

26 | Anti-IgE Therapy

Eckard Hamelmann and Ulrich Wahn

Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany

INTRODUCTION

Despite the advanced and increasing understanding of the pathophysiology of asthma and other allergic diseases, current treatment remains nonspecific and targets late events within the allergic cascade [e.g., antihistamines, β_2 agonists, topical and systemic corticosteroids (SCS), and chromones] (1). Although the majority of asthmatic patients are sufficiently treated with standard medication, a subpopulation of asthmatics remains who still suffer from the disease despite optimal drug treatment according to guidelines or encounter severe side effects from medication with high-dose inhaled and/or oral steroids. New treatment options are therefore required that target the pathophysiological cascade of allergen-mediated airway disease earlier and in a more *specific* way (2,3). Because of the pivotal role of IgE for the development and severity of allergic diseases, antagonizing or inhibiting IgE by anti-IgE antibodies provides a novel and promising approach to treat allergic asthma (4,5).

THE RATIONALE FOR TREATING ALLERGIC ASTHMA WITH ANTI-IG E

Role of IgE in Allergic Asthma

Binding of IgE to high-affinity (Fc ϵ RI) receptors on effector cells, such as mast cells and basophils, and subsequent exposure to allergen initiates a cascade resulting in release of proinflammatory mediators that contribute to the acute and chronic symptoms of allergic airway diseases (6).

The IgE molecule is comprised of fragments known as Fab (antigen-binding fragment) and Fc (crystallizable fragment) (Fig. 1). The Fab region binds to specific components (or epitopes) of the allergen, whereas the Fc region binds to Fc ϵ RI receptors present on mast cells and circulating basophils. Fc ϵ RI receptors consist of four polypeptide chains, $\alpha\beta\gamma_2$. The α chain binds to five amino acids (330–335) of the $\epsilon\epsilon_3$ domain of the Fc segment of IgE to orientate the IgE molecule so that it lies on its side with the allergen-binding site facing outward (Fig. 2) (6).

Binding of allergen to two or more membrane-bound IgE molecules results in receptor clustering, and through interactions involving the α and β chains, sets into motion intracellular biochemical events that trigger mast-cell or basophil activation (6). This activation releases a variety of preformed and newly generated proinflammatory mediators and cytokines, including histamine, interleukins, leukotrienes, and prostaglandins (type-I hypersensitivity reaction), and the release of IL-4, IL-13 (increasing IgE synthesis), and IL-5 (increasing eosinophil accumulation) that contribute to the chronic inflammatory response (Fig. 3). Eosinophilia is a well-recognized feature of inflammation in asthma and reflects asthma severity and the risk of exacerbations (7,8).

IgE upregulates the expression of Fc ϵ RI on mast cells and basophils (9). This results in mast-cell stimulation and mediator release at lower concentrations of allergen, and/or in the release of increased amounts of mediators and cytokines for a given level of stimulus (10). IgE also binds to Fc ϵ RI receptors on dendritic cells and enhances allergen uptake and presentation to T cells (11), leading to increased T-cell proliferation and eosinophil differentiation and activation.

The risk of developing asthma increases with increasing levels of serum IgE (12). However, asthma severity is poorly associated with total IgE levels (13). The association between specific IgE and asthma severity is currently under investigation. Fc ϵ RI receptors are upregulated on eosinophils, mast cells, macrophages, and dendritic cells in patients with rhinitis (14) and allergic asthma (15). In addition, a significant correlation has been observed between serum IgE levels and Fc ϵ RI expression on precursor dendritic cells (pDCs) from

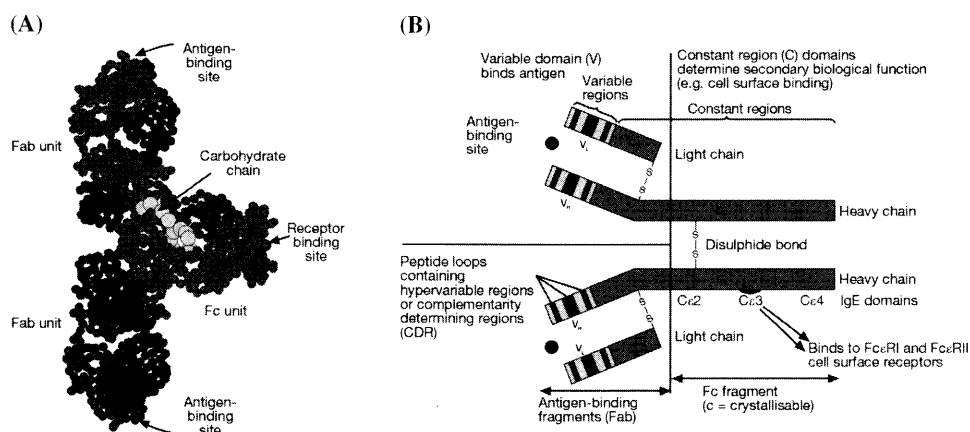


Figure 1 Molecular structure and schematic diagram of IgE.

