

Anti-IgE Therapy in Allergic Asthma

Claudia Rolinck-Werninghaus, Ulrich Wahn and Eckard Hamelmann*

Department of Paediatric Pneumology and Immunology, Charité, Campus Virchow, University Children's Hospital, Humboldt-University, Augustenburger Platz 1, D-13353 Berlin, Germany

Abstract: Despite the advanced and increasing understanding of the pathophysiology of asthma and other allergic diseases, current treatment remains unspecific and targets late events within the allergic cascade. Therefore, a novel and promising approach to treat allergic asthma is antagonizing IgE by anti-IgE antibodies. This review analyzes the role of IgE for the pathology of asthma, summarize the current data about action, safety and efficacy of anti-IgE therapy, and tries to give a rational approach for future indications and directions of treatment with anti-IgE antibodies.

Keywords: Asthma, atopy, allergic rhinitis, anti-IgE, monoclonal antibody, treatment.

INTRODUCTION

Despite the advanced and increasing understanding of the pathophysiology of asthma and other allergic diseases, current treatment remains unspecific and targets late events within the allergic cascade (e.g. antihistamines, beta-2-agonists, topical and systemic corticosteroids, and chromones) [1]. Although the majority of asthmatic patients are sufficiently treated with standard medication, a subpopulation of asthmatics remains that still suffer from the disease despite optimal drug treatment according to

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]. In the following review, we (i) analyze the role of IgE for the pathology of asthma, (ii) summarize the current data about action, safety and efficacy of anti-IgE therapy, and (iii) try to give a rational approach for future indications and directions of treatment with anti-IgE antibodies.

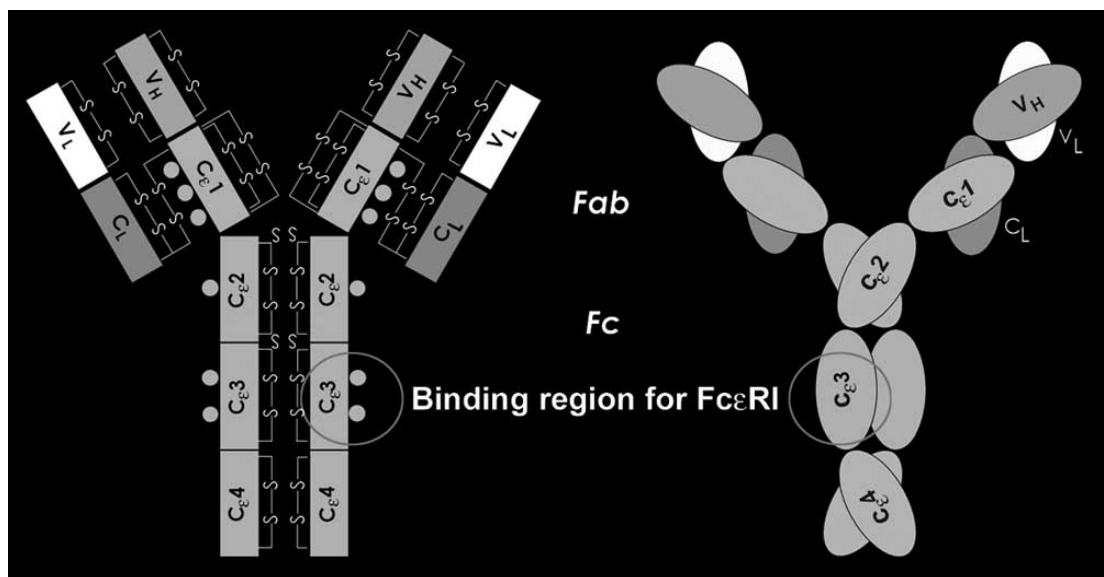


Fig. (1.1). IgE polypeptide structure.

official 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

1. The Role of IgE in Allergic Asthma

1.1 History

Increased production of specific IgE is the main and pathognomonic feature of allergic diseases. The term "allergy" was originally introduced by von Pirquet in 1906 describing "changed reactivity" of a host after the second or subsequent contact with an "agent". The clinical features of this nowadays immunologically defined hypersensitivity reaction comprise asthma, hay fever, urticaria and eczema, and were originally termed "atopy" by Coca and Cooke in

*Address correspondence to this author at the Department of Paediatric Pneumology and Immunology, Charité, Campus Virchow, University Children's Hospital, Humboldt-University, Augustenburger Platz 1, D-13353 Berlin, Germany; Tel: +49-30-450 566 182; Fax: +49-30-450 566 931; E-mail: eckard.hamelmann@charite.de

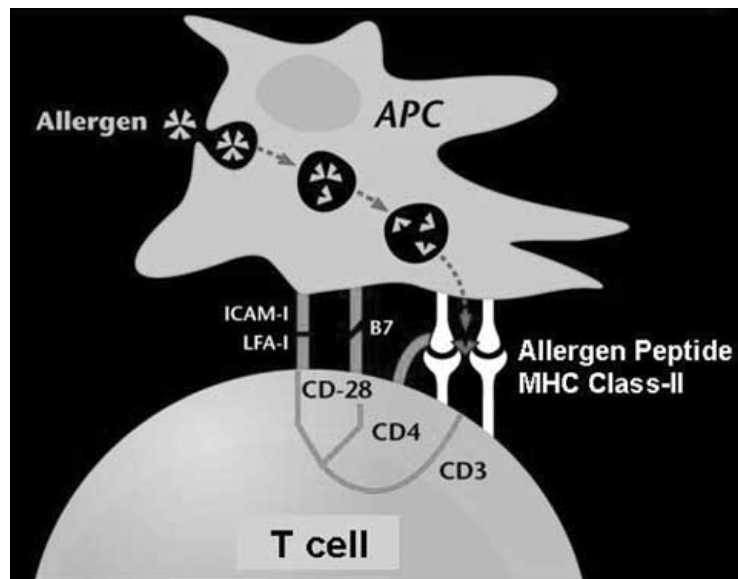


Fig. (1.2). Antigen presentation.

1923 [6]. The first suggestion of a soluble and thus transferable factor as the mediator of a hypersensitivity reaction was reported in 1919 by Ramirez [7]. Here, he describes a case of a man who experienced an acute asthmatic attack while entering a horse-drawn coach in New York's Central Park two weeks after having received a 600 ml blood transfusion from a man with a known horse allergy. Two years later, Prausnitz and Küster gave the first scientific explanation of the mechanism leading to such an allergic reaction, by showing that a serum factor (which they termed "reagin") was able to passively transfer hypersensitivity reactions from an allergic to the skin of a non-allergic patient [8]. It took another forty-five years before Ishizaka and colleagues [9, 10] and Johansson and colleagues [11] independently from each other demonstrated that this "reagin" was a novel class of serum antibodies – immunoglobulin-E: IgE [12]. And another thirty-five years later, we hold in our hands a novel therapeutic option for

treatment of asthma and other allergic diseases: anti-IgE antibodies.

