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Injection of anti-IgE antibodies will suppress IgE and allergic symptoms

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IgE molecules are known to play an important role in allergic diseases. The mechanisms leading to specific IgE antibody formation and the pathways of the IgE-mediated inflammatory reaction are schematically represented in Fig. 1. During an allergic response, B cells are activated by an MHC class II-restricted antigen-specific cognate interaction between these cells and helper T cells. The lymphokines interleukin (IL)-4 and IL-13, produced by helper T cells, then stimulate activated B cells to differentiate and produce IgE molecules (1-3). Two receptors for IgE have been identified: the high-affinity receptor (Fc ϵ RI) is expressed by mast cells, basophils, and antigen-presenting cells, and the low-affinity receptor (Fc ϵ RII or CD23) is expressed by B cells, monocytes/macrophages, dendritic cells, epithelial cells, and eosinophils. Interaction of allergens with IgE/Fc ϵ RI complexes on mast cells and basophils causes cross-linking of the receptors, and this triggers the release of a number of pharmacologic mediators and cytokines that mediate immediate and late hypersensitivity type responses, including allergen-induced bronchoconstriction (4, 5). In addition, interaction of allergens with IgE bound to the high- and low-affinity receptors on antigen-presenting cells can facilitate antigen presentation to antigen-specific T cells (6-8) and promote further release of IgE molecules, eosinophilia, and eosinophil activation by enhancing the production of IL-4 and IL-5 (9, 10).

A therapy that interferes with the binding of IgE molecules to both high- and low-affinity receptors should reduce the allergen-induced early- and late-phase reactions by preventing the release of mediators and cytokines from mast cells. In addition, it should inhibit the amplification of the inflammatory response mediated by helper T cells by

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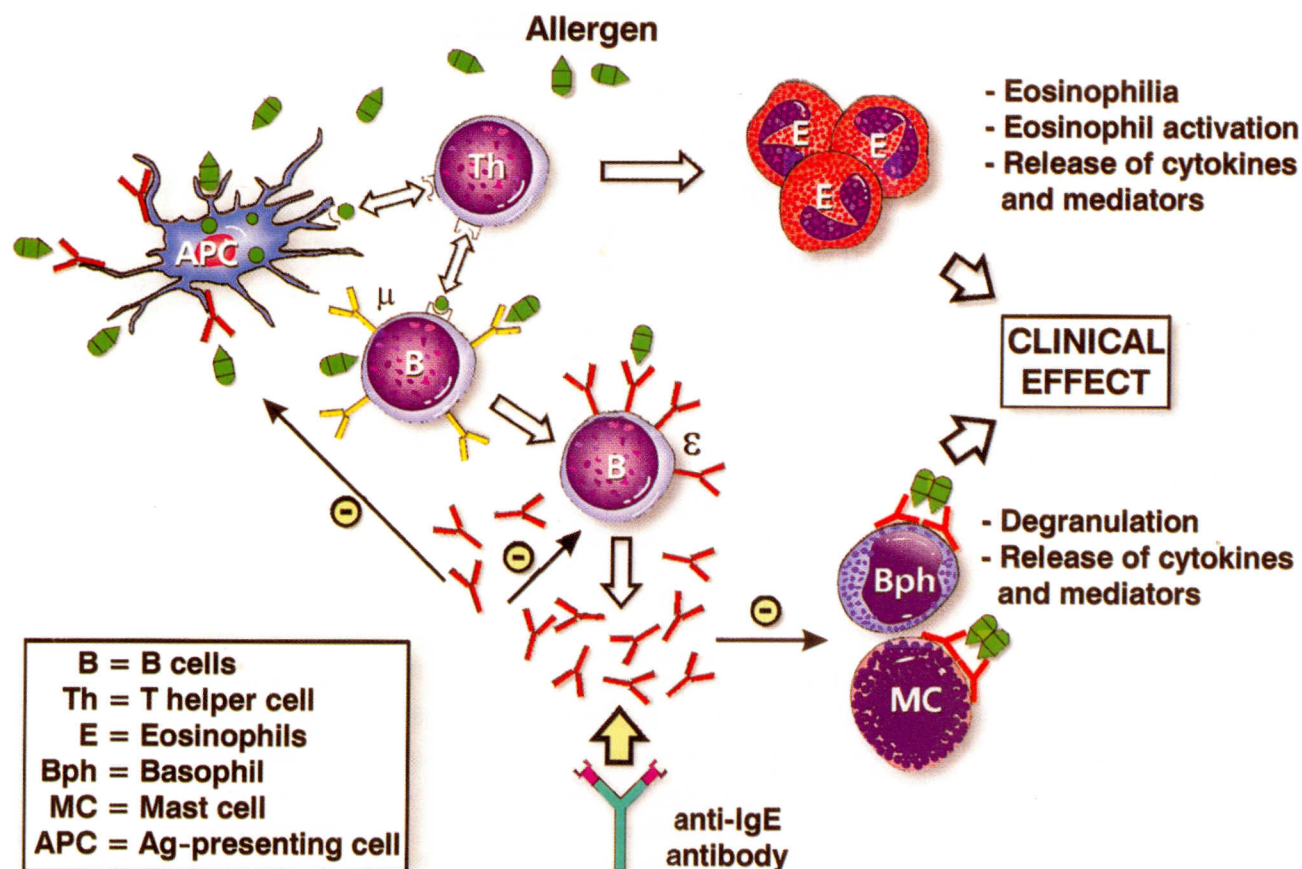