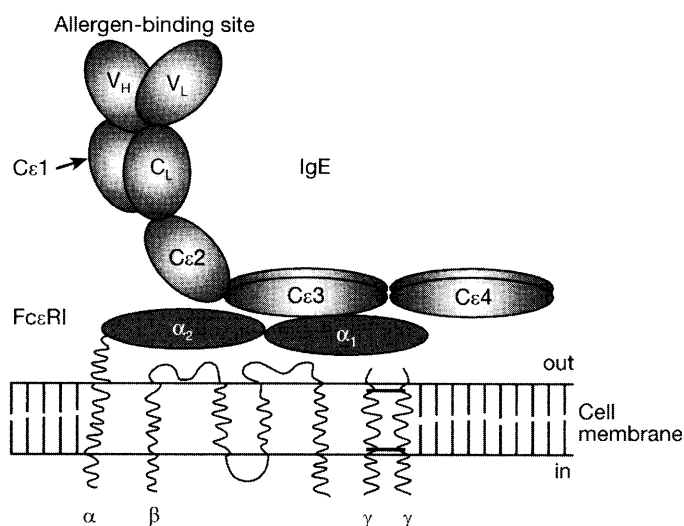


Figure 2 Binding of IgE to the high-affinity (FcεRI) receptor.

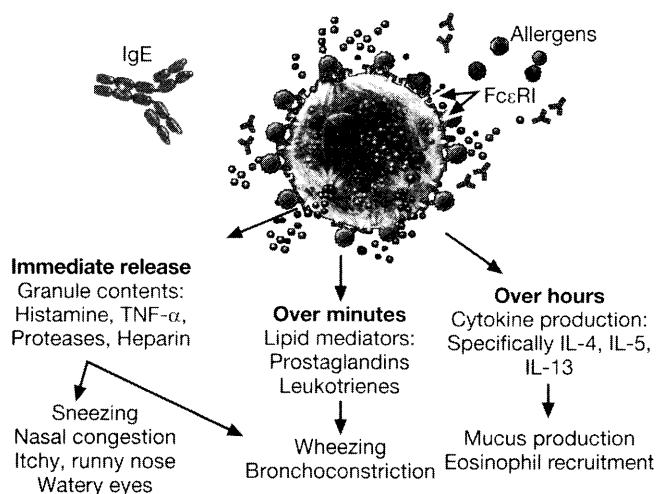


Figure 3 IgE-dependent release of inflammatory mediators.

subjects with allergic asthma (16). A possible relationship between FcεRI expression and fatal asthma has also been reported (17). This latter study examined postmortem human lung tissue and found that cases of fatal asthma were associated with higher levels of FcεRI+ cells within the lamina propria compared with subjects who died of other causes or with biopsy tissue from patients with mild asthma.

Targeting of IgE

Omalizumab (Xolair[®]) is a recombinant, humanized monoclonal antibody directly targeting IgE. Omalizumab reduces free IgE by approximately 95% by binding to the cε3 region on free IgE (Fig. 2), thereby blocking the binding of IgE to its specific high-affinity receptor. Importantly, anti-IgE treatment reduces the expression of FcεRI receptors on basophils as shown in subjects with perennial allergic rhinitis (PAR) and with positive skin test to dust mite (18,19). Basophil receptor density measurements were taken prior to treatment and three months after treatment initiation. With omalizumab treatment, basophil FcεRI density decreased by approximately 97% ($p = 0.0022$) (18). Reflecting the reduction in receptor density, the responsiveness of the basophils to challenge with dust mite antigen (*Dermatophagoides farinae*) decreased by approximately 90% ($p = 0.0022$) (18). During the period following discontinuation of omalizumab treatment, basophil FcεRI receptors were upregulated, concurrent with a gradual rise of serum-free IgE levels (to 16% of pretreatment levels over an 8-week period) (19). However, a more rapid rise in antigen-triggered histamine release responses by the cells implies a reduction of the threshold for basophil activation. Thus, the effects of omalizumab treatment on mast cells and basophils are achieved through a combination of (i) reduced free IgE levels and (ii) IgE receptor downregulation leading to the inhibition of IgE-mediated proinflammatory mediator release. This dual effect of omalizumab is important, since otherwise complete removal of free IgE would be necessary to elicit functional consequences on mast cells and basophils (18,19).

Omalizumab significantly reduces submucosal IgE+ and FcεRI+ cells in patients with allergic asthma. The effect of omalizumab on the number of cells expressing IgE or FcεRI was assessed in a placebo-controlled study in 45 patients with corticosteroid-naïve, mild-to-moderate asthma (20). Treatment with omalizumab for 16 weeks significantly reduced IgE+ cells in the bronchial submucosa compared with baseline or placebo (both $p < 0.001$). Similarly, treatment with omalizumab for 16 weeks significantly reduced FcεRI+ cells in the bronchial submucosa compared with baseline or placebo (both $p < 0.001$). As mentioned previously, a close correlation has also been observed between serum IgE levels and FcεRI expression on pDCs from subjects with allergic asthma (16). The effect of omalizumab on FcεRI receptor expression on pDC subtypes pDC1 and pDC2 (these subtypes promote the T cell to shift toward the Th1 and Th2 phenotype, respectively) has been assessed in a randomized, double-blind, placebo-controlled study in patients with seasonal allergic rhinitis (SAR) (21). Omalizumab significantly reduced FcεRI expression ($p \leq 0.002$) from day 7 onward for both pDC1 and pDC2 cells, indicating that omalizumab causes a rapid decrease in FcεRIα surface expression by DCs. By downregulating FcεRI expression on DCs, omalizumab may inhibit antigen processing and presentation to T cells.