1.2 Structure and Function of IgE

IgE, similar to other immunoglobulins, is comprised of two heavy and two light chains (Fig. 1.1). It is produced by allergen-specific plasma cells after isotype switch to the epsilon-chain. IgE-production is mainly under the control of T cells and T-cell cytokines) [13, 14]. As for most antigens, the initiation of allergen-induced adaptive immune reaction starts with the up-take and processing of the allergen by professional antigen presenting cells (APC) (Fig. 1.2). In the case of allergic immune reactions, naive T cells develop towards the so-called Th2-type, defined by the predominant production of Th2-cytokines, especially IL-4, IL-5 and IL-13 [15]. The TH-2 type cytokine profile is a prerequisite for differentiation of B cells to IgE-producing plasma cells, which requires two distinct signals, the first provided by IL-

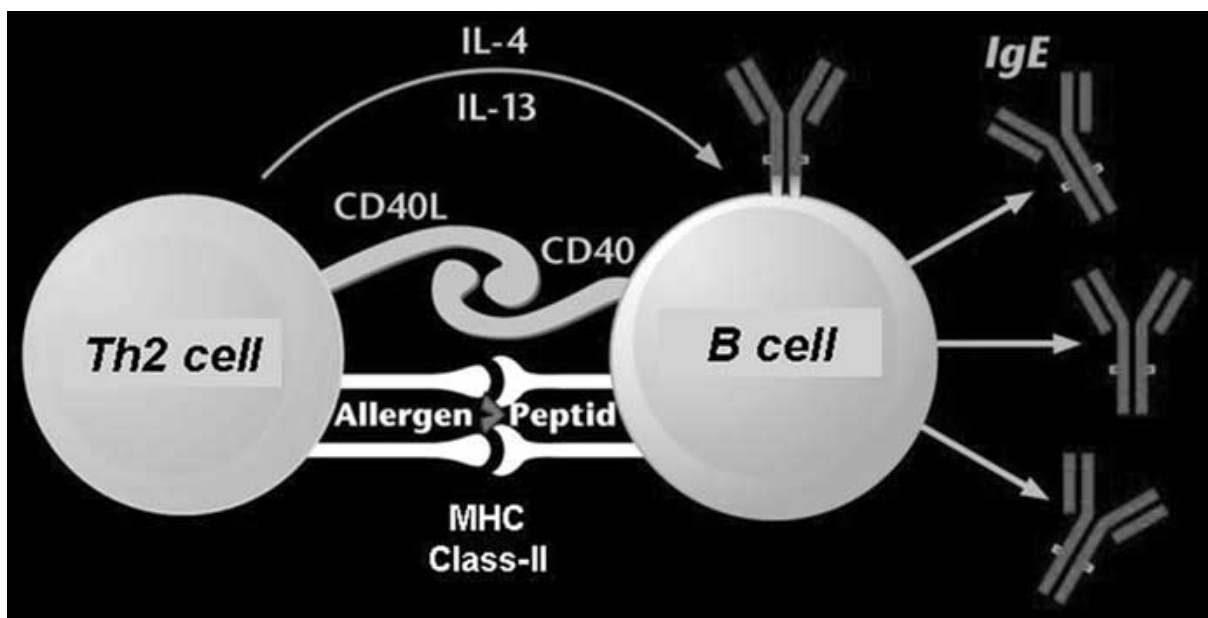


Fig. (1.3). T-B cell co-operation.

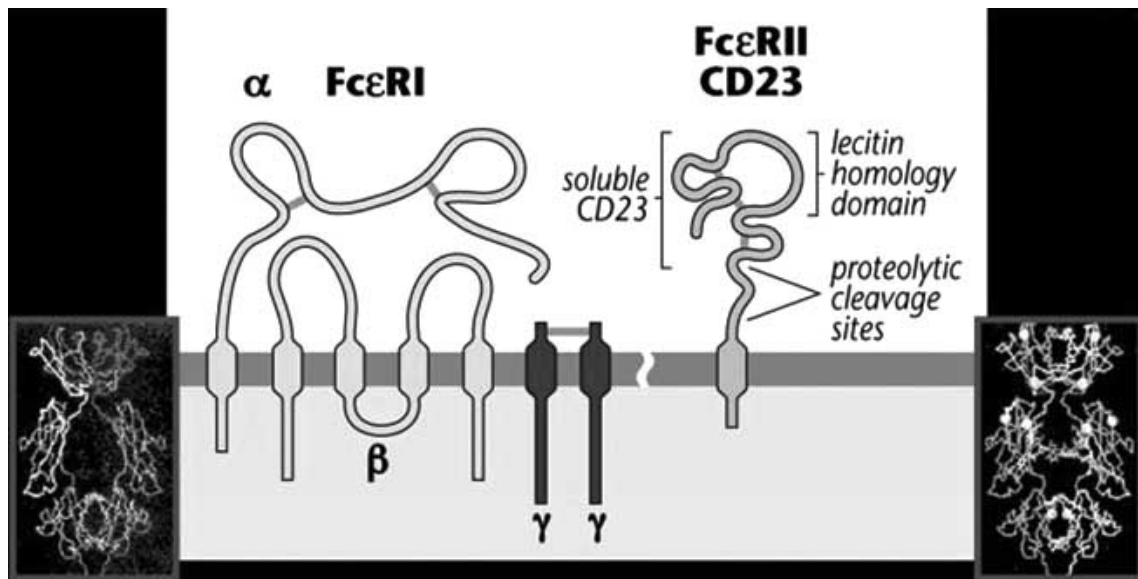


Fig. (1.4). High- and low-affinity receptors for binding of IgE.

4 and IL-13 [16-18], the second by interaction between the co-stimulatory antigen CD40 on the surface of B cells with CD40-ligand on T-cell surfaces [19, 20] (Fig. 1.3).

Biological activities of IgE are mediated through specific receptors, of which the high-affinity receptor (FcεRI) is mainly expressed on mast cells and basophils [21, 22], the low-affinity receptor (FcεRII, CD23) is expressed on B cells [23, 24] (Fig. 1.4). Whereas free serum IgE has a very short half-life of about two and a half days, mast cells remain sensitised for up to 12 weeks following binding of IgE to high-affinity receptors.

Re-exposure of sensitised patients with allergen leads to binding of specific allergen to IgE-FcεRI complexes on mast cells (Fig. 1.5). This activates the allergic cascade characteristic for the early IgE-mediated reaction [25, 26]. The cross-linking of receptors immediately triggers the release and production of pre-formed and newly synthesised mediators, such as leukotrienes, prostaglandins, cytokines

and chemokines (Fig. 1.6). These pro-inflammatory mediators cause, depending on the site of allergen exposure, immediate type of hypersensitivity reactions such as airway smooth muscle contraction, mucus hyper secretion, and mucosal oedema of upper or lower airways (early asthmatic reaction). The finding that human mast cells, after IgE-mediated activation, produce a wide range of cytokines [27, 28], suggests that IgE may contribute to subsequent inflammatory reaction such as airway eosinophilia and airway remodelling associated with the late asthmatic reaction (Fig. 1.7).

1.3 IgE and Allergic Asthma

There is good evidence for a strong relationship between IgE production and development and severity of allergic asthma. Two recent epidemiological studies by the same group suggest a close correlation between IgE serum levels and presence or severity of asthma [29, 30]. Especially childhood asthma is mainly found in atopic patients who are

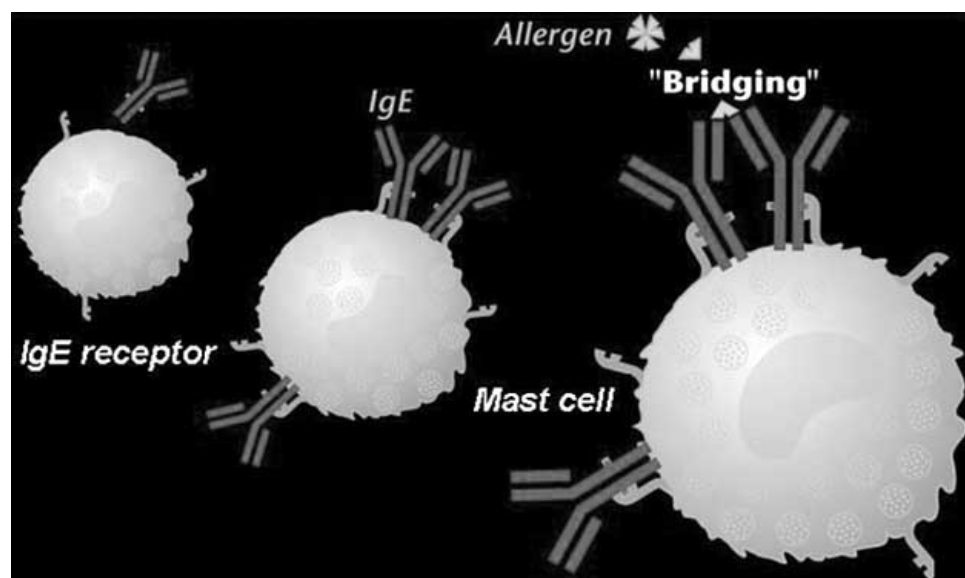


Fig. (1.5). IgE-binding to mast cells.

