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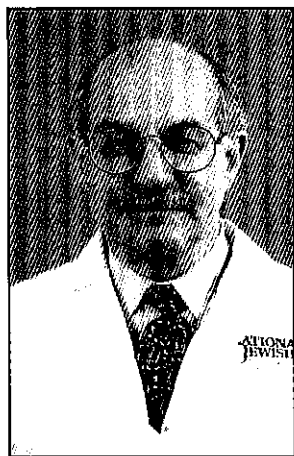
## Anti-IgE in the Treatment of Allergic Asthma

### INTRODUCTION

In 1989 Burrows et al. documented the close relationship between serum immunoglobulin E (IgE) and the development of asthma [1]. In allergic disorders IgE binds to high affinity receptors (FcεRI) on tissue mast cells and circulating basophils and leads to a characteristic sequence of events following an exposure to allergen. An exacerbation of allergic asthma follows a typical biphasic course. An early phase appears within minutes of exposure and a late phase at two to eight hours. During the early phase, inhaled allergen cross-links cell-bound IgE molecules and causes the release of histamine, a preformed inflammatory mediator. Other mediators of inflammation, including prostaglandins, leukotrienes, and cytokines, are synthesized and released [2]. The preformed and newly synthesized mediators produce mucosal edema and contraction of smooth muscle, responsible for bronchoconstriction during the early phase response [3]. The late phase response is also characterized by bronchoconstriction, but the long-term effects also include infiltration of the airways by eosinophils, bronchial hyperresponsiveness, and increased vascular permeability [3]. Although the role of IgE in the late asthmatic response is controversial, both early and late

phase responses can be passively transferred by IgE antibodies [4].

Despite discernible progress in the therapy of asthma, some patients still suffer from poorly controlled disease. Treatment with conventional immunotherapy has not been uniformly successful and it carries a small risk of serious adverse effects, most notably anaphylaxis.



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Patients with severe asthma continue to require systemic corticosteroids and are exposed to the risks of these medications [5]. More than half of the expenditures directed toward the care of asthma is spent on the treatment of the 5% of patients who fail to respond to existing therapy [5]. Newer treatment approaches are needed, and research has focused on reducing IgE production or blocking its action [6]. Such treatment would not require the identification of specific allergen sensitivity and should be broadly applicable. One approach has been the development of a monoclonal antibody to human IgE to interfere with the initiation of the inflammatory cascade.

### DEVELOPMENT OF ANTI-IgE

The first step in the development of anti-IgE was the production of a murine antibody, MAE

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11, directed against human IgE [7]. MAE 11 recognizes the high affinity receptor binding site on IgE and forms complexes with free IgE but not other immunoglobulins. MAE 11 blocks IgE binding to cell-membrane receptors, inhibiting the release of histamine and other mediators. Importantly, MAE 11 does not combine with IgE already bound to mast cells and basophils.

The next step was to develop a humanized form of the antibody.[7] The critical amino acids from the IgE-binding site of MAE 11 were grafted onto the constant region of human IgG to form rhuMAb-E25. More than 95% of the resulting amino acid sequences are human. rhuMAb-E25 blocks passive sensitization of human basophils and mast cells by IgE and prevents IgE-mediated activation of these cells. Just like MAE 11, it does not link to IgE already on basophils or mast cells.

Seven Phase I trials assessed the safety and efficacy of rhuMAb-E25 in human subjects with allergies [7]. An immediate, sustained, dose-dependent decrease in serum free (unbound) IgE was documented. Serum free IgE decreased within 5 minutes after intravenous and 24 h after subcutaneous administration of rhuMAb-E25. Free IgE could be reduced to the limit of assay sensitivity for four to six weeks after a single dose. Total IgE (the sum of free IgE and complexes of IgE:rhuMAb-E25) increased, consistent with a slower clearance of complexed IgE. None of the subjects developed antibodies to rhuMAb-E25. These trials demonstrated that rhuMAb-E25 could safely and effectively reduce serum free IgE to undetectable levels with a single monthly injection.