The depletion of IgE in airway tissue is associated with a marked reduction in airway eosinophils (20). Omalizumab significantly reduces eosinophil numbers in airway tissue and induced sputum in patients with mild or moderate allergic asthma (20). Omalizumab treatment reduced the percentage of inflammatory cells in the sputum that were identified as eosinophils (4.8% at baseline, 0.6% posttreatment, $p < 0.001$; $p = 0.05$ vs. placebo). The reduction in sputum eosinophil counts with omalizumab treatment was mirrored by a significant decrease in the numbers of eosinophils in both the epithelial and submucosal compartments.

The effects of omalizumab at a cellular level are reflected in clinical observations on patients with asthma. Omalizumab inhibited the early-phase and late-phase asthmatic responses to inhaled allergens as demonstrated in bronchial challenge tests (22,23). Assessed as the mean maximal fall in forced expiratory volume in 1 second (FEV₁), omalizumab reduced the early asthmatic response by 85% ($p = 0.01$) and the late asthmatic response by 65% ($p = 0.047$) compared with placebo in 18 patients with mild allergic asthma (22).

As omalizumab binds to the cε3 site (third domain of the constant region) on free IgE, the same site that binds to the FcεRI receptor (Fig. 2), omalizumab cannot interact with IgE molecules bound to FcεRI receptors on basophils and mast cells and does not activate effector

cells by receptor cross-linking (23). Omalizumab is therefore expected not to cause anaphylaxis in clinical use.

ANTI-IgE FOR TREATMENT OF ALLERGIC DISEASES

Drug Profile

The main *characteristics* of anti-IgE are therefore (24) that it

1. inhibits the binding of IgE to the high-affinity receptor, FcεRI;
2. recognizes and binds free but not complexed IgE, and not IgM, IgG, and IgA;
3. forms complexes with free IgE in serum;
4. is not specific regarding the allergen specificity of the target IgE antibody, meaning that it binds to any IgE molecule;
5. does not bind to IgE already bound to mast cells or basophils, meaning that it does not cause degranulation ("non-anaphylactic antibody");
6. blocks mast cell or basophil degranulation following passive sensitization in vitro or challenge with allergen in vivo;
7. decreases FcεRI expression on immune effector cells.

Clinical Pharmacology

The binding of anti-IgE to IgE results in the formation of small (~1000 kDa), nonprecipitating and non-complement-activating immune complexes (25) that are no longer able to bind IgE receptors. Anti-IgE concentrations were highest in the serum compartment and no specific organ deposition was observed. The immune complexes were eliminated by urinary excretion.

The decrease of IgE serum levels follows a dose-dependent response within five minutes after intravenous administration and within 24 hours after subcutaneous injections as seen in studies with single- and multidose studies in adults with and without allergic disease (26,27). The decrease of IgE lasted, depending on the antibody dose, for about four to six weeks after a single injection with anti-IgE (28). Further, anti-IgE was well tolerated in all of these trials.

The most effective route of administration was studied in a large phase II study in adults with SAR (29). Treatment via SC versus IV route at different dosages (0.15-mg/kg body weight SC, 0.15 mg/kg IV, or 0.5 mg/kg IV, 7 injections within 84 days) was compared. Pharmacodynamics between the SC and IV routes of administration did not differ. Anti-IgE decreased serum IgE levels in a dose- and baseline IgE-dependent fashion. However, not all routes of administration were similarly effective. Fahy et al. (30) studied the effects after aerosolized application of anti-IgE in patients with mild allergic asthma and did not find significant suppression of serum IgE levels and nor effects on the early asthmatic response to allergen, despite detectable levels of anti-IgE.

Since the reduction of free IgE below 25 IU/mL is a prerequisite for efficacy and for practical and safety reasons, 375 mg of omalizumab every two weeks is considered to be the maximum applicable SC dose at present. Higher dosages of omalizumab have not been studied so there is no advice concerning safety and efficacy. Therefore, a treatment of patients with total IgE levels above 400 to 1300 IU/mL, depending on the body weight, is not recommended.

