

CLINICAL THERAPEUTICS

Omalizumab for Asthma

Robert C. Strunk, M.D., and Gordon R. Bloomberg, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 16-year-old boy with a 15-year history of asthma from the age of one year and two visits to the emergency department in the past year presents for evaluation. He reports symptoms consistent with those of severe persistent asthma (including awakening from sleep five of seven nights) while taking a high-dose inhaled corticosteroid (fluticasone, 1000 μ g per day) in combination with a long-acting bronchodilator. Skin testing is positive for two species of house-dust mites, several molds, and pollen. The total serum IgE level is 436 IU per milliliter (normal range for age, 6 to 97). The patient is referred to a specialist, who recommends treatment with omalizumab.

THE CLINICAL PROBLEM

Asthma is a disease that causes debilitating daily symptoms and unexpected acute exacerbations of symptoms. Symptoms lead patients to limited activity, absences from work or school, hospitalizations and visits to the emergency department, and a reduced quality of life. As a result, patients and their family members have both personal and economic hardship. From the perspective of public and societal health, approximately 17 million people in the United States have been estimated to have asthma, one third of them children.¹ The burden of morbidity and mortality falls most heavily on blacks and Hispanics.¹⁻³ Asthma in the United States costs an estimated \$12.7 billion annually, with most of this cost attributable to direct medical expenditures and medication.⁴

IgE plays a central role in the pathophysiology of asthma (Fig. 1). The two essential phases in this pathophysiology are sensitization to allergen and clinical expression of symptoms on reexposure to the sensitizing allergen. During sensitization, inhaled antigen (i.e., aeroallergen) is taken up by antigen-presenting dendritic cells lining the airways. The allergen is then processed and presented to antigen-specific T cells. In some persons, these T cells respond by producing cytokines that stimulate the development of IgE-producing B cells. The Fc portion of circulating IgE then binds to high-affinity receptors (Fc ϵ RI) present on the surfaces of mast cells and basophils.^{5,6}

On reexposure, the sensitizing allergen cross-links IgE molecules present on mast-cell and basophil surfaces. This initiates degranulation and the release of inflammatory mediators, including histamine, prostaglandins, leukotrienes, chemokines, and cytokines. These mediators precipitate an immediate acute-phase reaction, resulting in acute bronchospasm, expressed clinically as an episode of acute asthma. Continued expression of mediators enlists an inflammatory response designated the late-phase reaction, which causes persistent symptoms, airway hyperresponsiveness, and bronchospasm.

IgE may also facilitate sensitization to allergens. Dendritic cells express Fc ϵ RI

From the Department of Pediatrics, Washington University School of Medicine, St. Louis.

N Engl J Med 2006;354:2689-95.

Copyright © 2006 Massachusetts Medical Society.