An unexpected result was the decrease in FcεRI expression in subjects treated with rhuMAb-E25 [2]. Patients with perennial rhinitis and positive skin test sensitivity to dust mite received intravenous

rhuMAb-E25 every two weeks. Basophils were isolated at the beginning and after three months of treatment and tested for histamine release, endogenous IgE density, and total and unoccupied FcεRI density. Serum free IgE fell rapidly after the first dose of rhuMAb-E25 and remained at approximately 1% of pretreatment values. IgE density on the basophil surface dropped more than 99%, from a pretreatment median of 220,000 molecules per basophil to an undetectable level at 3 months. (The calculated maximum expression at this point was approximately 2200 IgE molecules per basophil.) Total basophil FcεRI density was also measured. The median receptor number before sensitization was 220,000 per basophil; this dropped to 8300 at 3 months, a decrease in total FcεRI receptor density of approximately 97%. A 50% decrease in both serum free IgE and receptor number was noted by day 3.

It had been estimated that a reduction in plasma IgE by more than 99% would be necessary to decrease the response to allergen. MacGlashan's study demonstrated this degree of reduction in IgE; moreover it brought to light a decline in receptor density that enhances the effectiveness of rhuMAb-E25 treatment [2].

### **rhuMAb-E25 IN ALLERGIC ASTHMA**

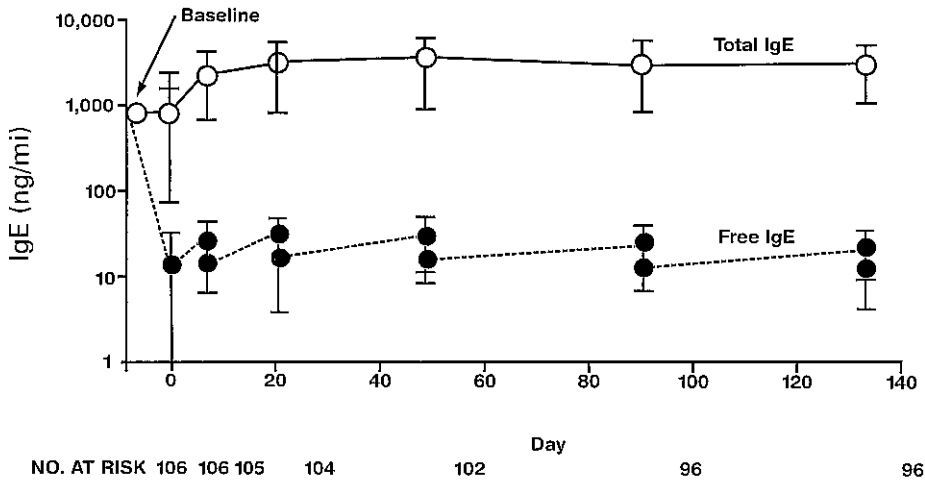
Fahy et al. conducted a randomized, double-blind, placebo-controlled study of the effect of rhuMAb-E25 on allergic airway responses[3]. Nineteen subjects with a history of mild asthma received nine weekly intravenous infusions of either placebo or rhuMAb-E25. Serum free IgE decreased significantly in the rhuMAb-E25 group, with marked attenuation of both early- and late-phase responses to inhaled allergen. Maximal bronchoconstriction was reduced by about 40% in the early phase and 60% in the late phase. The number of eosinophils in the induced sputum decreased in subjects treated with rhuMAb-E25.

These results not only indicate that IgE plays a role in the mediation of both phases of allergic airway response but also suggest the applicability of rhuMAB-E25 in the treatment of asthma [3,6].

A similar study by Boulet et al. also documented a reduction in serum free IgE and an attenuation of the early phase response [8]. This study did not examine the late phase response. Both groups found rhuMAB-

E25 to be safe; only one mild adverse reaction (transient urticarial rash) was noted, and none of the subjects developed antibodies to rhuMAB-E25 [6].