Safety and Tolerability

The safety and tolerability profile of omalizumab was evaluated in an analysis of data from completed phase I, II, and III studies involving more than 7500 adult and adolescent patients with asthma, rhinitis, or related conditions (31). More than 5300 of these patients received omalizumab, including 3700 with moderate-to-severe persistent asthma. In all controlled studies, adverse events (AEs) were reported in 74.8% of patients receiving omalizumab and in 75.2% of control group patients. Serious AEs were reported by 4.2% of patients receiving omalizumab and by 3.8% of control group patients. AEs were generally of mild-to-moderate severity and of short duration. Severe AEs occurred more frequently in the control group than in the omalizumab group (omalizumab 10.8%, control 12.6%). In placebo-controlled-allergic asthma studies, the overall incidence of suspected drug-related AEs was similar in the omalizumab and placebo groups (omalizumab 9.2%, placebo 7.6%). Postlaunch data in the

United States with approximately 40,000 patients are consistent with safety results obtained from omalizumab clinical trials. The most significant, serious AE is anaphylaxis or anaphylaxis-like reactions, which occur in 0.1% to 0.2% of treated subjects. Despite the infrequent occurrence of this event, the FDA recommended in 2007 a boxed warning on the label devoted to anaphylaxis. A numerical increase in malignancy in omalizumab-treated subjects is being investigated in an ongoing, long-term trial.

Anti-IgE for Treatment of Asthma

Treatment of asthma has substantially improved over the last decades. Inhaled corticosteroids (ICS) are the standard anti-inflammatory medication and normally effectively control symptoms of mild-to-moderate asthma. Some patients, however, remain symptomatic even with persistent ICS treatment, or even require systemic steroids to control the disease. In this patient group, the efficacy and safety profile of omalizumab has been extensively investigated in a series of clinical studies. Of particular interest is the INvestigationN of Omalizumab in seVere Asthma TrEatment (INNOVATE) study (32) since it assessed, in a 28-week randomized, placebo-controlled trial, the efficacy of omalizumab in patients with inadequately controlled, severe persistent allergic asthma despite high-dose ICS plus long-acting β_2 agonist (LABA). Efficacy was further analyzed in pooled data (33) from seven clinical trials with omalizumab carried out in patients with moderate-to-severe or severe asthma (32,34–41). Five of these seven studies were randomized, double-blind, placebo-controlled trials in which patients received omalizumab or placebo. Two studies were randomized and controlled but open label.

The INNOVATE Study

Patients included in the INNOVATE study (32) represented the asthma population with the most severe disease and the highest unmet medical need. All patients were receiving high-dose ICS [>1000 $\mu\text{g/day}$ beclomethasone dipropionate (BDP) equivalent] plus a LABA with requirements for additional controller medication in approximately 60%, including maintenance, oral corticosteroids in 22% of patients. Sixty-seven percent of the patients were considered to be at high risk of asthma-related death; quality of life (QoL) was profoundly restricted by an average of 31 missed school/work days due to asthma in the year prior to the treatment protocol. The primary endpoint was the incidence and frequency of exacerbations with one secondary outcome parameter of improvement in QoL.

Adding omalizumab to high-dose ICS plus a LABA significantly reduced the rate of clinically significant exacerbations, defined as asthma worsening requiring treatment with SCS, by 26% versus add-on placebo (adjusted post hoc for an observed imbalance in exacerbation history (0.68 vs. 0.91, $p = 0.042$)) (Fig. 4) (unadjusted result: 19% reduction (0.74 vs. 0.92, $p = 0.153$)). Even more importantly, omalizumab significantly reduced the severe exacerbation rate by 50% versus placebo (0.24 vs. 0.48, $p = 0.002$) (Fig. 4), translating into

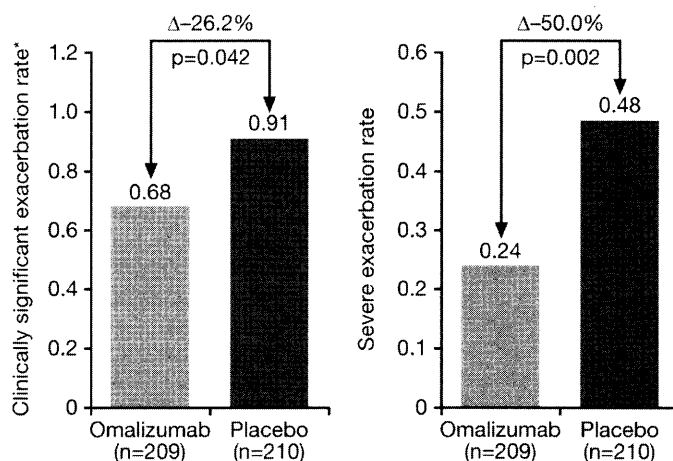


Figure 4 Effect of omalizumab on clinically significant and severe exacerbations. (*) Indicates adjustment due to a pre-study imbalance in exacerbation rate; -19.4% ($p = 0.153$) reduction unadjusted. Source: Adapted from Ref. 32.

reduced emergency visit rate by 44% versus placebo (0.24 vs. 0.43, $p = 0.038$). The number needed to treat (NNT) with omalizumab in addition to Global Initiative for Asthma (GINA) step 4 therapy to prevent one event above placebo per year was 2.2 for clinically significant exacerbations, 2.2 for severe exacerbations, and 2.8 for total emergency visits (32).