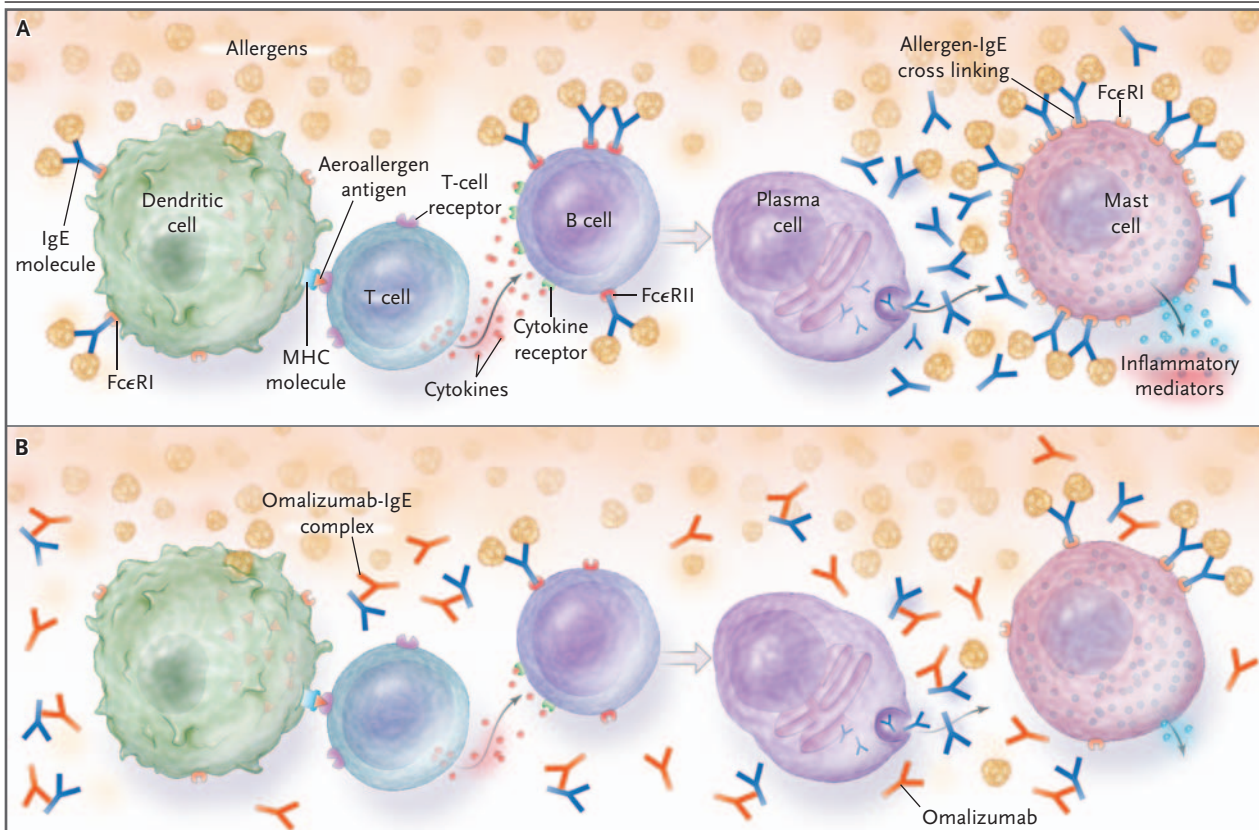


Figure 1. Pathophysiology of Asthma.

Aeroallergens initially interact with the immune system when they are taken up by dendritic cells (Panel A). This process occurs by phagocytosis and may be enhanced after initial sensitization by the binding of allergen-specific IgE to high-affinity receptors (FcεR1) on the surface of dendritic cells. Dendritic cells process the allergen and present it, bound to major-histocompatibility-complex (MHC) molecules, to T cells. T cells are stimulated by the interaction of MHC-bound antigen with surface T-cell receptors, causing T-cell proliferation and the subsequent release of cytokines. These cytokines stimulate B cells to become plasma cells that produce IgE. B cells express low-affinity Fcε receptors (FcεR2); interaction of IgE with these receptors may influence B-cell differentiation and regulation of IgE synthesis. IgE produced by plasma cells binds to the surface of mast cells and basophils and, when cross-linked by allergen, induces degranulation and the release of inflammatory mediators. This process results clinically in an acute asthma attack. Omalizumab is a monoclonal anti-IgE antibody that binds to the Fc region of the IgE molecule (Panel B). In so doing, omalizumab prevents IgE from binding to cell-surface receptors. Omalizumab is unable to bind to IgE molecules that are already bound to FcεR1; as a result, it cannot induce anaphylaxis. Reduced binding of IgE to FcεR1 on mast cells and basophils inhibits degranulation and the release of inflammatory mediators. There is also marked down-regulation of FcεR1. Reduced IgE binding to FcεR1 on dendritic cells may reduce the ability of these cells to process antigen efficiently. Reduced IgE binding to FcεR2 on B cells is thought to alter B-cell differentiation and the regulation of IgE synthesis. All these effects may contribute to the prevention of acute exacerbations of asthma.