Figure 1. Schematic representation of mechanisms leading to IgE production and IgE-mediated inflammatory reaction in allergic individuals, and inhibitory effects of anti-IgE antibodies (-).

preventing IgE-dependent allergen presentation. In contrast to the currently available treatments for allergic diseases, such a therapy would be specifically directed against a crucial mechanism of the allergic response (11, 12).

On the basis of studies *in vitro* or in animal models of allergic inflammation, a number of different strategies have been considered to inhibit IgE synthesis. These have included the use of STAT-6 inhibitors, which interfere with the signal transduction of IL-4 and IL-13 in B cells (13), or the use of molecules that interfere with the binding of IL-4 to its receptor on B cells, such as IL-4 antagonists and neutralizing antibodies to IL-4 (14). IgE production has also been shown to be partially inhibited by anti-CD23 antibodies (15). However, none of these strategies have resulted in the development of compounds capable of inducing clinical benefit in allergic conditions.

At present, one of the most promising approaches is the neutralization of IgE by antibodies directed against the region of IgE molecules that interacts with IgE receptors. These antibodies bind to the low- and high-affinity receptor-binding portions of human IgE located in the C ϵ 3 domain (11, 12). They therefore bind to circulating free IgE and to IgE

expressed on B cells that are anchored within the B-cell membrane with the C ϵ 3 domain exposed. They do not bind to IgE bound to cells bearing the Fc ϵ RI or the Fc ϵ RII, because the epitope on IgE against which they are directed is already attached to those receptors and masked (Fig. 2). Consequently, they prevent the binding of IgE to effector cells and do not cause cross-linking of IgE receptors on mast cells and basophils or lysis of cells bearing IgE receptors (Figs. 1 and 2). They might also inhibit new IgE production by targeting IgE-switched B cells (Figs. 1 and 2). These nonanaphylactogenic antibodies do not interfere with the production of IgM, IgG, and IgA1 antibodies by B cells, probably because the IgE heavy chain locus is encoded downstream of μ , γ 1, γ 2, γ 3, γ 4, and α 1 (11) (Fig. 2). They can express a high degree of isotype specificity and therefore can selectively neutralize IgE without affecting other antibody classes (11). In addition, anti-IgE antibody administration cannot result in extensive immune complex formation since the concentration of IgE in human blood is only 0.01% of total immunoglobulins (16).