Clinically meaningful, add-on omalizumab treatment also provided significant QoL improvements for patients with changes in Asthma Quality of Life Questionnaire (AQLQ) baseline scores of 0.91 in the omalizumab group compared with 0.46 in the placebo group ($p < 0.001$). Improvements were achieved in significantly more patients taking omalizumab compared with placebo (60.8% vs. 47.8%, $p = 0.008$), measured across the domains of activity limitations, asthma symptoms, emotional function, and environmental exposure.

Pooled Analysis

Efficacy of treatment with omalizumab was further assessed in an analysis of pooled data from seven clinical trials (including INNOVATE) (33) comprising a total of 4308 patients, with 2511 patients receiving omalizumab and 93% of patients with severe persistent asthma (GINA 4). Five of these studies were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies and included large patient groups with moderate-to-severe asthma and requirements for daily ICS therapy. The protocol for these five studies was similar, consisting of four phases with (i) a run-in period of 4 weeks to stabilize disease while on therapy with BDP, (ii) a stable phase with no change in corticosteroid therapy for 16 weeks, (iii) a corticosteroid-withdrawal phase with tapering of corticosteroid dosages by 25% every 2 weeks for 8 weeks, and (iv) an extension period with stable, lowest tolerated dose of BDP and continuation of placebo or anti-IgE therapy for 5 months beyond the first 28 weeks. Omalizumab was administered SC at a dose of 0.016 mg/kg body weight/IU total serum IgE, once every four weeks or every two weeks, depending on dose, starting after the run-in period.

Adding omalizumab to current asthma therapy in the larger pooled population from all seven studies consistently supported the findings seen in the INNOVATE study: add-on omalizumab significantly reduced asthma exacerbation rates by 38.3% versus placebo (0.91 vs. 1.47, $p < 0.0001$) (Table 1), and total emergency visits were significantly less frequent (by 47% vs. control, 0.332 vs. 0.623, $p < 0.0001$). Accordingly, hospital admission rates were reduced by 51% ($p = 0.041$), emergency room visits by 60% ($p = 0.013$), and unscheduled doctor visits by 43% ($p = 0.0003$).

QoL was measured in six clinical trials, with 1221 patients receiving omalizumab and 1032 receiving placebo or control medication across the six studies (42). Omalizumab consistently improved QoL, resulting in significantly greater improvements in AQLQ overall score compared with placebo/control (AQLQ overall score: 1.01 vs. 0.61, $p < 0.001$). The proportion of patients recording a clinically meaningful improvement in AQLQ overall score of ≥ 0.5 point was significantly higher in the omalizumab group compared with placebo/control (66.3% omalizumab vs. 52.4% placebo/control, $p < 0.001$).

Table 1 Effect of Omalizumab Vs. Placebo on Asthma Exacerbation Rates

Study	Difference in annual exacerbation rate	Reduction vs. control/placebo (%)	Significance (p value)
INNOVATE study (32)	0.49	26.6	0.042 ^a
ETOPA study (34)	1.49	60.4	<0.001
SOLAR study (38)	0.29	37.5	0.027
Busse study (37)	0.40	40.3	<0.001
Solèr study (34)	0.70	57.6	<0.001
Holgate study (39)	0.42	26.5	0.165
ALTO study (41)	0.18	15.3	0.077
Pooled (33)	0.56	38.3	<0.0001

Pooled analysis.

^aAdjusted for an observed relevant imbalance in pre-study history of clinically significant asthma exacerbations between the omalizumab (0.68/yr) versus placebo (0.91/yr) group.

Source: From Ref. 30.

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Anti-IgE for Treatment of Allergic Rhinitis

Beside studies on asthmatic patients, safety and efficacy of treatment with anti-IgE was evaluated in clinical trials on patients with seasonal and PAR.

Anti-IgE for Treatment of SAR

The first large-scale (240 adults), double-blind, placebo-controlled, multicenter phase II trial was performed to assess optimal dosing regimens and test the efficacy of anti-IgE for the treatment of ragweed-induced SAR (29). Omalizumab decreased serum IgE levels in a dose- and baseline IgE-dependent fashion, and specific IgE levels correlated significantly with symptom scores. Only patients with IgE levels below detection level (<25 IU/mL) on treatment with omalizumab experienced a marked reduction of symptoms. However, the average symptom score before and during the peak of the season was small (before season 0.6, during season 0.91 in placebo, and 0.7–0.8 in anti-IgE groups, n.s.), making the study less capable of proving a difference with treatment even if one existed. The use of rescue medication was similar between the groups, suggesting that omalizumab had relatively little effect. Furthermore, neither overall specific skin test reactivity was altered over the course of the study nor did the scores of QoL estimations differ. The one exception of a change in specific IgE was the high-dose anti-IgE group, which showed a marginally significant increase in average, endpoint titration allergen concentration.