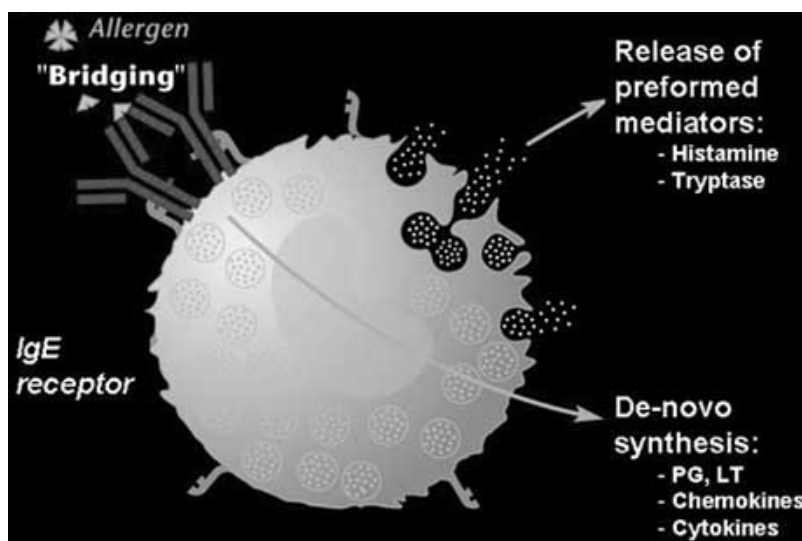


Fig. (1.6). Degranulation of mast cells.

sensitised to common environmental allergens, such as house dust mites, tree and grass pollens [31, 32]. Similar, persistent wheezing and early sensitisation are both associated with high total IgE serum levels in children at all age [32]. Moreover, increased levels of total IgE have been shown to be associated with prevalence rates for asthma even in non-atopic subjects that do not produce specific IgE to common allergens [30]. This may underscore the findings that many non-specific factors such as infections and air pollutants are able to stimulate polyclonal IgE production [33]. In contrast to the allergic asthmatics, patients with non-allergic asthma, representing about 50% of adult and 20-30% of childhood patients, have negative skin tests to common allergens and normal total IgE serum levels. Although these patients tend to have a more severe type of airway disease, they clearly show signs of a very similar inflammatory airway response as observed in patients with allergic asthma [34]. Interestingly, in patients of the non-allergic group, a significant local IgE production in the airways has recently been described [35], indicating that IgE

may also play a role in asthma pathogenesis for this subgroup of patients [36]. The association with increased IgE serum levels and disease severity found in bronchial asthma is also obvious for other allergic diseases such as seasonal allergic rhinitis (SAR), insect venom allergy or food allergies. Based on these findings it was postulated that antagonizing IgE with a blocking antibody theoretically provides an effective and novel tool for treatment of allergic diseases.

2. Anti-IgE for Treatment of Allergic Diseases

2.1 Drug Profile

Anti-IgE antibody is a recombined humanized monoclonal antibody specific against the binding site of IgE for its high affinity receptor (FcεRI) [37]. This binding site is located within the third domain of the heavy chain (Cε3; Fig. 1.1) [38]. In the development, a murine antibody, MAE1, has been generated, which recognised the residues in

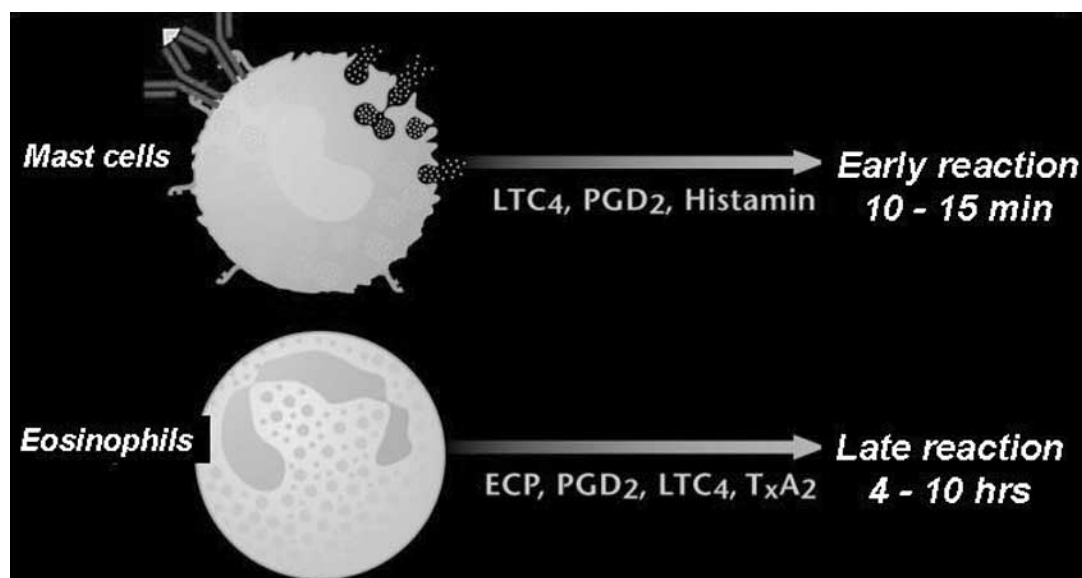


Fig. (1.7). IgE-mediated immune reaction in allergic asthma.

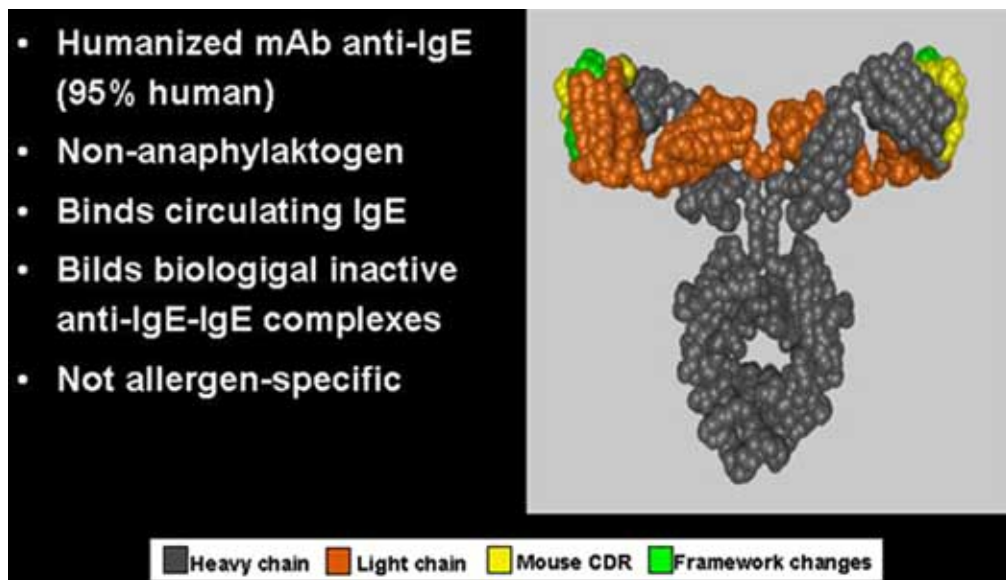


Fig. (2.1). Anti-IgE antibody.

the Cε3 domain of IgE responsible for binding to FcεRI [39]. Subsequently, this murine antibody was converted into the humanised version, containing 95% of a human IgG1 antibody and only 5% of the murine IgE-specific epitope, in order to avoid sensitisation with foreign proteins (E25, Omalizumab). The drug is now commercially available and was named Xolair® (Fig. 2.1) [40].

The main *characteristics* of anti-IgE are that it:

- i) inhibits the binding of IgE to the high-affinity receptor, FcεRI;
- ii) recognizes and binds free but not complexed IgE, and not IgM, IgG and IgA;
- iii) forms complexes with free IgE in serum;
- iv) is unspecific regarding the allergen-specificity of the target IgE antibody; meaning that it binds to any IgE molecule;

- v) does not bind to IgE already bound to mast-cells or basophils, meaning that it does not cause degranulation ("non-anaphylactic antibody");
- vi) blocks mast cell degranulation following passive sensitisation *in vitro* or challenge with allergen *in vivo* (Fig. 2.2);
- vii) decreases FcεRI expression on immune effector cells.