and have been found to bind IgE, which is thought to focus antigen at the cell surface.^{7,8} In addition, IgE binds to low-affinity Fcε receptors (FcεR2) on B cells, where it alters differentiation and regulation of further IgE synthesis.^{9,10}

TREATMENT

EFFECT OF THERAPY WITH OMALIZUMAB

Omalizumab (Xolair, Genentech) is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds to the IgE molecule at the same epi-

tope on the Fc region that binds to FcεR1.^{11,12} This design means that omalizumab is not anaphylactogenic, since it cannot interact with IgE that is already bound to cell surfaces and thus cannot induce degranulation of mast cells or basophils.^{8,13} Instead, omalizumab binds to circulating IgE, regardless of allergen specificity, forming small, biologically inert IgE-anti-IgE complexes without activating the complement cascade.^{8,12,14} An 89 to 99 percent reduction in free serum IgE (i.e., IgE not bound to omalizumab) occurs soon after the administration of omalizumab, and low levels per-

sist throughout treatment with appropriate doses.^{14,15} Proof-of-concept studies have shown that omalizumab reduces both early- and late-phase asthmatic responses after allergen inhalation challenge,¹⁶ has a marked effect on late-phase as compared with early-phase skin responses,¹⁷ decreases eosinophil numbers in sputum¹⁸ and submucosal bronchial specimens,¹⁸ and also down-regulates FcεRI on basophils,¹⁹ mast cells,²⁰ and dendritic cells.²¹ A reduction in the expression of FcεRI on basophils and mast cells decreases the binding of circulating IgE, thus preventing the release of inflammatory mediators. A reduction in the expression of FcεRI on dendritic cells may decrease allergen processing and presentation.

EVIDENCE OF A CLINICAL BENEFIT

There are four core randomized, double-blind clinical trials that have compared omalizumab, administered subcutaneously, with placebo.²²⁻²⁵ In these trials, patients had had asthma for at least one year and required treatment with inhaled corticosteroids. All patients had at least one positive skin test to a perennial aeroallergen (specifically, dust mites, cockroaches, or dog or cat dander), as well as an elevated total serum IgE level. During the course of each trial, inhaled corticosteroids were initially maintained at a stable dose, followed by a phase of dose reduction to the lowest dose required for asthma control.

These trials all demonstrated a clinical benefit from omalizumab, although the specific findings varied. Three of the trials evaluated patients with moderate-to-severe persistent asthma (requiring doses of inhaled beclomethasone, or its equivalent, ranging from 168 to 1200 μg per day). Two of these three trials included adolescents and adults,^{22,23} and one was a study of children 6 to 12 years of age.²⁴ In these three trials, treatment with omalizumab as compared with placebo was associated with significantly fewer exacerbations of asthma per patient, and a significantly lower percentage of patients had an exacerbation. In addition, the dose of inhaled corticosteroids required to control symptoms was significantly less among patients treated with omalizumab than among those who received placebo.

The fourth trial evaluated patients with more severe asthma who required high-dose inhaled corticosteroids for symptom control (fluticasone, ≥ 1000 μg per day).²⁵ In this trial, no significant effect on the frequency of exacerbations was seen, although the dose of inhaled corticosteroids re-

quired to control symptoms was significantly lower among patients treated with omalizumab.

A fifth clinical trial involved patients who required at least 1000 μg per day of inhaled beclomethasone plus a long-acting bronchodilator for symptom control.^{26,27} The study demonstrated a decrease in the rate of exacerbations of asthma only after adjustment for an imbalance in the number of exacerbations in the year before enrollment.²⁷ Among several secondary outcomes in these trials, quality-of-life measures stand out as being notably improved.

CLINICAL USE

The role of omalizumab in the management of asthma has not yet been precisely defined. Patients with persistent asthma (defined as asthma with symptoms that occur more than two days a week or nocturnal symptoms that occur more than twice a month^{28,29}) have several treatment options in addition to the use of inhaled β -adrenergic agonists. These include environmental control (i.e., the elimination or minimization of exposure to aeroallergens), pharmacologic control (i.e., the use of inhaled corticosteroids, leukotriene modifiers, or both), and possibly, immunologic control (i.e., immunotherapy for relevant antigens). In addition, evaluation for coexisting conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease may prove beneficial.