The results of the previous study (29) warranted further evaluations of the efficacy of anti-IgE therapy in SAR, utilizing higher anti-IgE doses in a second randomized, double-blind, placebo-controlled, multicenter phase III study involving 251 adults (17–66 years), with moderate-to-severe SAR to birch pollen (history ≥ 2 years, positive specific skin test, baseline serum IgE 30–700 IU/mL) (43). Twenty-one percent of actively treated patients reported complete control of symptoms (vs. 2% of placebo treated), 59% reported some improvement (vs. 35%), and only 2% experienced worsening (vs. 13%) (43). Average daily nasal symptom severity scores did not change during the course of the study in the anti-IgE group (0.71 at baseline vs. 0.70 total average during study), but increased in the placebo group during the pollen season (0.78 vs. 0.98, $p < 0.001$). Similarly, ocular symptom severity scores decreased in anti-IgE-treated patients (0.47–0.43), but increased in the placebo group (0.43–0.54), resulting in a significant difference between the groups ($p = 0.031$). Importantly, the average use of rescue medication was significantly lower in the anti-IgE group compared with the placebo group (0.59 vs. 1.37 tablets/day, $p < 0.001$), and the proportion of days on which no SAR medication was required was almost twice as high (49% vs. 28%, $p < 0.001$). Statistically significant differences in favor of anti-IgE were similarly observed for estimation of QoL. The rather limited effect of anti-IgE treatment may be explained by an unexpected early pollen season during that specific year of the trial in Scandinavia, which resulted in the beginning of anti-IgE treatment less than one week in advance of the first pollen exposure in more than 50% of all patients. Conclusively, this study confirmed that anti-IgE was safe and effective in controlling birch pollen-induced SAR compared with placebo, reducing use of rescue medication and improving QoL.

Anti-IgE for Treatment of PAR

An additional study investigated the efficacy of anti-IgE on mean daily nasal severity scores in 289 adults and adolescents with moderate-to-severe symptomatic PAR in a 16-week, double-blind subcutaneous treatment [at least 0.016 mg/kg/IgE (IU/mL) per 4 weeks] (44). The mean daily nasal severity score was significantly lower in anti-IgE-treated patients than with placebo ($p < 0.001$) and was paralleled by a reduction in use of rescue antihistamine ($p \leq 0.005$ overall) and improved QoL of patients.

Anti-IgE for Treatment of SAR in Combination with SCIT

Subcutaneous allergen immunotherapy (SCIT) is the only curative treatment for SAR and allergic asthma, and beneficial effects can be observed even years after discontinuation (45,46). Especially in children, administration of SCIT may prevent the development of lower airway disease or asthma in subjects with upper airway disease or rhinitis. Application of SCIT, however, is limited by the number of allergens that can be administered per injection, the lack

of standardized vaccines for all important allergens, and the limited ability to determine the optimal dose (47). In addition to these limitations, SCIT carries the rare risk of serious side effects, such as anaphylactic reactions (5.4 severe events per million injections) and even death (1 per 2.5 million injections). Since anti-IgE reduces the serum concentration of IgE and thereby reduces IgE-mediated reactions, it was hypothesized that concomitant treatment of anti-IgE and SCIT may improve the risk-benefit ratio of SCIT in polysensitized patients during the consecutive pollen seasons and thereby may prove clinically superior to treatment with SCIT alone.

Anti-IgE Plus SCIT for Treatment of SAR in Children and Adolescents

A randomized, double-blind, parallel-group, multicenter phase III study in children with SAR investigated whether combined therapy with SCIT and anti-IgE is superior to single treatment alone (48). Two hundred and twenty-one patients (6–17 years) with moderate-to-severe SAR and sensitization to birch and grass pollen were started on SCIT-birch (2 groups) or SCIT-grass (2 groups) for 14 weeks prior to start of the birch pollen season. After SCIT titration (12 weeks), placebo or anti-IgE was added for 24 weeks to one of the two groups of the respective SCIT arms. When analyzed separately by season, the two groups receiving unrelated SCIT (i.e., birch-SCIT for grass season and grass-SCIT for birch season, respectively) were considered as placebo controls. Anti-IgE was administered SC at two- or four-week intervals at a dose equivalent to a minimum of 0.016 mg/kg/IU IgE/mL serum in four weeks. Primary endpoint was symptom load, the sum of mean daily symptom severity score plus mean daily rescue medication use.

Combination therapy of anti-IgE and SCIT 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 SCIT alone ($p < 0.001$). Reduction of symptom load due to combination therapy was highly significant in allergen seasons, birch and grass, when compared with the SCIT alone (Fig. 5).

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 reduction of the median rescue medication score of about 80% compared with the two SCIT groups. Oral Corticosteroids (OCS) as the last rescue medication to be used was reported by 15 patients receiving SCIT + placebo compared with five patients on SCIT + anti-IgE. Symptom severity, the second component of symptom load, was significantly reduced by the combination of anti-IgE with SCIT in the separate groups. Moreover, experimental support for the clinical benefit was provided by the relationship of serum IgE and in vitro mediator release. The decline of serum IgE levels accomplished by anti-IgE treatment correlated with the decreased leukotriene release after in vitro stimulation of mast cells with allergen (49).