2.2 Clinical Pharmacology

Preclinical and phase I studies were conducted to investigate safety and efficacy of anti-IgE. In summary, the data showed that anti-IgE is a safe and well tolerated drug that can effectively reduce serum IgE levels. All reported side-effects were in the range of placebo, and no antibody formation against anti-IgE antibodies was detected.

The binding of anti-IgE to IgE results in the formation of small (~1000 kDa), non-precipitating and non-complement-activating immune complexes [41]. These are no longer able

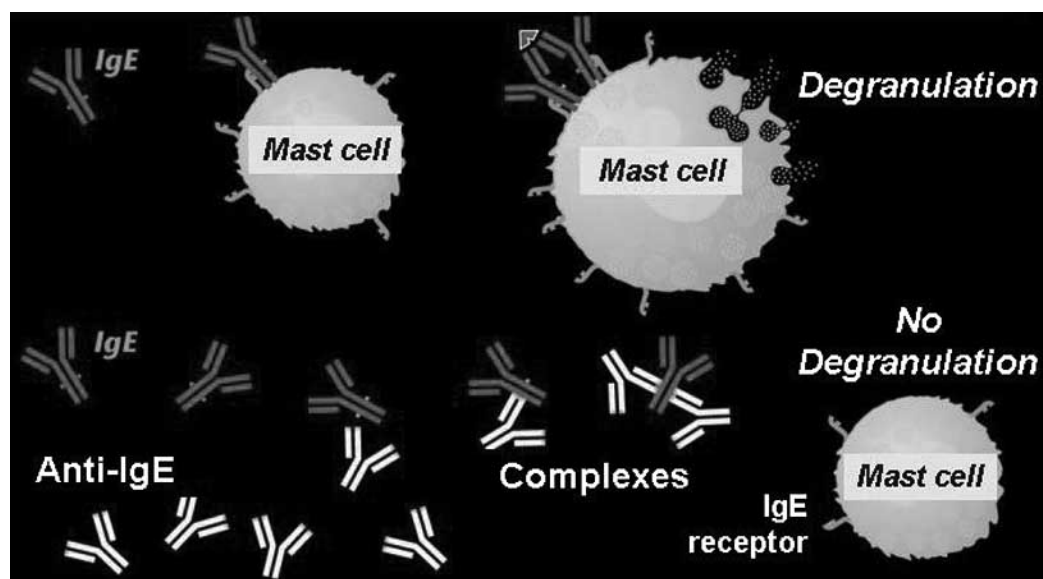


Fig. (2.2). Inhibits IgE-mediated immune reactions.

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 [41]. In addition to the reduction of circulating IgE, treatment with anti-IgE also suppresses IgE-receptor expression on basophils *in vitro* [42] and *in vivo* [43] and further also on dendritic cells *in vivo* [44], supporting that IgE receptor expression is regulated by and associated with IgE serum levels.

The decrease of IgE serum levels follows a dose-dependent manner as soon as 5 min after intravenous application and within 24 hrs after subcutaneous injections as seen in studies with single- and multi-dose studies in adults with and without allergic disease [45, 46]. The decrease of IgE lasted, depending on the antibody dose, for about 4-6 weeks after a single injection with anti-IgE [47]. Further, anti-IgE was well tolerated in all of these trials.

The most effective route of application was studied in a large *phase II* study in adults with SAR [47]. Treatment *via* sc versus iv route at different dosages (0.15 mg/kg bodyweight 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 (Fig. 2.3). However, not all routes of administration were similar effective. Fahy et al studied the effects after aerosolised application of anti-IgE in patients with mild allergic asthma and did not find significant suppression of serum IgE levels and no, despite detectable levels of anti-IgE, effects on the early asthmatic response to allergen [48].

Since the reduction of free IgE below 25 IU/mL is a prerequisite for efficacy (refer to Fig. 2.4 [47]), and for practical and safety reasons, 375 mg of Omalizumab every 2 weeks is considered to be the maximum applicable s.c. dose at present. Therefore, a treatment of patients with total IgE levels above 400 to 1300 IU/mL, depending on the body weight, does not seem feasible.

2.3 Anti-IgE and Asthma

Treatment of asthma has substantially improved over the last decades. Inhaled steroids (ICS) are the standard anti-inflammatory medication and normally effectively control symptoms of mild to moderate asthma. Some patients, however, remain symptomatic even under persistent treatment with ICS, or even require systemic steroids to control the disease. Anti-IgE is therefore a possible candidate for add-on therapy for this group of patients. Results of the clinical studies are discussed in this chapter.

2.3.1 Effects of Anti-IgE on Early- and Late-Phase Allergic Responses

Two studies demonstrated that intravenous or subcutaneous administration of anti-IgE is able to reduce early- and late-phase allergic responses after bronchial challenge with in patients with asthma [49, 50]. In randomised, double-blind, placebo-controlled, parallel-group studies 11 [49] and 19 [50] adults with mild asthma were investigated, respectively. Anti-IgE was administered intravenously at a dose of 2 mg/kg bodyweight on day 0 and at a dose of 1 mg/kg on days 7, 14, 28, 42, 56, and 70. The provocative dose of inhaled allergen needed to cause a 15% fall in FEV1 (PC15) after bronchial allergen challenge was measured as primary endpoint. IgE serum levels and the early allergic response were significantly reduced by anti-IgE treatment, as demonstrated by a significant smaller reduction in FEV1 and a significant increase in median allergen PC15 after allergen challenge on days 27, 55, and 77 [49]. For the late-phase response to allergen, assessed 2 to 7 hours after allergen provocation a similar effect was observed [50]. Interestingly, the rise in sputum eosinophils following allergen challenge, an inflammatory reaction linked to the development of the late asthmatic response was also significantly reduced by anti-IgE treatment. Unspecific hyperresponsiveness, asthma symptom score and overall lung function did not improve after treatment with anti-IgE compared to placebo.

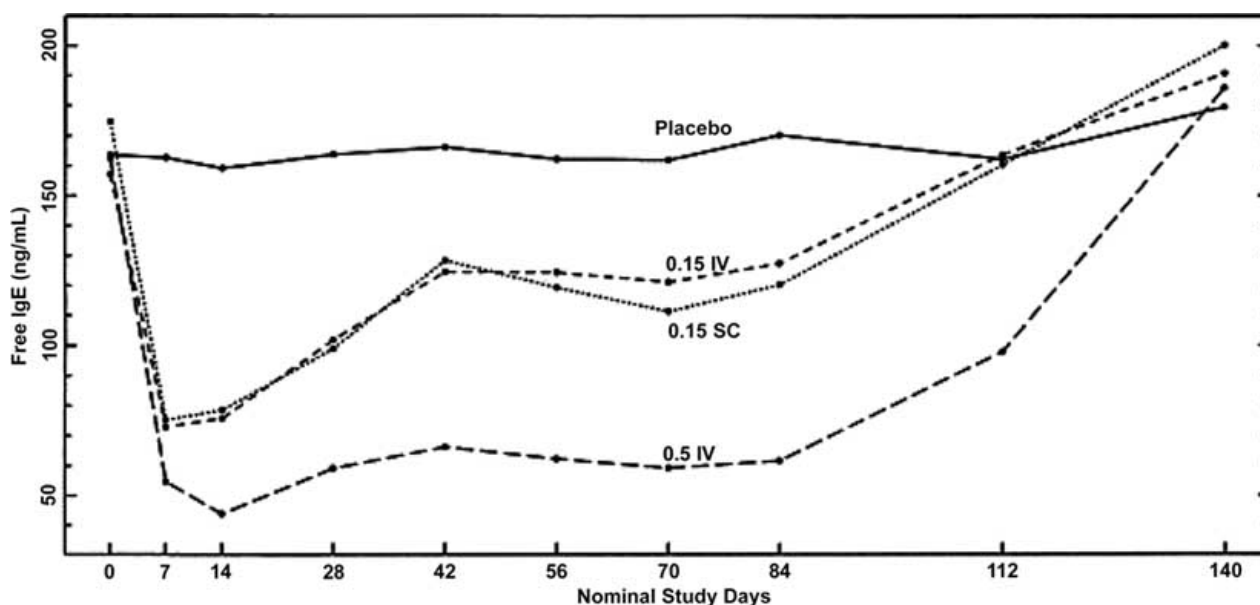


Fig. (2.3). Intravenous or subcutaneous application of anti-IgE reduces free IgE serum levels in a dose-dependant manner [47].

