Effects of anti-IgE in asthmatic subjects

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Introductory articles

The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects

JV Fahy, HE Fleming, HH Wong, JT Liu, JQ Su, J Reimann, RB Fick, HA Boushey

A humanized murine monoclonal antibody directed to the FcεRI-binding domain of human IgE (rhuMAb-E25) has been shown to inhibit the binding of IgE to mast cells without provoking mast cell activation. To examine the effects of neutralizing IgE on allergic airway responses, we assessed the effects of 9 wk of treatment with rhuMAb-E25 in a parallel group, randomized, double-blind, placebo-controlled study of 19 allergic asthmatic subjects. We found that treatment with rhuMAb-E25 reduced the serum IgE, increased the dose of allergen needed to provoke an early asthmatic response, reduced the mean maximal fall in FEV₁ during the early response (30 ± 10% at baseline to 18.8 ± 8%, versus 33 ± 8% at baseline to 34 ± 4% after placebo; p = 0.01), and reduced the mean maximal fall in FEV₁ during the late response (24 ± 20% at baseline to 9 ± 10% versus 20 ± 17% at baseline to 18 ± 17% after placebo; p = 0.047). We conclude that an anti-IgE monoclonal antibody, which inhibits binding of IgE to its receptor, suppresses the early- and late-phase responses to inhaled allergen in allergic asthmatic subjects. Targeting IgE with rhuMAb-E25 might be a useful treatment for allergic asthma. (Am J Respir Crit Care Med 1997;155:1828–1834)

Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response

L-P Boulet, KR Chapman, J Côté, S Kaira, R Bhagat, VA Swystun, M Lavolette, LD Cleland, F Deschesnes, JQ Su, A Devault, RB Fick, DW Cockcroft

Inhaled allergens, acting through IgE-dependent mechanisms, are important triggers of asthma symptoms and inducers of airway hyperresponsiveness and airway inflammation. The effect of anti-IgE recombinant humanized monoclonal antibody-E25 (rhuMAb-E25) on the provocation concentration of allergen causing a 15% fall in FEV₁ (allergen PC₁₅) during the allergen-induced early asthmatic response (EAR) was assessed in a multicenter, randomized, double-blind, parallel group study. Ten of 11 allergic asthmatic subjects randomized to receive intravenous rhuMAb-E25, 2mg/kg on study day 0 and 1mg/kg on Days 7, 14, 28, 42, 56, and 70 completed the study; nine received intravenous placebo. The allergen PC₁₅ was measured on Days –1, 27, 55, and 77 and methacholine PC₂₀ on Days –2, 42, and 76. rhuMAb-E25 was well tolerated and only one patient (active group) was withdrawn because of a generalized urticarial rash after the first dose. Compared with baseline values (Day –1), the median allergen PC₁₅ on Days 27, 55, and 77 were increased by 2.3, 2.2, and 2.7 doubling doses (1 log PC₁₅/0.3) respectively with rhuMAb-E25 and –0.3, –0.1, and –0.8 doubling doses with placebo (p ≤0.002). Methacholine PC₂₀ improved slightly after rhuMAb-E25, this change becoming statistically significant on Day 76 (p <0.05); no change was observed in the placebo group. Mean serum-free IgE fell by 89% after rhuMAb-E25 while there was no significant change after placebo. The inhibitory effects of rhuMAb-E25 on allergen-induced EAR suggest that it may be an effective, novel antiallergic treatment for asthma. (Am J Respir Crit Care Med 1997;155:1835–1840)
The role of IgE in induction, maintenance and triggering of asthma

The link between allergy and asthma is long established, and the majority of patients with asthma have evidence of IgE-mediated hypersensitivity to airborne allergens. However, the role of pollens in triggering acute episodes seems less certain. Admissions to hospital are lower during the hay fever season than in the three months preceding or following the UK grass pollen season, but it seems likely that fragmented pollen grains may be responsible for the epidemics of acute asthma associated with thunderstorms.

Allergen avoidance has been advocated in asthma and can lead to modest reductions in non-specific bronchial responsiveness but only extreme forms of avoidance have had any significant clinical benefit. In the context of occupational asthma where complete allergen avoidance is definitely achievable, it is clear that some patients improve markedly on ceasing exposure but others continue to have asthmatic symptoms for many years, even though they are no longer exposed to the allergen that induced their asthma. Factors that have been associated with the persistence of occupational asthma include the duration of exposure before developing symptoms, the duration of continuing exposure after the onset of asthma, and the degree of eosinophilia. So while it remains an article of faith that reductions in allergen load are likely to be helpful in reducing the inflammatory process in allergic asthma, it seems likely that other factors also contribute to the maintenance of established allergic inflammation.