Patients who are particularly likely to benefit from the use of omalizumab include those with evidence of sensitization to perennial aeroallergens who require high doses of inhaled corticosteroids that have a potential for adverse side effects, those with frequent exacerbations of asthma associated with unstable disease, and possibly, those with severe symptoms related in part to poor adherence to daily medication. Analyses of pooled data from published clinical trials have indicated that patients who had a response to omalizumab had a ratio of observed to expected forced expiratory volume in one second (FEV_1) of less than 65 percent, were taking doses of inhaled corticosteroids equivalent to more than 800 μg of beclomethasone dipropionate per day, and had had at least one visit to the emergency department in the past year.^{30,31} Patients requiring daily oral corticosteroids to control their asthma may be less likely to have a response to omalizumab.

A total serum IgE level should be measured in all patients who are being considered for treatment with omalizumab, because the dose of omalizu-

mab is determined on the basis of the IgE level and body weight. The recommended dose is 0.016 mg per kilogram of body weight per international unit of IgE every four weeks, administered subcutaneously at either two-week or four-week intervals (Table 1). This dose is based on the estimated amount of the drug that is required to reduce circulating free IgE levels to less than 10 IU per milliliter.

Monitoring of total serum IgE levels during the course of therapy with omalizumab is not indicated, because these levels will be elevated as a result of the presence of circulating IgE–anti-IgE complexes.¹³ No other laboratory tests seem to be necessary, since there have been no clinically significant laboratory abnormalities noted during treatment.

PREPARATION FOR USE

Omalizumab is supplied as a lyophilized, sterile powder in single-use, 5-ml vials designed to deliver either 150 or 75 mg on reconstitution with sterile water (not normal saline) for injection. The powder requires 15 to 20 minutes or more to dissolve. There are fewer injection-site reactions when the solution is not injected until it is completely clear. The solution is viscous and must be carefully drawn up into the syringe before it is administered. The injection itself may take 5 to 10 seconds to administer. Once prepared, the drug must be used within four hours if at room temperature or eight hours if refrigerated. Because of these re-

quirements for preparation and the high cost of the drug, some practitioners require patients to schedule appointments for injection, and many do not prepare the injection until the patient arrives. This results in visits that take 60 minutes or more, since 30 minutes of observation is recommended after the injection. In general, current asthma symptoms are not a contraindication to the administration of omalizumab.

Total serum IgE levels will generally increase during treatment, because of the presence of circulating IgE–anti-IgE complexes.³³ An investigative method for measuring free serum IgE levels has recently been reported and may provide an opportunity for monitoring optimal omalizumab dosing.³³ In addition, recent *in vitro* studies of the effect of omalizumab on the accuracy and reproducibility of assays of total and allergen-specific IgE antibodies³⁴ suggest that the use of a specified commercial assay may help optimize dosing and maximize omalizumab therapy. There is, at present, no reported clinical experience with such approaches.

COST

Omalizumab is considerably more expensive than conventional asthma therapy. The cost of treatment may range from \$4,000 to \$20,000 per year, depending on the dose,³⁵ with an average of approximately \$12,000 per year. This compares with approximate costs per year of \$1,280 for monte-

Table 1. Dosing Schedule for Subcutaneously Administered Omalizumab, According to the Baseline Serum IgE Level and Body Weight.*

Baseline Serum IgE Level <i>IU/ml</i>	Body Weight				
	30–60 kg	61–70 kg	71–80 kg	81–90 kg	91–150 kg
	<i>dose in milligrams</i>				
30–100	150	150	150	150	300
101–200	300	300	300	300	225
201–300	300	225	225	225	300
301–400	225	225	300	300	—
401–500	300	300	375	375	—
501–600	300	375	—	—	—
601–700	375	—	—	—	—

* Adapted from the Xolair package insert.³² The recommended dose is 0.016 mg per kilogram of body weight per international unit of IgE every four weeks, administered subcutaneously at either four-week (*italic*) or two-week (*roman*) intervals for adults and adolescents (persons 12 years of age and older) with allergic asthma. Dashes indicate that no dose should be prescribed.

lukast (Singulair, Merck), \$2,160 for the combination of fluticasone dipropionate and salmeterol (Advair, GlaxoSmithKline), and \$680 for extended-release theophylline (Uniphyll, Purdue).