2.3.2 Effects of Anti-IgE on Asthma Symptom Scores

The promising results of the early studies had to be confirmed in a large-scale study investigating the efficacy of anti-IgE in the treatment of asthma. Dosing was adapted to individual body weight and serum IgE levels to ensure a constant ratio of IgE to anti-IgE antibody [51].

The study was designed as a multicenter, randomised, double-blind, parallel-group, placebo-controlled study and 317 adolescent and adult patients (11-50, mean 30 yrs) with moderate to severe persistent allergic asthma and requirement for daily inhaled or oral ($n=35$) steroids were included. Anti-IgE treatment was given iv at a dose of 2.5 (low dose) or 5.8 (high dose) $\mu\text{g/kg}$ bodyweight/ng serum IgE on days 0 and 4 (half dose) and on day 7 and in biweekly intervals for 20 weeks (full dose). Stable steroid medication for first 12 weeks was applied, and then steroid dosages tapered during last 8 weeks. As primary outcome asthma symptom scores (daily symptom diary, max. score 7) were recorded. Secondary outcomes were steroid/ beta-2-agonist use, lung function parameters (PEF, FEV1), and the number of asthma exacerbations. 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. The proportion of patients at 12 weeks with at least a 50% reduction in asthma symptom scores was significantly higher following both verum treatment regimen with either the low or high dose of anti-IgE than after placebo (49% and 47% vs. 24%, $p<0.001$). The mean reduction of symptom scores from the mean baseline score 4.0 for all patients was significantly higher in both the low- (2.8) and the high dose (2.8) anti-IgE group, compared to placebo (3.1), although patients in the placebo also enhanced during the course of the study [51].

The requirements for inhaled or oral steroids were reduced in patients treated with anti-IgE: 78% of patients receiving the high dose ($p=0.04$) and 57% of the low dose group ($p=0.23$, n.s.) had at least a 50% reduction in overall steroids after 20 weeks, compared to 33% of patients receiving placebo. The decrease in oral or inhaled steroid

medications was associated with a decrease of beta-2-agonist use by 1.8 puffs/ day in the high-dose anti-IgE group ($p = 0.02$) and by 1.2 puffs/day in the low-dose anti-IgE group ($p = 0.24$) compared with 0.8 puff/day in the placebo group [51].

Morning PEF at 12 weeks increased with anti-IgE treatment compared to placebo (low-dose, 18.6 L/min, $p = 0.10$; high-dose, 30.7 L/min, $p = 0.001$; placebo, 11.3 L/min). Similarly, at the end of the study PEF was improved by anti-IgE compared to placebo (low-dose 20.8 L/min, $p = 0.046$; high-dose, 29.9 L/min, $p = 0.02$; placebo, 10.2 L/min). FEV1 improvements were statistically not significant (low-dose, +2.1%, $p = 0.49$; high-dose, +1.9%, $p = 0.81$; placebo, +1.0%) [51].

During the 20-week study period, 28% of patients in the low-dose anti-IgE group ($p = 0.01$) and 30% of patients in the high-dose anti-IgE group ($p = 0.03$) reported asthma exacerbations, compared with 45% of patients receiving placebo, even though steroid use was reduced to a higher degree in the anti-IgE groups.

In summary, this study showed that anti-IgE improved asthma symptoms, reduced exacerbation rates and allowed to reduce oral or inhaled steroid medications without requirement for increased rescue medication. Improvements by anti-IgE therapy were modest, but significantly better than in the placebo group, and occurred despite reductions in steroid and beta-2 agonist therapy. Safety and tolerability of anti-IgE antibodies were without complains.

2.3.3 Effects of Anti-IgE on Asthma Exacerbation

To evaluate the efficacy of anti-IgE in the treatment of asthma, three identically designed (Fig. 2.4) large-scale *phase III* studies were performed: protocol 008 in the U.S. [52], protocol 009 in EU, US, South Africa and Australia [53], and protocol 010 in asthmatic children in the US [54]. In contrast to the *phase II* study [51], anti-IgE was administered subcutaneously rather than intravenously and only once every four weeks for patients with low and intermediate IgE baseline serum levels. Primary endpoints

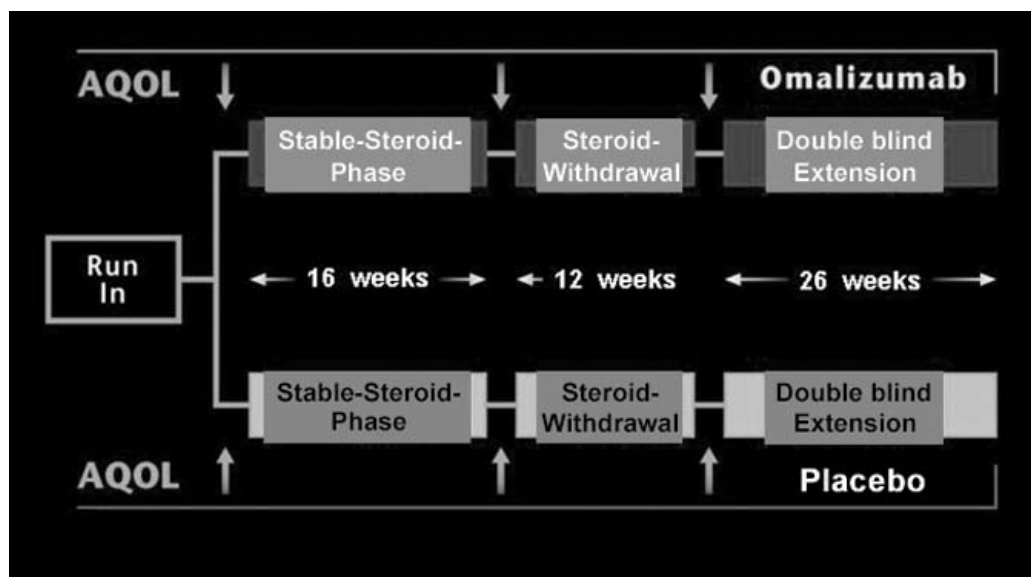


Fig. (2.4). Study design for phase III trials with anti-IgE for treatment of asthma [78-80].

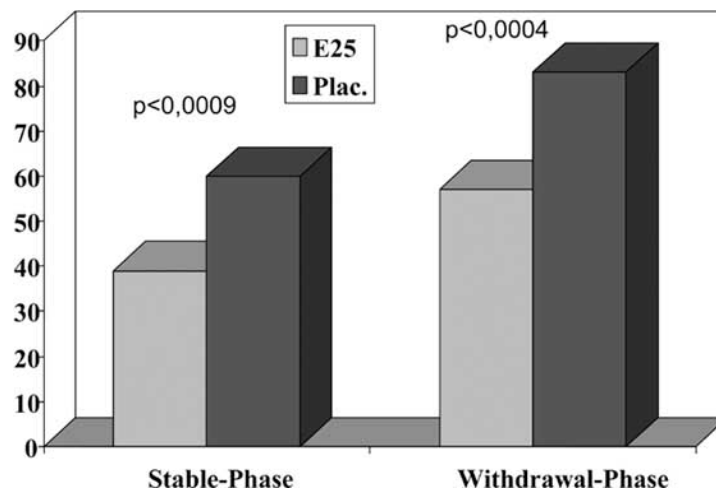


Fig. (2.5). Percentage of patients suffering from exacerbations during stable-steroid and steroid-withdrawal phases and treatment with anti-IgE [derived from 51].

now were the incidence and frequency of exacerbations (PEF <50% of personal best, >50% increase in beta-2-agonist use, FEV1 >20% below baseline). Secondary outcome parameters were symptom scores, FEV1, PEF, and beta-2-agonist use.