![Figure 1](https://example.com/f1.png)

**Figure 1** Two signal model of B cell isotype switching. On first exposure to any antigen, B cells can make IgM without requiring assistance from T cells. Some cells with the same specificity will be maintained as memory B cells to provide a more rapid response in the event of re-exposure. Memory T cells recognizing fragments of the antigen may also develop. To make IgE, these two cell types must cooperate: in this model, a memory B cell recognizes the allergen via its surface immunoglobulin, thereby trapping it. The antigen is ingested and then digested into short fragments, which are then presented on the B cell surface in the groove of MHC class II molecules. These antigen-MHC complexes are shown to passing T cells within the regional lymph node or spleen. When a CD4+ T cell that recognizes the MHC-antigen fragment complex meets the antigen-presenting B cell, the T cell antigen receptor is activated, sending internal signals to the cell to produce autocrine growth factors (for example, IL-2) as well as activating adhesion mechanisms to lock the two cells together. If the T cell is preprogrammed to facilitate IgE switching (that is, a Th2 cell), then IL-4 is also produced; this has autocrine effects as well as inducing transcription of the Ca immunoglobulin gene in the B cell (germline transcripts). Upon activation the T cell expresses CD40 ligand, which binds to CD40 on the B cell surface and provides the second signal needed to switch the B cell over to IgE production. Meanwhile, the B cell displays the B7 counter-receptor which signals via CD28 on the T cell to augment IL-4 production. Under these twin influences the B cell germline DNA is rearranged, with excision of the intervening immunoglobulin DNA and the production of mature IgE transcripts.
Much attention has been focused on the role of the cytokines IL-4 and IL-5 in coordinating the inflammatory response in asthma. IL-4 provides a key signal in the process by which B cells switch over from making IgM or IgG antibodies towards making IgE. This process of “isotype switching” is tightly controlled. On initial exposure to antigens the naïve B cell can make IgM or IgM antibodies without requiring help from T cells. Concurrently, there is expansion of “memory” B cells recognising parts of the antigen. Upon subsequent exposure memory B cells can process antigen and can use their surface MHC class II molecules to present antigenic fragments to T cells, thereby obtaining help from T cells for making a secondary immune response (fig 1). In individuals predisposed to making IgE responses T cells may be skewed towards production of IL-4 and IL-5 (the so-called Th2 phenotype) and if such a T cell interacts with a memory B cell, then the B cell may be directed to switch over to make IgE. Two separate signals are required: a contact signal delivered through the CD40 molecule and its ligand, and a soluble signal delivered by IL-4.20 In man, but not in rodents, the cytokine IL-13 can substitute for IL-4.21 IL-4 was originally thought to be produced exclusively by T cells but, when bronchial and nasal biopsy specimens were stained for IL-4 protein, it was found that IL-4 protein was present mainly in mast cells.22 Mast cells release IL-4 when stimulated23: in atopic subjects this may lead to an IL-4-rich environment in the bronchial mucosa and hence to immune deviation towards the Th2 phenotype and a greater likelihood of switching to IgE on subsequent exposure to potential allergens.

The cytokine IL-5 is intimately involved in the differentiation, maturation and activation of eosinophils. The eosinophil is derived from a common granulocytic bone marrow precursor cell and differentiates sequentially under the influence of IL-5, GM-CSF and finally IL-5 to become a mature eosinophil.15 IL-5 is also a selective activator of the mature eosinophil.15 IL-5 is made by T cells but has also been found in mast cells, eosinophils, and epithelial cells.15,16

Although the genes for IL-4 and IL-5 are located very close together on chromosome 11q13–15, recent evidence indicates that their expression is not coordinately regulated.24 Expression of mRNA for IL-5 is a feature of both allergic and non-allergic asthma25 and there is a close correlation between T cell activation and serum IL-5 concentrations in various forms of asthma.26

A number of interesting insights into the relative contributions of IL-4 and IL-5 to asthma have emerged in studies of occupational asthma to isocyanates. Isocyanate asthma is a particularly interesting model which bridges the gap between atopic asthma, where exposure to the inciting allergen is lifelong, and intrinsic asthma where, as far as we can tell, extrinsic allergens and IgE are not involved. Typically, isocyanate asthma develops after a latent period in which exposure occurs without symptoms. IgE antibodies cannot be directly implicated should be seen in the context that SIT was being given through the CD40 molecule and its ligand, and a soluble against IL-5 can prevent airways hyperresponsiveness.