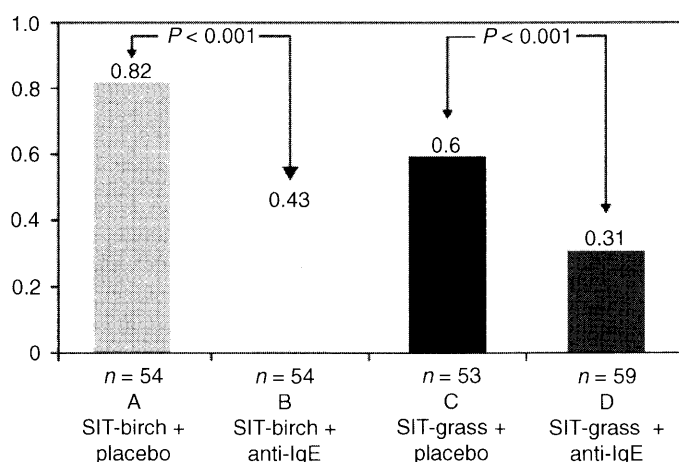


Figure 5 Treatment with allergen-specific immunotherapy with birch (SIT-birch) or grass (SIT-grass) allergen combined with omalizumab reduces symptom load (sum of symptom score + rescue medication score) during entire pollen season (birch and grass). Source: Adapted from Ref. 48.

Anti-IgE Plus Rush-SCIT for Treatment of SAR in Adults

Rush immunotherapy (rush SCIT) is a method of accelerated desensitization with aeroallergens and offers an attractive alternative since it potentially provides better compliance, faster response, and lower costs compared with conventional SCIT. However, rush SCIT is accompanied with a higher risk of systemic anaphylactic reactions due to IgE-mediated type-I hypersensitivity reactions (50). In a 2006 trial, the outcomes in safety and efficacy of the combination of rush SCIT and anti-IgE for SAR were analyzed (51). Patients with ragweed-induced SAR were included in a three-center, double-blind, placebo-controlled phase III trial. The objective was to examine whether omalizumab, given 9 weeks before and 12 weeks together with rush-SCIT, increases safety and efficacy compared with SCIT alone. A total of 159 patients between the ages of 18 and 50 years, with a minimum two-year history of ragweed SAR and no recent immunotherapy, were randomized into four treatment groups: (i) rush SCIT + anti-IgE, (ii) placebo-rush SCIT + anti-IgE, (iii) rush SCIT + placebo anti-IgE, and (iv) placebo-rush SCIT + placebo anti-IgE.

The number, scope, and severity of AEs associated with rush SCIT were highest in those patients receiving rush SCIT with placebo anti-IgE, a fivefold increase in the risk to develop AE compared with placebo SCIT ($p = 0.001$). Only small differences in AEs were noted between study groups receiving omalizumab plus rush SCIT (33.3%), omalizumab plus placebo-rush SCIT (29.7%), or placebo omalizumab plus placebo-rush SCIT (18.9%). AE increased in a dose response in correlation with the total amount of allergen administered. The percentages of patients with severe adverse events (SAE) during rush SCIT were 2.6 for omalizumab plus rush SCIT, 0 for omalizumab only, and 15.0 for rush SCIT only, compared with 5.0 for placebo-only group. Patients receiving omalizumab in combination with rush-SCIT showed a significant improvement in severity scores during the ragweed season compared with patients on rush-SCIT alone (0.69 vs. 0.86, $p = 0.044$).

In summary, treatment with omalizumab prior to and during rush SCIT offers substantial protection from serious IgE-mediated allergic reactions due to SCIT. The data of the discussed studies show that omalizumab treatment results in safer and more effective use of SCIT, even with accelerated treatment programs.

Anti-IgE for Treatment of Food Allergy

The potent anti-allergic effect of anti-IgE therapy has also been demonstrated in adult patients with food allergy (52). In this study, the threshold amount of peanut leading to allergic symptoms after oral intake was significantly increased after injection of anti-IgE antibody, showing the significant consequences of a treatment directly targeting IgE-mediated immediate type of hypersensitivity reactions.

CONCLUSION

Current pharmacotherapy of bronchial asthma decreases airway inflammation and provides symptomatic relief of bronchoconstriction, but does not specifically target the underlying disease. It is sufficient for the majority of adult and pediatric patients, but not for a subpopulation of patients still suffering severe symptoms or restrictions of QoL with traditional medical regimens. For this group of patients, additional strategies for treatment are needed. The enhanced understanding of the mechanisms underlying the development of allergic diseases, such as asthma, has prompted the development of several novel strategies toward an immunological approach of therapy. These tend not to act as nonspecific anti-inflammatory drugs reducing the ongoing allergic response, but rather to reduce the development of allergic diseases by a specific approach in the allergic inflammatory response. The first line of these immune-modulating regimens have now passed initial evaluations in clinical trials, and the results are not always in favor of the new compounds (53,54). The conclusion one may draw from these first studies is that the clinical situation of asthma in humans is clearly more complex than the experimental situation in animal models (55,56). Simply targeting one single cellular or molecular mediator or pathway may not be adequate to effectively interfere with the complex and redundant inflammatory processes involved in the development of human asthma (57).