The use of murine anti-human IgE monoclonal antibodies (mAbs) as therapeutic agents has been limited by the occurrence of an anti-antibody response after repeated

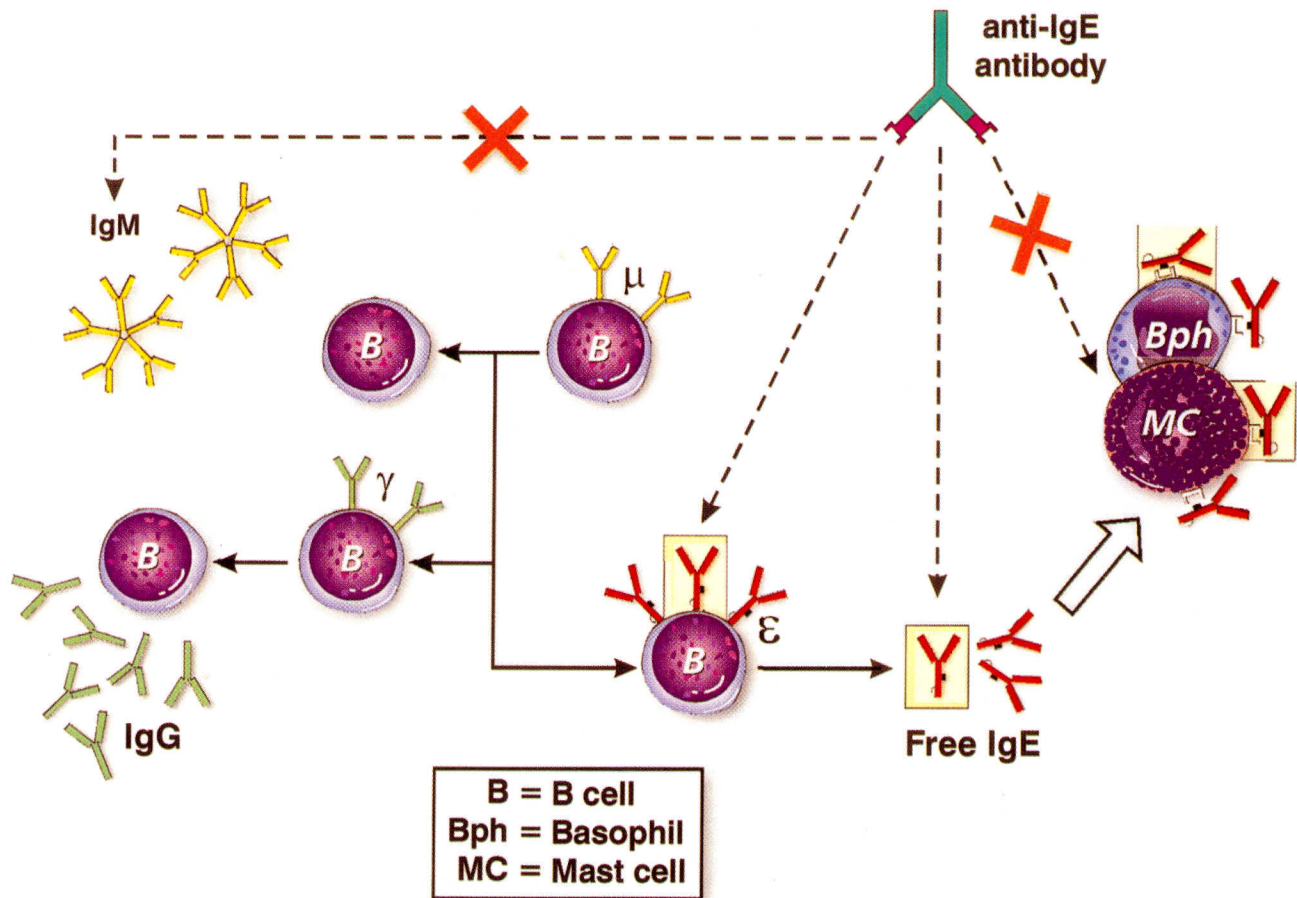


Figure 2. Mechanisms of action of nonanaphylactogenic anti-IgE antibodies.

administration of xenogenic antibodies. This antigenic response can decrease the efficacy of the antibodies by reducing their half-life through the formation of antibody-antiantibody complexes, and it can result in anaphylactic reactions (17–21). Since the antigenic response against the constant region of a xenogenic mAb represents approximately 90% of the total response, the potential for an antiantibody response has been reduced by generating recombinant hybrid mAbs. These mAbs retain specificity for the antigen because they retain the mouse variable regions, while the constant regions of the immunoglobulins are replaced by human constant regions.

