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The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

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SOCIETY Volume 341(26), 23 December 1999, pp 2006-2008

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Anti-IgE Antibody Therapy for Asthma [Editorials]

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Over the past 10 years there have been striking improvements in the treatment of
asthma, largely as a result of the earlier and more widespread use of inhaled

corticosteroids. The development of new treatments for asthma has proved difficult, although several immunologic approaches are undergoing preclinical and clinical assessment. [1] Antileukotrienes are the only new class of drugs to treat asthma that have been introduced in the past 25 years, but their efficacy is somewhat limited and unpredictable, as compared with that of inhaled corticosteroids.

Mild asthma can be controlled in most patients by relatively low doses of inhaled corticosteroids, and moderate asthma can be controlled by adding an inhaled long-acting beta-agonist or a low dose of theophylline. A few patients have more severe asthma and require high doses of inhaled corticosteroids or regular treatment with oral corticosteroids. In this issue of the Journal, Milgrom et al. [2] report on the efficacy of a recombinant humanized monoclonal antibody against IgE (rhuMAb-E25) for the treatment of moderate-to-severe allergic asthma. This approach is an important step forward, since severe asthma is poorly controlled by existing therapies other than oral corticosteroids, whose long-term use is associated with several adverse effects. [3]

Twice-weekly intravenous injections of rhuMAb-E25 lead to a rapid, dose-related, and sustained fall in plasma IgE levels in patients with atopic asthma. [4-6] The medication is still experimental and has yet to be approved for prescription sales. The antibody is designed to bind to the part of the IgE molecule that interacts with the high-affinity IgE receptor (Fc(epsilon)RI) on mast cells and basophils, thus preventing the activation of these cells by cross-linking of bound IgE. [7]

Initial studies in patients with mild asthma showed that, as expected, rhuMAb-E25 reduced the early bronchoconstrictor response to inhaled allergen, which is prompted by the activation of mast cells. [5,6] However, somewhat surprisingly, it also reduced the late response to allergen - an acute inflammatory response orchestrated by T cells

and associated with the infiltration of eosinophils that occurs approximately six hours after inhalation of the allergen. [5] Treatment with rhuMAb-E25 also reduced the number of eosinophils in the sputum and decreased airway hyperresponsiveness, indicating that it has a long-term antiinflammatory effect. [5,6] Such findings suggest that rhuMAb-E25 affects cells other than mast cells and basophils and may inhibit low-affinity IgE receptors (Fc(epsilon)RII or CD23) on other cells, such as macrophages and T cells, as observed in mice. [8] Furthermore, inhibition of the production of IgE by B cells, to which the antibody binds, helps keep circulating levels of IgE low. [7]

One additional surprising finding is that rhuMAb-E25 reduces the number of high-affinity IgE receptors on circulating basophils (and presumably tissue mast cells), with the numbers returning to normal after treatment is stopped. [9] Thus, circulating IgE appears to regulate the expression of high-affinity IgE receptors. The administration of nebulized rhuMAb-E25, however, does not reduce circulating levels of IgE or affect the response to allergen challenge, demonstrating that systemic administration is necessary. [10]

Milgrom et al. conducted a placebo-controlled study of rhuMAb-E25 in 317 subjects with moderate-to-severe perennial allergic asthma who were taking inhaled or oral corticosteroids. During the first 12 weeks of treatment, while corticosteroid therapy was continued, intravenous injections of either a high dose or a low dose of rhuMAb-E25 every two weeks significantly reduced the symptoms of asthma and improved the subjects' quality of life, with a moderate increase in airway function and a reduced need for the use of bronchodilators as rescue medication. During the next eight weeks of the study, the doses of inhaled or oral corticosteroids were tapered. There were greater reductions in the doses of inhaled and oral corticosteroids and higher rates of discontinuation of these drugs in the high-dose and the low-dose groups than in the

placebo group. In the group of 35 subjects who required oral corticosteroids at baseline, there was a significant reduction in the requirement for oral corticosteroids, and nearly twice as many subjects in the high-dose group as in the placebo group were able to stop taking oral corticosteroids.