Once the gene for IL-4 and IL-5 is introduced into the process, two cytokines are now a significant part of the immune response. One is a helper cytokine and the other is an activator of the mature eosinophil. The helper cytokine is IL-4 and the activator is IL-5. The two cytokines are produced by T cells but also by other cells such as mast cells and eosinophils. The two cytokines are produced in response to the exposure to an allergen, and the production of these cytokines is a key step in the development of asthma.

The expression of IL-4 in asthma is closely linked to upregulation of IL-5, while upregulation of IL-4 is perhaps more closely related to IgE and allergic sensitisation but not directly to the clinical syndrome of asthma.25,26 Experimental studies of the role of IL-4 and IL-5 in allergic disease have been hampered by the lack of a really good animal or in vitro model of asthma. There are many models of allergic sensitisation and it is relatively easy to demonstrate that sensitised animals will develop airways eosinophilia and increased airways resistance, but these are essentially models of acute allergen exposure rather than models of the disease we recognise as asthma. In particular, almost none of the models give any long lasting airways inflammation or anything similar to the airways remodelling and collagen deposition that occur in chronic human asthma. With these caveats, animal models have shown that T cells are the main source of IL-5, but not IL-4, in the lungs of antigen-challenged mice.20 Detailed discussion of these studies can be found elsewhere27 but it has been consistently shown that monoclonal antibodies directed against IL-5 can prevent airways hyperresponsiveness in several species including mice, guinea pigs, and monkeys.20

**Immunotherapy for asthma**

Rather than attacking the messengers, could one not try to intervene at the level of the IgE antibody? This was for many years considered to be the basis for classical injection immunotherapy. The immunisation schedules for specific injection immunotherapy (SIT) were developed in the last years of the 19th and the first decade of the 20th centuries, long before the discovery of IgE in 1967. During the 1920s and 1930s the concept of “blocking antibodies” was advanced by Cooke and, indeed, it is true that SIT induces an increase in IgG antibodies directed against the injected allergen with a gradual decline in specific IgE titres after an initial increase. However, the beneficial effects of SIT come on much more rapidly than the antibody changes and it is now generally believed that SIT must work by a form of immune deviation, driving T cells away from the Th2 phenotype towards a Th1 phenotype.

Although SIT is the treatment of choice for hymenoptera sensitivity and it retains a place in the management of allergic rhinitis, there is considerable doubt about its value in the management of asthma. Firstly, there is less clarity about the importance of specific allergy in the expression of asthma; secondly, many patients are multiply sensitised and SIT is a highly targeted therapy which only addresses the allergen used in the injections; thirdly, and most importantly, there is no doubt that patients with asthma are at much greater risk of severe adverse reactions to SIT. Of the 27 UK fatalities associated with SIT between 1952 and 1985, the precise indication for SIT was known in 17 cases, and 16 of these were being treated for asthma.20 This should be seen in the context that SIT was being given much more often for hay fever than for asthma. Similarly, in the confidential inquiry by the American Academy of Allergy and Immunology into deaths associated with SIT, almost all the fatal cases were being treated for asthma and the mode of death was catastrophic bronchoconstriction rather than circulatory collapse or other features of anaphylaxis.20