Both chimeric and reshaped, humanized mouse nonanaphylactogenic anti-human IgE mAbs have been developed (11, 12, 22). A chimeric mAb (CGP 51901) and a humanized mAb (CGP 56901) have been generated from the parental mouse TES-C21 mAb, and a humanized recombinant human mAb E25 has been generated from the mouse antibody MAE11. Like most humanized antibodies, the humanized anti-IgE mAbs have been designed by comparing the sequence of the relevant murine antibody to a database of human antibody sequences, and selecting the human

antibody with the best homology to the murine antibody. TES-C21 and MAE11 were humanized by using the most common framework found among human IgG antibodies to graft the murine antigen-binding loops. Thus, the humanized recombinant anti-IgE mAbs possess little or no expected antigenicity (12, 21–28).

Since the administration of anti-IgE mAbs results in the formation of IgE/anti-IgE complexes, it is important to report here that the maximal size of immune complexes generated *in vitro* and *in vivo* with both CGP 51901 and E25 has been 2–3 IgE molecules with 2–3 anti-IgE molecules (11, 29). This size corresponds to that of human IgM, and such immune complexes are unable to activate human complement.

Effect of anti-IgE mAbs on serum IgE levels

Both the chimeric antibody CGP 51901 and the humanized antibody E25 have been tested in subjects with elevated serum IgE (29, 30). Their administration has resulted in a dose-dependent decrease in serum free IgE levels.

