released during an allergen-mediated immune cascade, therefore missing many pathways that are independent of IgE. In support of this, experimental data from mouse models demonstrated that development of allergen-mediated airway disease may occur independently of B cells [55], IgE

Figure 6. Symptom load

Symptom load (sum of symptom score + rescue medication score) during entire pollen season (birch and grass) after treatment with allergen-specific immunotherapy with birch (SIT-birch) or grass allergen (SIT-grass) combined with anti-IgE or placebo. Reproduced from Kuehr *et al.* [52••] with permission.



production [55,56] or IgE-mediated mast-cell activation [57], and that treatment with anti-IgE antibodies was ineffective once a robust inflammatory response had been established [58].

In comparison, SIT is a truly immune modulating approach aiming to cure an allergic disease by implementing allergen-specific (clinical) tolerance. This courageous venture is limited by several facts: SIT is restricted to a very thorough diagnosis clearly identifying a responsible allergen and to the availability of highly purified or recombinant allergens; SIT, of course, is allergen specific, and thus may not be appropriate for many of the polysensitized patients; and, most importantly, SIT bears the risk of severe anaphylactic side effects with sometimes fatal consequences, limiting its application especially for asthmatic patients.

For these reasons, a combination of SIT and anti-IgE therapy may be a very successful treatment option for the future. Anti-IgE antibodies are not allergen specific and thus may add to the beneficial effects of SIT, a very significant improvement for the often multisensitized SAR patients, who suffer for long pollen seasons and frequently experience comorbidity of the lower airways. Thus, treatment with anti-IgE antibodies may help to prevent the 'allergic march', the development of allergen-mediated airway diseases such as bronchial asthma, in patients with predisposing SAR. Effective control of SAR thus may provide preventive or therapeutic treatment of concomitant respiratory diseases. Simultaneous treatment with anti-IgE and SIT will definitely lower the risks of severe allergen-mediated side effects, allowing a broader application as well as more rapid dosing and higher allergen doses for SIT.

Future trials need to examine the efficacy of combination therapy with anti-IgE and SIT in comparison with standard medication for treatment of several allergic diseases. Furthermore, cost/benefit analysis of the advantages of the addition of anti-IgE needs to be performed. New areas of potential indications for this combination have to be investigated, especially those in which IgE plays a major role in the development of the disease. Food allergies in infancy require expensive diets, insect venom-allergic patients are at risk of anaphylactic reactions, and pediatric asthma is often associated with high (allergen-specific) IgE serum levels. In such cases, a combination of anti-IgE therapy with SIT may be a very valuable and even cost-reducing treatment protocol with a curative approach and limited risk. Future trials need to delineate the optimal target group of patients that may ideally benefit from anti-IgE plus SIT therapy.

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