Milgrom et al. carried out a larger, multicenter clinical trial, enrolling 317 subjects with moderate-to-severe perennial asthma [9]. Subjects were randomly assigned to one of three groups: placebo, high-dose rhuMAB-E25, or low-dose rhuMAB-E25. The study comprised four phases:



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**Figure 1.** Mean ( $\pm$ SD) Serum Concentrations of Total and Free IgE in Subjects Given a Low Dose of rhuMAB-E25 for 20 Weeks.

Serum free IgE concentrations decreased rapidly by more than 95 percent (base-line level, 1060 ng per milliliter [441.7 IU per milliliter]). A log (base 10) scale is shown.

1. a 4-week enrollment and run-in;
2. 12 weeks of intravenous treatment with placebo or rhuMAB-E25 (half dose days 0 and 4, full dose day 7, full dose once every 2 weeks thereafter) plus established corticosteroid therapy;
3. an 8-week continuation of rhuMAB-E25 with tapering of corticosteroids; and
4. a 10-week follow-up.

The primary outcome measures were daytime and nocturnal asthma symptom scores at week 12, before corticosteroid therapy was tapered. Secondary outcomes included the use of bronchodilators as rescue medication, doses of oral and inhaled corticosteroids, and asthma-specific quality of life measures. Safety and tolerability of the anti-IgE antibody were evaluated. Serum total and free IgE was measured.

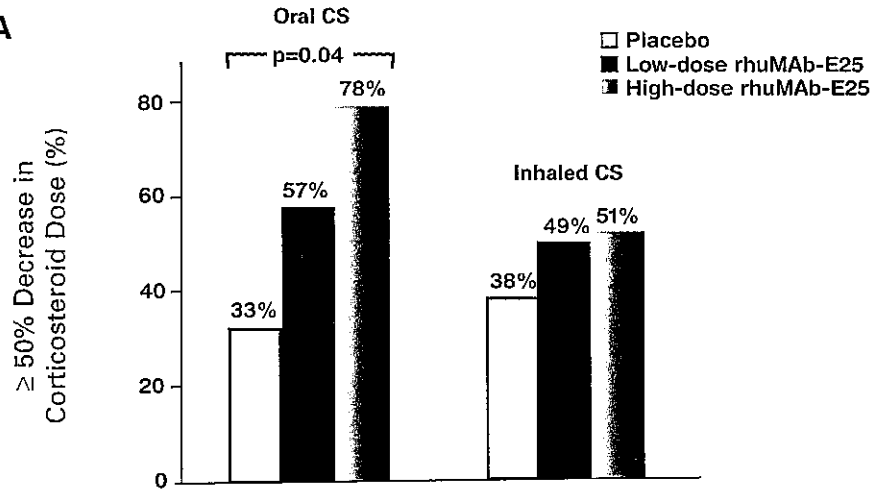
Serum free IgE fell rapidly after subjects received the first dose of rhuMAB-E25, decreasing by more than 95%, and remained low throughout the 20 weeks of treatment [Figure 1]. Total serum IgE increased with the formation of rhuMAB-E25:IgE complexes, which are cleared more slowly than free IgE but do not pose a risk of immunopathogenicity. No significant differences were noted in the number of adverse events among the three groups, and none of the subjects developed antibodies to rhuMAB-E25 after 20 weeks of treatment.

Asthma symptom scores improved significantly at 12 weeks in both the high- and low-dose rhuMAB-E25 groups as compared with placebo-treated subjects [ $p=0.008$ ,  $p=0.005$ , respectively]. Approximately half the subjects in both rhuMAB-E25 treatment groups demonstrated a reduction of more than 50% in weekly symptom scores as compared with one-fourth of the placebo group. Notably, this improvement continued through week 20, despite the reduction in the requirement for corticosteroid treatment.