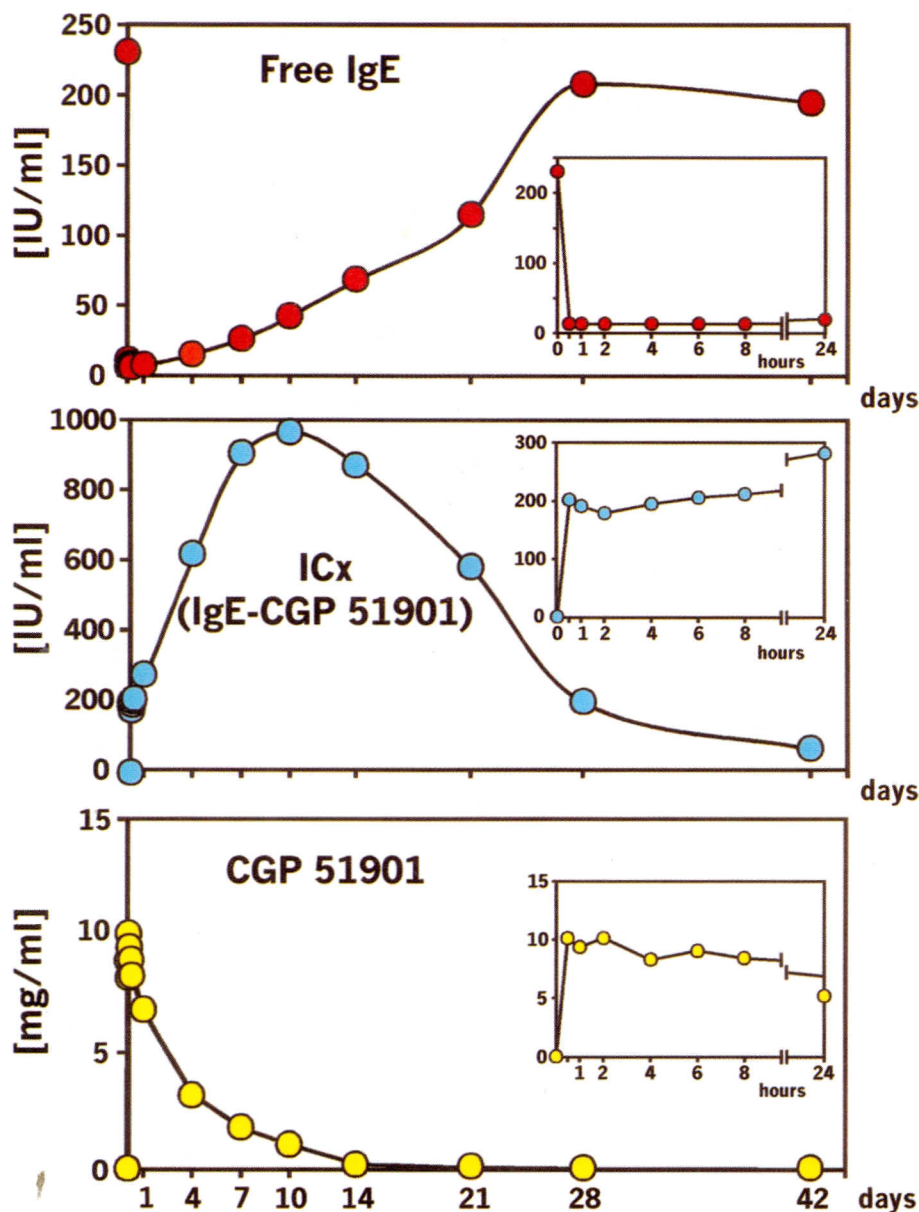


Figure 3. Results of pharmacodynamics and pharmacokinetics obtained with intravenous injection of 30 mg of CGP 51901 in one atopic subject.

In 23 atopic subjects, single intravenous doses of 3, 10, 30, and 100 mg of CGP 51901 induced an immediate fall in the concentration of circulating free IgE. Free serum IgE levels decreased by more than 95% after the highest dose, with a mean recovery to 50% of baseline levels by 39 days. Although free IgE had been suppressed, there was an increase in total IgE (sum of IgE-anti-IgE complexes and free IgE), indicating a slow clearance of the immune complexes (29). Fig. 3 shows the results obtained in one atopic subject with the intravenous administration of 30 mg of CGP 51901. After injection, there was a sharp decrease in the serum concentrations of free IgE, and the decrease lasted several days. At the same time there was an increase in the concentration of CGP 51901-IgE complexes that mirrored

the fall in the levels of free IgE. The concentrations of CGP 51901 increased rapidly, as expected after intravenous administration. The decrease was biphasic, with the first phase consistent with the binding of the antibody to free IgE and a much lower elimination rate, reflecting CGP51901 and complexes clearance and binding of the antibody to newly synthesized IgE.

E25 was also shown to induce and maintain extremely low IgE levels for a long period of time (30). In an open trial, 45 atopic subjects received 0.015 or 0.03 mg of E25/kg/total serum IgE intravenously every 2 weeks. After 182 days of treatment, serum IgE levels were still less than 2% of the baseline value. After reduction of the dose, serum IgE levels promptly began to return to pretreatment values.

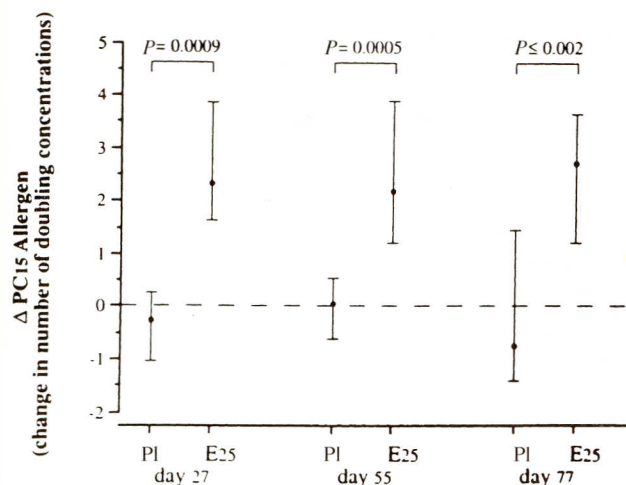


Figure 4. Effect of E25 and placebo (PI) on allergen-induced bronchoconstriction measured as PC₁₅. Change in allergen PC₁₅ during treatment is reported as median change in doubling concentrations of allergen and 25th-75th quartiles. Reproduced by permission of Boulet et al. (35).

Antibodies against the anti-IgE mAbs were measured in all the clinical trials performed. A weak antigenic reaction was measured in only one of the subjects treated with the chimeric antibody CGP 51901 (28) and in none of those treated with the humanized mAb E25. Both antibodies were well tolerated.

These studies indicate that the use of anti-IgE mAbs is safe and effective in reducing serum IgE levels in atopic individuals.

Effect of anti-IgE mAbs in allergic rhinitis

The efficacy of the anti-IgE mAbs in seasonal allergic rhinitis has been tested in two phase II clinical studies (31, 32).