All studies were multicenter, randomised, double-blind, parallel-group, placebo-controlled studies and included large patient groups: 523 (protocol 008) and 546 (protocol 009)

adolescent and adult patients (12-75, mean 40 yrs) with moderate to severe asthma and requirements for daily ICS therapy and 334 children (protocol 010) (5-12, mean 9 yrs) with moderate to severe asthma and stable disease with daily ICS. Each protocol had four phases (Fig. 2.4): i) a run-in period of 4 weeks to stabilise disease while on therapy with beclomethasone (BDP) (adult patients had to be

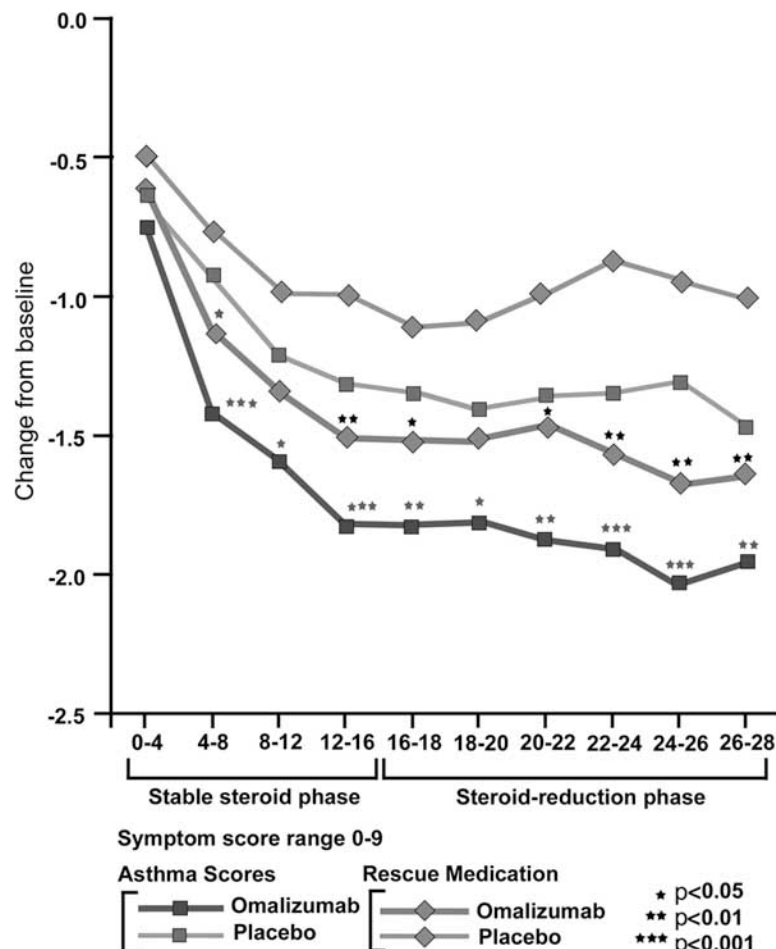


Fig. (2.6). Symptom scores and rescue medication use during stable steroid and steroid-withdrawal phases of anti-IgE therapy [52].

symptomatic), ii) a stable-phase with stable steroid medication for 16 weeks, iii) a steroid-withdrawal with tapering of steroid dosages by 25% every 2 weeks for 8 weeks and iv) and extension period with stable lowest tolerated dose of BDP for the next 4 weeks, and continuation of placebo or anti-IgE therapy for 5 months. Anti-IgE was administered sc at a dose of 0.016 mg/kg bodyweight/IU total serum IgE, once every four weeks starting with the stable phase.

The main findings of the *Phase III* trials were similar and confirmed the results of the *Phase II* trial [51]: treatment with anti-IgE was significantly more effective than placebo in reducing the number of exacerbations, in both the stable-steroid and the steroid-withdrawal phase (Fig. 2.5). The mean number of exacerbations in the anti-IgE treatment group during the stable-steroid and the steroid-withdrawal phases were 58% and 52% lower than for placebo, respectively ($p < 0.001$ for both) [52], despite significantly lower use of ICS (126 μ g/d BDP in the anti-IgE vs. 210 μ g/d in the placebo group) or complete withdrawal of BDP (43% anti-IgE vs. 19% placebo, $p < 0.001$) 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. Similar, beta-2-agonist use was significantly lower in the anti-IgE group than in the placebo group during the stable-steroid phase (Fig. 2.6). Lung function improved significantly more for patients receiving anti-IgE compared to placebo (PEF: 18.5 l/min vs. 6.9 l/min, $p < 0.05$; FEV1: 4.3% vs. 1.4%, $p < 0.02$). Very similar, treatment of asthmatic children with anti-IgE (protocol 010) showed significantly better results than placebo during the steroid withdrawal-phase for frequency and incidence of exacerbation (number of episodes per patient: 0.42 vs. 2.72, $p < 0.001$), for median reduction of BDP doses (100% vs. 67%, $p = 0.001$), for complete discontinuation of steroids (55% vs. 39% of patients, $p = 0.004$), and for use of rescue medication (daily number of puffs: 0 vs. 0.46, $p = 0.004$). In contrast to the studies in adults, asthma was well controlled (not symptomatic) on entry to the children study [54]. Differences between anti-IgE and placebo treated patients therefore were only obvious during the steroid-withdrawal phase. No statistical differences occurred for symptom scores or spirometry measurements (PEF) between the two groups [54].

Two recent phase-III studies investigated the efficacy of anti-IgE on improvement of asthma-related QoL in patients with moderate to severe asthma [55, 56]. Both found that the clinical benefit achieved by anti-IgE treatment was paralleled by clinically meaningful improvements in asthma-related QoL.

Taken together, the *phase III* studies showed that treatment of adults and children with moderate to severe asthma with anti-IgE is safe, statistically lowers the number of disease exacerbations and reduces the requirements for ICS use.

2.4 Anti-IgE and SAR

Beside studies on asthmatic patients, safety and efficacy of treatment with anti-IgE was evaluated in several studies on SAR. Despite optimised drug treatment protocols, a

significant proportion of patients with SAR remains symptomatic and suffers from disease [57]. SIT, the only available curative approach [58, 59], is restricted with regards to polysensitized and very young patients. But it is especially the polysensitized group of patients that requires therapy for several months of the year and suffers highest from decreased QoL [60] and reduced productivity at the school or the working place [61]. Therefore, new treatment options targeting more specifically in the allergic cascade are desirable. Several clinical trials on treatment of patients with SAR with anti-IgE have been performed and will be summarized in this chapter.

Efficacy of Anti-IgE in Treatment of SAR in Adults

The first large-scale (240 adults), double-blind, placebo-controlled, multicenter trial was performed to assess optimal dosing regimens and test the efficacy of anti-IgE for the treatment of (ragweed-induced) SAR [47].

Primary endpoint of the study [47] was the average of daily symptom scores during season, and the number of days that patients experience symptoms. Further QoL was assessed. The protocol had 3 active treatment (each $n=60$) and 2 placebo arms ($n=20$ placebo sc, $n=40$ placebo iv). Patients in the active arms received 1 iv loading dose (day 0, 1 month before ragweed season), followed by anti-IgE doses (in mg/kg body weight) of 0.15 mg/kg sc, 0.15 mg/kg iv, or 0.5 mg/kg iv on days 7, 14, 28, 42, 56, 70, and 84, followed by a 42-day observation period.

Anti-IgE decreased serum IgE levels in a dose- and baseline IgE-dependent fashion (Fig. 2.3), and specific IgE levels correlated significantly with symptom scores. In none of the treatment groups, IgE levels were consistently decreased to less than 25 IU/mL. However, only patients with IgE levels below detection level (<25 IU/mL) experienced a marked reduction of symptoms. Moreover, the averaged symptom score before and during the peak of the season was only small (before season 0.6; during season 0.91 in placebo and 0.7 to 0.8 in anti-IgE groups, n.s.), and use of rescue medication similar between the groups. Further, neither specific skin test reactivity was altered over the course of the study (exception: high dose anti-IgE group with a marginally significant increase in average end-point titration concentration) nor did the scores of QoL estimations differ.