The only novel approach for therapy of asthma that went beyond trial status and was accepted for clinical treatment of severe (Europe) or moderate-to-severe (United States) allergic asthma is omalizumab, Xolair. Targeting IgE aims at the common and most distinct phenotype evident in all patients suffering from allergic diseases: increased IgE serum levels. Although atopy may be a coincident rather than a causal factor in the pathogenesis of asthma, there is a significant body of evidence demonstrating a pivotal role of IgE in the development of bronchial asthma and allergic airway disease. Even in patients with apparently nonallergic asthma and normal IgE serum levels, production of IgE in the airways has been found (58). On the other hand, experimental data from murine models demonstrates that development of airway inflammation and hyperreactivity to nonspecific stimuli may occur independent of B cells (59), IgE production (59,60), or IgE-mediated mast-cell activation (61). In these models of allergen-mediated inflammatory response of the airways without B-cell activation, treatment with anti-IgE antibodies is not likely to affect the development of airway inflammation or Airway Hyperresponsiveness (AHR) (62). The human equivalent could be asthma without a significant allergic component, and anti-IgE antibody therapy would likely be less effective even with airway inflammation, eosinophilia, and possibly increased total IgE.

The pooled analysis of seven large-scaled clinical *phase III* trials with omalizumab in patients with bronchial asthma showed that it is effective for patients with symptomatic, moderate-to-severe allergic asthma (33). Similarly, a meta-analysis of eight studies listed in the Cochrane Airways Group Asthma trials register and contributing a total of 2037 mild-to-severe allergic asthmatic participants underscored the efficacy of omalizumab for treatment of allergic asthma (63,64) (the latter being the more recent update). Herein, significant increases in the number of participants who were able to reduce or completely withdraw their daily steroid intake were observed (Table 2). Importantly, this benefit was also shown for patients with severe asthma, suggesting effects by anti-IgE beyond mere reduction of steroid requirements. Finally, omalizumab is safe and well tolerated and improved QoL in all studies observing this parameter (42). Although some of the improvements in symptom scores, exacerbation rates, and lung function data during the course of the trials were also seen in the placebo-treated group, presumably demonstrating the benefits of continuous physician monitoring, the differences between omalizumab and placebo treatment group reached significance for almost all important endpoints in favor of anti-IgE.

A major limitation for a broader use of anti-IgE is the high cost-benefit ratio that by far exceeds that of present standard asthma medication (ICS plus LABA), which provide good asthma control for the majority of patients. Therefore, omalizumab was launched for treatment of adults and children with corticosteroid-dependent or corticosteroid-resistant asthma who require high doses of oral or inhaled steroids and who still have poor asthma control. In such patients, analysis of the direct and indirect costs related to frequent exacerbations and hospitalization may validate the higher costs of anti-IgE therapy. Finally, future trials ideally should better delineate predictors to better define "responders" versus "nonresponders" for anti-IgE therapy. This will ultimately help identify the target group of asthmatic patients and, subsequently, candidates among patients suffering from other allergic diseases who will offer the lowest cost-benefit ratio for anti-IgE therapy.

Table 2 Efficacy of Omalizumab Vs. Placebo for Treatment of Patients with Allergic Asthma with ICS Therapy

Outcomes	No. of trials	No. of participants	Steroid phase	Odds ratio (95% CI)
No. of participants with exacerbation	4	1634	Steroid reduction	0.47 0.37–0.60
No. of participants with at least one exacerbation	4	1651	Stable steroid intake	0.49 0.38–0.64
Complete steroid withdrawal	4	1634	Steroid reduction	2.50 2.00–3.13
≥50% Reduction in steroid usage	4	1634	Steroid reduction	2.50 2.02–3.10

Results of the Cochrane analysis.

Abbreviation: ICS, inhaled corticosteroids.

Source: From Ref. 65.

SALIENT POINTS

- Increased production of IgE is a cardinal feature of allergic diseases and asthma.
- IgE-mediated activation of mast cells is a key element of the early asthmatic reaction and significantly contributes to airway inflammation and airway hyperreactivity.
- Targeting of IgE is an effective anti-allergic approach for treatment of asthma and other allergic diseases since it directly addresses a key element in the pathophysiology.
- Anti-IgE (omalizumab, Xolair) is the first approved "biological" therapy available for treatment of severe allergic asthma.
- Several phase III and phase IV omalizumab clinical trials on subjects with moderate-to-severe asthma show significant reduction of exacerbation rates and corticosteroid therapy and improvement in QoL versus placebo.
- Clinical trials with omalizumab for treatment of other allergic diseases, such as seasonal or PAR or food allergy, are promising and warrant further investigation.

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