**Why try anti-IgE?**

It was against this background that steps were taken to try to develop more general forms of immunological...
efficacy of the antibody combining site). Indeed, cross-
that there may be a clinical e-
and encouraging diversity within the antibody rep-
asthma and rhinitis share some common basic mech-
e
receptor. Such an antibody should be
else prevent the IgE from binding to the Fc
would not be able to remove IgE antibodies that were
already bound to mast cells through the Fc receptor
so the value of such an approach in abolishing IgE to
depend on two principal parameters: the con-
e
RI binding site of IgE. Suitable mouse
antibodies which bound free IgE but did not stain
mast cells. It is noteworthy that E25 did not a-
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reduction in allergen induced bronchospasm provided
that IgE was not permanently bound to airways mast
cells. It is noteworthy that E25 did not affect the im-
mediate skin test reaction, indicating that IgE bound to
skin mast cells was not displaced during the treatments
and proceeded to generate monoclonal antibodies which
recognise the FcεRI binding site of IgE. Suitable mouse
antibodies which bound free IgE but did not stain
mast cells were developed and then “humanised” by retaining
the antigen combining site and engineering this into a
human immunoglobulin (IgG₃) molecule. 44 Once
achieved, the antibody could be mass produced to yield
sufficient quantities for use in man. The monoclonal
antibody used in both of the index studies 44, 45 binds
well to free IgE but does not degranulate mast cells, so
there is no specific risk of triggering anaphylaxis by
causing widespread release of mast cell mediators. The antibody has been considered as an auto-
and non-auto
v
ons and is non-immunising in the sense that it does not
induce antibodies directed against human IgG or
so far significant amounts of antibody directed against
the anti-IgE combining site. Prior experience with
monoclonal antibody therapies suggests that “anti-idio-
typic” antibodies may well develop with prolonged use
as the human immune system should be tolerant of the
constant part of IgG but does not have any system for
specific tolerance to the idotype (the specific antigenic
features of the antibody combining site). Indeed, cross-
recognition of idiotypes has long been considered an
advantageous feature of the immune system, allowing
downregulation of clones that become overexpressed
and encouraging diversity within the antibody rep-
ertoire. 46
One feature of E25 that may not be instantly obvious
is that, although it will not bind to surface IgE that is
bound to FcεRI, it does have the potential for mod-
ulating or eliminating other cells bearing IgE which
express the lower affinity IgE receptor (FcεRII or
CD23). CD23 is expressed by B cells, platelets, eos-
ninophils, and some T cells and binds to IgE through a
completely separate site on the Fc portion of IgE 47 so
the E25 binding site should, at least theoretically, still
be accessible and allow E25 to bind and eliminate those
effectors cells which bear FcεRII.

What do the index papers really tell us and is
E25 a viable therapy for asthma?
The two recent papers show firstly that E25 dramatically
reduces the baseline concentration of circulating IgE.
This is to be expected in the short term since the
monoclonal antibody is specifically designed to bind
free IgE molecules. Substantial concentrations of E25
could be measured up to 28 days after administration 48
which may account for the persistent suppression of
total and specific IgE. However, the production of IgE
may be damped down as well. Another study using E25
has recently been published in which E25 was given to
240 patients with allergic rhinitis. 49 Unlike the two index
articles, 45, 46 Casale et al used three different treatment
regimes (two different doses intravenously, one sub-
cutananeously) plus corresponding placebo controls.
The reduction in total and specific IgE concentrations was
dose dependent but IgE was suppressed completely in
only 11 of the 180 subjects who received active therapy.
Both total and specific IgE remained low four weeks after
the last infusion but IgE concentrations had returned
to baseline by eight weeks after the last infusion.
The airways response to allergen challenge is known
to depend on two principal parameters: the con-
centration of allergen-specific IgE and the degree of non-
specific bronchial reactivity. Indeed, this relationship is
so tight that one can use skin test reactivity (a surrogate
of ragweed specific IgE, but there were no overall
statistically significant differences in symptom scores
between the five treatment groups). 42 This study tells us
that there may be a clinical effect on allergic rhinitis
provided one can eliminate circulating allergen specific
IgE, but it cannot be assumed that asthma will ne-
cessarily respond in the same way since, even though
asthma and rhinitis share some common basic mech-
anois, the mechanisms of disease expressions are quite

Figure 2 Allergy, viral infection and irritant stimuli as
inflammatabe stimuli or the asthma, atopic dermatitis and...
LEARNING POINTS

- The role of IgE in asthma remains uncertain; it is obviously more important in children with atopic disease than in adults, only some of whom have clear evidence of allergic sensitisation.

- Anti-IgE antibodies that bind to free IgE but not to mast cell bound IgE can be administered safely to atopic patients without triggering anaphylaxis.

- Pretreatment with anti-IgE can blunt the response of sensitive individuals to inhaled allergen.

- A priori, there are several reasons for thinking that anti-IgE would be more effective in acute allergen challenge than in chronic asthma.

- Further trials are indicated in selected subgroups to address the efficacy of anti-IgE in real asthma.

- The clinical efficacy of anti-IgE may help to establish whether we should concentrate more on the trigger factors or the downstream consequences of asthma.

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