In adults with allergic rhinitis caused by mountain cedar, treatment with CGP 51901 was initiated within 2 weeks before the onset of the pollen season and continued with biweekly injections, at doses of 15, 30, or 60 mg (31). The anti-IgE mAb prevented the development of symptoms during the pollen season in a dose-dependent manner. This effect was achieved in subjects whose IgE levels were reduced by at least 85% from the baseline value. Approximately 25% of the patients treated with the highest dose did not need additional medication during the season, whereas 35 out of 36 patients in the placebo group needed symptomatic treatment.

These results clearly demonstrate that anti-IgE therapy is efficacious in allergic rhinitis. Repeated administration of anti-IgE mAbs may allow recovery from chronic mucosal

inflammation due to recurrent allergen exposure, thereby preventing or reversing some common complications of the chronic inflammatory process, particularly sinusitis and polyps.

Effect of anti-IgE mAbs on allergen-induced asthmatic responses

Antigen challenge represents a good model for mimicking the changes occurring in the airways of subjects with allergic asthma after natural exposure to an allergen. This model has been repeatedly used in the development of antiasthmatic drugs to predict their efficacy before embarking on large and expensive trials, since drugs capable of affecting bronchial responses to allergen inhalation, particularly the late asthmatic response, have been effective in the clinical setting (33, 34).

The ability of E25 to affect the allergen-induced early asthmatic response has been tested in one randomized, double-blind study (35). After an initial loading dose of 2 mg/kg, E25 was administered intravenously to 10 allergic asthmatic patients, on study days 7, 14, 28, 42, 56, and 70, at a dose of 1 mg/kg. Nine patients received placebo. The allergen concentration inducing a 15% fall in FEV₁ (PC₁₅) was measured on days 1, 27, 55, and 77. The results of E25 administration showed a significant increase in the PC₁₅ that was 2.2–2.7 doubling doses higher than the baseline value (Fig. 4). The magnitude of this increase was equal to or greater than that reported with inhaled corticosteroids (36).

Another randomized, double-blind study (37) was designed to test the effect of E25 on both the early and late asthmatic responses to allergen inhalation and on some inflammatory parameters measurable in induced sputum. Either E25 (0.5 mg/kg) or placebo was injected weekly for 9 weeks. An allergen inhalation test was carried out before and at the end of the treatment phase. Anti-IgE administration produced a significant attenuation of the early asthmatic response and reduced the magnitude of the late asthmatic response by more than 60% (Fig. 5). These effects were statistically significant compared with placebo (all $P < 0.025$). In addition, airway hyperresponsiveness to inhaled methacholine measured 24 h after allergen inhalation was lower at the end of treatment with E25 than before ($P < 0.025$). Treatment with E25 had a small effect on inflammatory parameters as compared to placebo, probably because higher concentrations of the allergen were inhaled after E25 administration than after placebo. Nonetheless, the allergen-induced increase in the number of eosinophils and the release of eosinophil

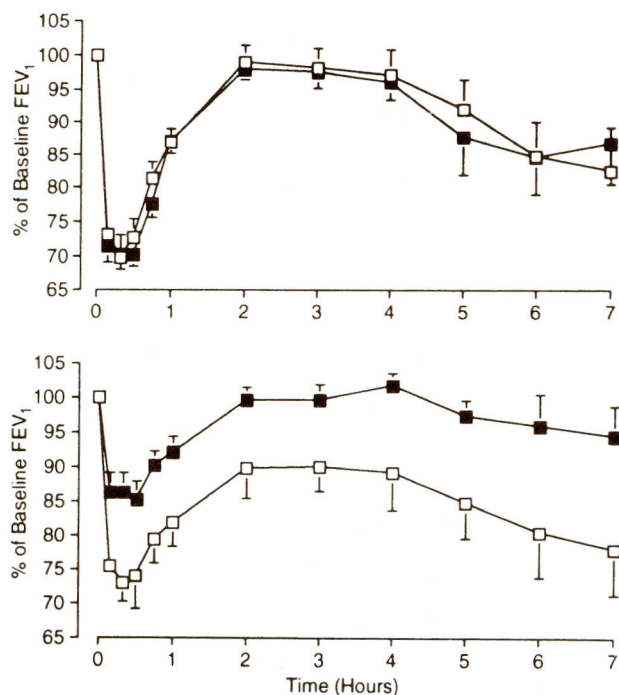


Figure 5. Effect of E25 on allergen-induced early and late asthmatic responses. Changes in FEV₁ in first hour after allergen challenge (early response) and from 2 to 7 h after allergen challenge (late response) in placebo- (top panel) and E25- (lower panel) treated groups are reported as mean percentage of baseline values $\pm$ SD before treatment (closed squares). Reproduced by permission of Fahy et al. (37).

cationic protein in sputum were lower after treatment with the anti-IgE mAb than before (all $P < 0.05$).