In conclusion, the results of this study showed that (i) clinical efficacy is only achieved in patients with significantly reduced IgE levels, and (ii) for significant suppression of IgE levels, higher doses of anti-IgE are required. This resulted in a dosing regimen taking individual body weight and basic IgE levels into account: 0.005 mg anti-IgE/kg bodyweight/week for each IU baseline IgE /mL serum, doses between 150 to 375 mg per application period of 2 or 4 weeks. Because equivalent results were seen with iv and sc dosing regimens, the latter was preferred in consecutive trials due to practical reasons.

Effects of Anti-IgE on Symptom Scores in SAR in Adults

The results of the previous study [47] warranted further evaluations of the efficacy of anti-IgE therapy in SAR, utilising higher anti-IgE doses in a second randomised, double-blind, placebo-controlled, multicenter 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) [62]. Conclusively, this study confirmed that anti-IgE was safe and showed that it is effective in controlling birch pollen-induced SAR compared with placebo, with reduced use of rescue medication and improved QoL. Twenty-one percent of verum treated patients reported complete control of symptoms (vs. 2% of placebo treated), 59% estimated improvement (vs. 35%), and only 2% experienced worsening (vs. 13%) [62]. The study investigated the average daily nasal symptom severity score (7 symptoms, 4-point scale) as primary outcome, and further the number of rescue antihistamine tablets per day, the proportion of days with any SAR medication use, and rhinoconjunctivitis-specific QoL. During the birch pollen season, 300 mg of anti-IgE (n=164) or placebo (n=86) were administered sc depending on baseline IgE levels (≤ 150 IU/mL at week 0 and 4, ≥ 150 IU/mL weeks 0, 3 and 6). With the above dosage serum IgE levels were decreased to less than 25 IU/mL in 113 (69%) of subjects treated with anti-IgE, and this was significantly correlated with a better clinical outcome. Average daily nasal symptom severity 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 (0.78 versus 0.98, $p < 0.001$). Ocular symptom severity scores decreased in anti-IgE treated patients (0.47 to 0.43), but increased in the placebo group (0.43 to 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 to the placebo group (0.59 versus 1.37 tablets per day, $p < 0.001$), and the proportion of days on which no SAR medication was required was almost twice as high (49% versus 28%, $p < 0.001$). Statistically significant differences in favour of anti-IgE were similarly observed for estimation of QoL. The rather shallow 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 1 week in advance of the first pollen exposure in more than 50% of all patients.

Effects of Anti-IgE in Perennial AR in Adults

The most recent study investigated the efficacy of anti-IgE on mean daily nasal severity scores in 289 adults and adolescents with moderate-to-severe symptomatic perennial allergic rhinitis (PAR) in a 16 weeks' double-blind subcutaneous treatment (at least 0.016 mg/kg/IgE (IU/mL) per 4 weeks) [63]. 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 patients' QoL.

2.5 Anti-IgE in Combination with SIT

SIT is considered as the only curative treatment for SAR and allergic asthma, and beneficial effects can be observed even years after discontinuation [64, 65]. Especially in children, administration of SIT may prevent the extension of upper airway disease to the lower airways. Application of SIT, however, is limited by several requirements: small panel of sensitizations, clear relationship between specific allergic sensitization and clinical symptoms, and

administration of adequate doses of standardised allergens [66]. Beside these limitations, SIT carries the risk of serious side effects, such as anaphylactic reactions. Since anti-IgE reduces the serum concentration of IgE and thereby reduces IgE-mediated reactions, it was hypothesised that concomitant treatment of anti-IgE and SIT may improve the risk/benefit ratio of SIT in polysensitized patients during the consecutive pollen seasons and thereby may prove clinically superior to treatment with SIT alone.

Anti-IgE in Combination with SIT in Children with SAR

A randomised, double-blind, multicenter study *Phase III* study in children with SAR was initiated to investigate whether combined therapy with SIT and anti-IgE is favourable to single treatment alone [67]. Children and adolescents (n=221; 6-17 years) with moderate-to-severe SAR and sensitisation to birch- and grass-pollen (history ≥ 2 years, IgE specific to birch and grass CAP class ≥ 2 , total serum IgE levels 30-1300 IU/mL) were investigated. Primary outcome was a variable called symptom load (sum of mean daily symptom severity score plus mean daily rescue medication use). The protocol had 4 treatment arms: each subject was started on SIT-birch (2 groups) or SIT-grass (2 groups) for ≥ 14 weeks prior to start of birch-pollen season (Build up phase: 12 injections, 1-week intervals. Maintenance phase: 5 injections, 4-week intervals). 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 analysed separately by season, the two groups receiving unrelated SIT were considered as placebo controls. Anti-IgE was administered sc 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 over the entire pollen seasons (birch and grass) by 48% compared to SIT alone ($p < 0.001$). Reduction was highly significant for both analyses, SIT-birch + anti-IgE vs. SIT-birch + placebo, and for SIT-grass + anti-IgE vs. SIT-grass + placebo (Fig. 2.7). In the grass-pollen season, the relevant SIT to grass pollen reduced symptom load by 32% compared to irrelevant treatment with SIT-birch + placebo (0.61 vs. 0.89, $P=0.1$). The addition of anti-IgE to the relevant SIT-grass had a highly significant effect with 57% decrease in mean symptom load compared to SIT-grass alone (0.26 vs. 0.61, $p=0.001$). Addition of anti-IgE to the unrelated SIT-birch (considered as treatment with anti-IgE alone) reduced symptom load by 45% compared with unrelated SIT-birch alone (0.49 vs. 0.89, $p < 0.001$). Unexpectedly in the birch pollen season, the patients treated with SIT-birch (+ placebo) alone showed a comparable symptom load of 0.46 versus 0.44 ($p=0.43$) compared with the group treated with SIT-grass (+ placebo). This may be caused by pollen exposure before adequate cumulative SIT doses were administered and may also reflect the very modest symptom load scores in this group.

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 anti-IgE resulted in reduction of the median rescue medication score of 78% compared to SIT-birch groups (0.06 vs. 0.27; $p < 0.001$) and by as much as 81% compared to SIT-grass groups (0.03 vs. 0.16; $p =$

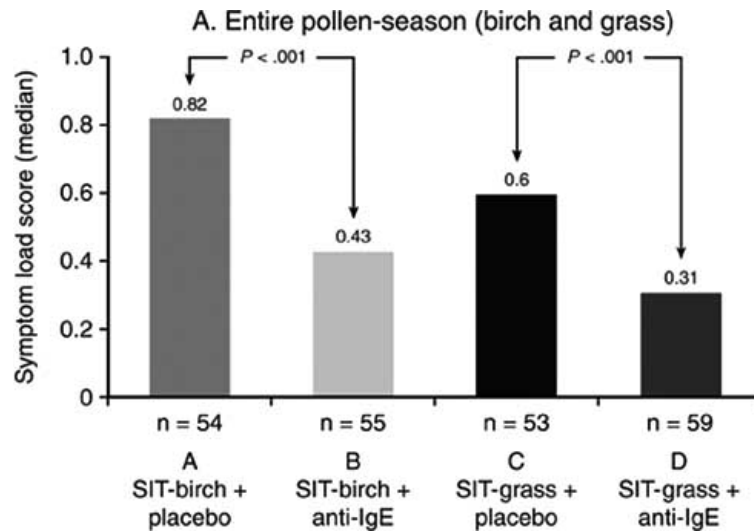


Fig. (2.7). Symptom load (sum of symptom score + rescue medication use score) during entire pollen-season (birch and grass) and treatment with anti-IgE [67].

0.001). Oral corticosteroids as the last rescue medication to be used was reported by 15 patients receiving SIT + placebo compared to 5 patients on SIT + anti-IgE. Symptom severity, the second component of symptom load, was significantly reduced by the addition of anti-IgE in the separate SIT groups (0.24 vs. 0.40; $p < 0.001$).