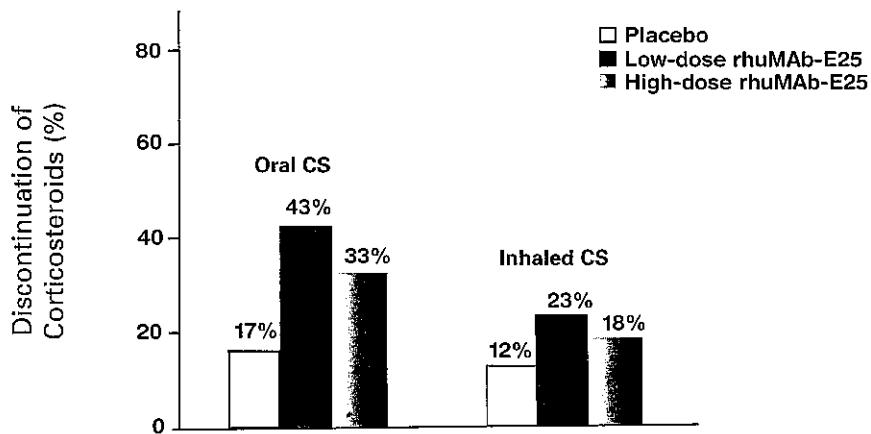
Beta-agonist use declined at 12 weeks in both rhuMAB-E25 groups as compared to the placebo group, and the reductions were maintained at week 20. In the 35 subjects who required oral corticosteroids, the median decrease was 50% in the high-dose group, 65% in the low-dose group, and 0% in the placebo group. More than three-fourths of the high-dose group and over half of the low-dose group were able to curtail oral corticosteroids by more than 50%, as compared with one-third of the placebo group [Figure 2]. One-third of the high-dose group, 43% of the low-dose group, and 17% of the placebo group were able to discontinue oral corticosteroids. Approximately one-half of the subjects in each rhuMAB-E25 group were able to reduce their dose of inhaled corticosteroids by at least 50%, compared with 38% of the placebo group. More of the rhuMAB-E25-treated subjects were able to stop taking inhaled corticosteroids completely [Figure 2B]. Exacerbations of asthma were reduced at 20 weeks in subjects in the rhuMAB-E25-treated groups compared with the placebo group.

The cumulative results of this study support the role of anti-IgE therapy in treating moderate to severe asthma. Not only did asthma symptom scores improve during the first 12 weeks of rhuMAB-E25 treatment, but the improvement was maintained during the next 8 weeks even with significant cutbacks in both inhaled and oral corticosteroid use. Furthermore, subjects receiving either dose of rhuMAB-E25 had greater improvement in the quality of life scores than the placebo group.

Two other recent randomized, double-blind, placebo-controlled, parallel group studies evaluated the safety and efficacy of rhuMAB-E25 in adults [10] and children (6-12 years) [11] with allergic asthma. Both used the same three-phase study design: baseline period, stable

**A**

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**B**

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**Figure 2.** Results of Efforts to Taper the Dose of Corticosteroids. Panel A shows the percentage of subjects in each group who were able to reduce their daily corticosteroid dose by at least 50 percent at 20 weeks. Panel B shows the percentage of subjects in each group who were able to discontinue corticosteroid therapy. In the placebo, low-dose, and high-dose groups, 12, 14, and 9 subjects, respectively, were taking oral corticosteroids and 93, 92, and 97 subjects were taking inhaled corticosteroids. Subjects who discontinued the study had their last recorded dose carried forward.

treatment with placebo or rhuMAB-E25, and reduction of inhaled corticosteroid while continuing test drug or placebo. Both found that rhuMAB-E25 treatment decreased the need for inhaled corticosteroids and at the same time reduced the number of asthma exacerbations and the use of rescue medication.

## SUMMARY

rhuMAB-E25 offers a promising new approach to the treatment of allergic asthma. This monoclonal antibody that combines with the FcεRI-binding site on IgE has been developed to block the pathogenesis of allergic disease. rhuMAB-E25 treatment decreases not only serum free IgE but also FcεRI expression. In patients with allergic asthma, both the early and late phase asthmatic reactions are attenuated. The effect on the late phase reaction provides evidence that rhuMAB-E25 suppresses the inflammatory process in asthma. Treatment with rhuMAB-E25 improves asthma scores while it reduces the use of beta-agonist rescue and the need for both inhaled and oral corticosteroids. The safety and efficacy of rhuMAB-E25 have been demonstrated in both adults and children.

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