Taken together, these studies provide the first direct evidence of the involvement of IgE in the pathophysiology of both the early and late asthmatic reactions to allergen inhalation, and predict therapeutic utility of E25 and similar anti-IgE mAbs in asthma.

Effect of anti-IgE mAbs in allergic asthma

In epidemiologic studies, the levels of circulating IgE have been reported to correlate with the occurrence of symptoms of asthma (38) and bronchial hyperresponsiveness (39, 40). In addition, one epidemiologic study on acute asthma has demonstrated a significant correlation between IgE levels and the risk of emergency room admission (41). These results suggest that anti-IgE therapy may be effective in preventing the clinical expression of the disease in atopic individuals and that it may reduce the severity of symptoms and the number of acute exacerbations in atopic subjects who are already asthmatic.

The E25 mAb has been tested in allergic patients with moderate to severe asthma. They were on treatment with

inhaled steroids and bronchodilators. A subgroup of them was receiving oral steroids. The study design involved two phases. During the first 12-week phase, either E25 or placebo was added at random and double-blind to a standard treatment for moderate to severe bronchial asthma that included inhaled β_2 -receptor agonists and inhaled or oral steroids, and was chosen on the basis of the current guidelines (42). A reduction in the dose of the inhaled and oral steroids was attempted during the second 8-week phase (43). Results after E25 administration showed a significant reduction of symptoms and improvement of the peak expiratory flow rates, with a simultaneous decrease in the use of rescue medications with β_2 -receptor agonists. The most remarkable effect of E25 during the first study phase was its ability to reduce the number of asthma exacerbations by approximately 50% (42). During the second study phase, patients on treatment with E25 reduced their dose of inhaled and oral steroids by 50%. In spite of that, the improvement observed during the first phase continued during the second phase, and the number of asthma exacerbations was reduced even more (43). The patients in the placebo group were able to reduce the dose of inhaled steroids by only 25% and no reduction in the dose of oral steroids was possible (43).

These results demonstrate the effectiveness of anti-IgE mAbs in chronic asthma and their ability to reduce the use of steroids in patients who would otherwise need continuous administration of these agents.

Since anti-IgE mAbs are IgE-specific, they should be able to modify the increase in airway hyperresponsiveness associated with the allergen-induced inflammatory response, while not effecting the airway hyperreactivity of stable asthmatic patients, which is probably the consequence of airway remodeling. Some results from another randomized, double-blind study (35), carried out in 10 atopic patients with asthma, indicate that this is not the case. In that study, repeated injections of 1 mg/kg of E25 on study days 7, 14, 28, 42, 56, and 77, after an initial loading dose of 2 mg/kg, induced a significant reduction in the airway hyperresponsiveness to inhaled methacholine ($P = 0.048$ on day 76). Since the patients tested were mild asthmatic subjects with few or no symptoms and no recent or concurrent natural exposure to the relevant allergen, this effect on airway hyperresponsiveness was unexpected.

Conclusions

IgE molecules play a key role in the development and maintenance of allergic reactions. The inhibition of IgE

function by preventing the binding of IgE to specific receptors on effector cells represents a valid therapeutic strategy in allergic diseases such as allergic asthma and seasonal allergic rhinitis. The development of chimeric and humanized anti-IgE mAbs has provided the first agents capable of obtaining this effect efficiently and safely. Unlike other agents currently employed to treat allergic reactions, these agents specifically interfere with a central mechanism of the allergic response. Like desensitization therapy with

allergens, anti-IgE therapy requires parenteral administration. However, unlike desensitization, anti-IgE mAbs do not induce anaphylaxis, and their efficacy does not depend on the allergen-reactivity profile of the patients.

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