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

In comparison to the study on SAR in adults [62], where 44% of patients were recruited less than 1 week and 10% of patients were recruited even after the start of the unexpectedly early pollen season, in the study in children, anti-IgE was administered already 45 days prior to the start of the birch-pollen season.

The main requirements for successful anti-IgE therapy of patients with SAR therefore may be concluded from the three SAR trials: i) the dose regimen has to be adopted to personal body weight and IgE base levels; ii) IgE serum levels have to be reduced substantially; and iii) start of the anti-IgE treatment has to be early enough and far in advance of the pollen season/ allergen exposure.

2.6 Anti-IgE and Food Allergy

More recently, the potent anti-allergic effect of anti-IgE therapy has been demonstrated in patients with food allergy [68]. In this study, the threshold amount of peanuts leading to allergic symptoms after oral intake was significantly increased after injection of anti-IgE antibody, showing the powerful consequences of a treatment directly targeting IgE-mediated immediate type of hypersensitivity reactions (Fig. 2.8).

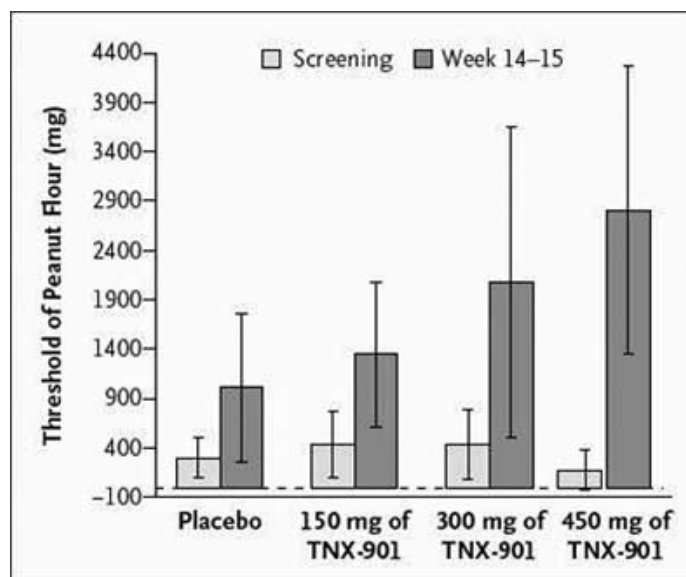


Fig. (2.8). Mean threshold doses of peanut flour eliciting allergic symptoms after oral food challenge in peanut allergic patients at time of screening (light grey) or after sc treatment with either anti-IgE (TNX-901: 150, 300, or 450 mg) or placebo every four weeks for four doses [68].

3. CONCLUSION

Current pharmacotherapy of bronchial asthma decreases airway inflammation and provides symptomatic relief of bronchoconstriction, but it does not specifically target the underlying disease. It is sufficient for the majority of adult and paediatric patients, but there is a sub-population of patients that are still suffering severe symptoms or restrictions of QoL under existing medical regimens. For this group of patients, additional strategies for the treatment have to be established. The enhanced understanding of the mechanisms underlying the development of allergic diseases such as asthma has incited several novel strategies towards an immunological approach of therapy. They tend not to act just as unspecific anti-inflammatory drugs reducing the ongoing allergic response, but rather to stop the development of allergic diseases by a specific approach early 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 favour for the new compounds [69, 70]. The conclusion one may draw from these first studies is, that the clinical situation of asthma in humans clearly is more complex than the experimental situation in animal models [71, 72]. 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 [73].

The most advanced of the novel approaches for therapy of asthma is treatment with anti-IgE antibodies, Xolair®. We already know that Xolair® is effective for the treatment of SAR [62, 67, 74], and most likely for the therapy and/or prevention of food allergy [68]. Targeting IgE aims at the common and most distinct phenotype obvious in all patients suffering from allergic diseases: increased IgE serum levels. Although atopy may be a corresponding rather than a causal factor in the pathogenesis of asthma, there are quite a lot of evidential data demonstrating a pivotal role for IgE in the development of bronchial asthma: Increased IgE serum levels are associated with prevalence rates and disease severity [29, 30], asthma in children is almost always associated with production of allergen-specific IgE and positive skin test reactivity against environmental allergens [29, 75], and even in patients with non-allergic asthma, despite normal IgE serum levels, an extensive production of IgE in large areas of the airways has been found [35]. On the other hand,

experimental data from murine models demonstrate that development of airway inflammation and hyperreactivity to unspecific stimuli may occur independently from B cells [76], IgE-production [76, 77] or IgE-mediated mast-cell activation [78], and in these models with a robust allergen-mediated inflammatory response of the airways, treatment with anti-IgE antibodies does not effectively stop development of airway inflammation or AHR [79].

The findings of clinical *phase II* and *III* trials with anti-IgE antibody treatment in patients with bronchial asthma showed that anti-IgE is an effective therapy for patients with symptomatic, moderate to severe allergic asthma. A recent 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 anti-IgE for treatment of allergic asthma [80, 81] (the latter being the most recent update). Significant increases in the number of participants who were able to reduce or completely withdraw their daily steroid intake were observed (Table 3.1). Further, participants treated with anti-IgE were less likely to suffer an asthma exacerbation (three trials). Finally, this benefit was also shown for patients with severe asthma, suggesting effects by anti-IgE beyond mere reduction of steroid requirements. Similarly important, anti-IgE was safe and well tolerated and improved QoL. Another retrospective analysis of the existing asthma trials (including 767 patients on anti-IgE and 638 with placebo) revealed that the rate of unscheduled, asthma-related outpatient and emergency room visits was significantly lower for the anti-IgE-treated patients, and hospitalisations due to asthma exacerbations were markedly reduced in patients receiving anti-IgE [82]. 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, but differences between the anti-IgE and the placebo treated group reached significance for almost all important endpoints in favour for anti-IgE.

Taken together these data show that anti-IgE was significantly more effective than placebo in reducing the frequency and occurrence of exacerbations, improving symptom control and reducing the requirements for beta agonist and steroid medication, important issues especially for consideration of future treatment strategies for childhood

Table 3.1. Efficacy of Subcutaneous Anti-IgE Versus Placebo for Treatment of Patients with Allergic Asthma with Inhaled Steroid Therapy: Results of the Cochrane Analysis [81]

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)

Severity	Indication
Step I	no indication
<i>Mild intermittent</i>	
Step II	seasonal exacerbation (?)
<i>Mild persistent</i>	
Step III	poor asthma control
<i>Moderate</i>	despite optimal medication
Step IV	with ICS and LABA
<i>Severe persistent</i>	

Fig. (3.1). Stepwise approach for managing asthma with Omalizumab.

asthma. As a consequence, a possible positioning of anti-IgE therapy in the stepwise approach for managing asthma is shown in Fig. 3.1.

Future trials have to examine the efficacy of anti-IgE in comparison with standard medication and for treatment of patients with severe (allergic) asthma. A major limitation for a broader use of anti-IgE is the high cost-to-benefit ratio that by far exceeds that of present standard asthma medication, resulting in good asthma control for the majority of patients (ICS plus long acting beta agonists). Therefore, anti-IgE has to be assessed for treatment of adults and children with steroid-dependent or steroid-resistant asthma who require high doses of oral or inhaled steroids and still have poor asthma control or suffer from severe side effects of the steroid medication. In such patients, analysis of the direct and indirect costs related to frequent exacerbations and hospitalisation may validate the higher costs of anti-IgE therapy. Finally, future trials have to delineate predictors to better define "responders" versus "non-responders" of additional anti-IgE therapy. This will help to ultimately outline the target group of asthmatic patients with the greatest benefit from anti-IgE therapy.

ABBREVIATIONS

AR	=	Allergic rhinitis
BDP	=	Beclomethasone dipropionate
FEV1	=	Forced expiratory volume in 1 second
ICS	=	Inhaled corticosteroids
iv	=	Intravenous
PEF	=	Peak expiratory flow
QoL	=	Quality of life
SAR	=	Seasonal allergic rhinitis
sc	=	Subcutaneous
SIT	=	Specific immunotherapy

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