Treatment with rhuMAb-E25 has been well tolerated in all studies to date, with no specific adverse effects, apart from an urticarial rash after the first dose in a small number of subjects. [7] There is no evidence that antibodies develop against rhuMAb-E25, presumably because of the "humanization" of the antibody (more than 95 percent of the sequences of the protein are of human rather than murine origin). Moreover, the immune complexes formed by the interaction of rhuMAb-E25 with IgE appear to be removed by the reticuloendothelial system, with no evidence of damage to the kidney or other organs or tissues. Concern that reducing the plasma levels of IgE might impair immunity to parasitic infections has been addressed by experiments in mice. Mice infected with *nippostrongylus* and *schistosoma* surprisingly had increased rates of elimination of parasites, rather than decreased rates. [7]

Although asthma has been the main focus of studies of anti-IgE antibody, this approach may have a role in the treatment of other atopic diseases, including allergic rhinitis and atopic dermatitis. Twelve weeks of treatment with rhuMAb-E25 reduces symptoms and the use of other medications in patients with seasonal allergic rhinitis. [11] Many patients with asthma also have allergic diseases, and rhinitis many worsen in these patients as asthma is brought under control. By reducing the levels of IgE, rhuMAb-E25 therapy could ameliorate all these atopic diseases, avoiding the need for a multidrug approach.

Most patients with asthma have atopy, with specific IgE antibodies to antigens in

inhaled allergens, such as house-dust-mite allergen, cockroach allergen, pollens, and molds, which drive the inflammatory process in the airways. Immunotherapy directed against common allergens has been disappointing as a treatment for asthma and has a small risk of serious adverse effects. [\[12,13\]](#) Immunotherapy is directed at specific allergens, whereas anti-IgE antibodies nonspecifically inhibit IgE.

A small proportion of patients with asthma have no evidence of atopy, as assessed by skin-prick tests of common allergens or total and specific IgE levels in plasma. These patients, who have nonatopic, or "intrinsic," asthma, tend to have more severe disease. A recent study suggests that IgE may be produced locally in the airways [\[14\]](#) and that anti-IgE antibody may therefore also be effective in these patients.

The findings of Milgrom et al. suggest that treatment with anti-IgE antibody may be useful in patients with severe asthma who require oral corticosteroids. Such treatment may allow the dose of oral corticosteroids to be reduced or the drug to be discontinued, thus eliminating the side effects associated with long-term use of these drugs. The need to give rhuMAb-E25 by intravenous injection is a problem, but further studies to determine the optimal dose may lead to less frequent or subcutaneous administration. In the future it may be possible to identify small-molecule inhibitors of IgE. The use of injections may also be a way to increase compliance with long-term therapy. A humanized monoclonal antibody is likely to be very expensive, but more than half the health care spending on asthma is accounted for by patients with severe asthma, who make up less than 5 percent of all patients with the disease. [\[15\]](#) Furthermore, alternative therapies for corticosteroid-dependent asthma, such as methotrexate, cyclosporine, and oral gold (Auranofin), are problematic and have a high incidence of adverse effects. [\[16\]](#) Further studies of anti-IgE antibody in larger numbers of patients with corticosteroid-dependent asthma are needed to explore the

potential of this exciting new therapeutic approach.

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REFERENCES

1. Barnes PJ. Novel therapeutic strategies for allergic diseases. Nature 1999;402:31-8. [\[Context Link\]](#)
2. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. N Engl J Med 1999;341:1966-73. [Catalogo Biblioteca ISS Full text \(pacchetto Ovid\)](#)
[Bibliographic Links](#) [\[Context Link\]](#)
3. Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998;12:1209-18. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
4. Corne J, Djukanovic R, Thomas L, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. J Clin Invest 1997;99:879-87. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
5. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early-and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
6. Boulet LP, Chapman KR, Cote J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 1997;155:1835-40. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
7. Jardieu PM, Fick RB Jr. IgE inhibition as a therapy for allergic disease. Int Arch Allergy Immunol 1999;118:112-5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
8. Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. J Exp Med 1996;183:1303-10. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
9. Saini SS, MacGlashan DW Jr, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. J Immunol 1999;162:5624-30. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

10. Fahy JV, Cockcroft DW, Boulet LP, et al. Effect of aerosolized anti-IgE (E25) on airway responses to inhaled allergen in asthmatic subjects. Am J Respir Crit Care Med 1999;160:1023-7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
11. Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997;100:110-21. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
12. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334:501-6. [Catalogo Biblioteca ISS Full text \(pacchetto Ovid\) Bibliographic Links](#) [\[Context Link\]](#)
13. Barnes PJ. Is immunotherapy for asthma worthwhile? N Engl J Med 1996;334:531-2. [Catalogo Biblioteca ISS Full text \(pacchetto Ovid\) Bibliographic Links](#) [\[Context Link\]](#)
14. Menz G, Ying S, Durham SR, et al. Molecular concepts of IgE-initiated inflammation in atopic and nonatopic asthma. Allergy 1998;53:15-21. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
15. Barnes PJ, Jonsson B, Klim JB. The costs of asthma. Eur Respir J 1996;9:636-42. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
16. Hill JM, Tattersfield AE. Corticosteroid sparing agents in asthma. Thorax 1995;50:577-82. [Catalogo Biblioteca ISS Buy Now Bibliographic Links](#) [\[Context Link\]](#)

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