RESPONSE TO TREATMENT

Response to treatment can take several weeks to become apparent.¹³ Among patients in a clinical trial who had had a response to omalizumab by 16 weeks, 87 percent had done so by 12 weeks.³⁰ These data suggest that patients should be treated for at least 12 weeks before efficacy is assessed. Given that serum IgE levels and the numbers of FcεR1s increase after therapy is discontinued,³⁶ it seems that treatment needs to be continued for efficacy to persist, but no studies have been reported on the duration of effects after discontinuation. If treatment is interrupted before nine months have elapsed since the last injection, treatment should be resumed at the dose initially prescribed. Dosing may need to be adjusted in the event of substantial changes in body weight (Table 1).

ADVERSE EFFECTS

Potential safety concerns identified by the Food and Drug Administration (FDA) in reviewing trial data on omalizumab included risks of the development of cancer and anaphylaxis. Cancer developed in more patients exposed to omalizumab than in those who received placebo (20 of 4127 [0.5 percent] and 5 of 2236 [0.2 percent], respectively).³⁷ They were predominantly epithelial or solid-organ cancers; one case of hematologic or lymphatic cancer was noted. Since the majority of patients treated with omalizumab have been observed for only a year, the effect of longer exposure or of use in patients who are at increased risk for cancer is not known. Therefore, omalizumab probably should not be used in patients with a history of cancer or a strong family history of cancer until this risk relationship is better understood.

Omalizumab is intended to prevent any risk of anaphylaxis, since the agent cannot interact with IgE that is already bound to cell surfaces. However, in clinical trials, three patients (<0.01 percent) had anaphylaxis.³⁷ Two of the reactions were temporally associated with omalizumab administration; the reactions were not immediate but occurred within two hours after the first injection.

Other adverse events seen more often with omalizumab than with placebo in clinical trials have included rash, diarrhea, nausea, vomiting, epistaxis, menorrhagia, hematoma, and injection-site reactions.³⁷ The most common adverse events were viral infections, upper respiratory tract infections, sinusitis, and headaches, but these were not more common with omalizumab than with placebo and therefore are unlikely to be side effects of the drug. An analysis of the safety data among children after the use of omalizumab for 1 year, which included a 28-week core study and a 24-week open-label extension,²⁴ showed upper respiratory tract infections and headache to be more frequent in the omalizumab group than in the placebo group. Eleven patients (4.9 percent) in the omalizumab group had urticaria; only one case was severe enough that the patient discontinued participation in the study.³⁸

Theoretically, the administration of omalizumab could induce antibodies to the murine components of the drug. However, no immune complex-mediated pathologic conditions that might develop as a result of the formation of such antibodies have been observed. Also, the potential for omalizumab to interfere with the role of IgE in the clearance of parasitic infections is a possible concern. Although no clinical problems related to such an effect have been seen, this might be a potential concern in specific populations. Further information is needed on the safety profile of omalizumab after long-term use.

AREAS OF UNCERTAINTY

The clinical trials of omalizumab enrolled patients with precisely defined characteristics of asthma, including sensitivity to specific perennial aeroallergens (i.e., dust mites, cockroaches, and dog or cat dander). The role of omalizumab in patients with asthma who have allergies to other aeroallergens, such as molds or pollens, or who have negative allergy skin tests, has not been defined. It is also not clear to what extent omalizumab might be effective in patients with total serum IgE levels outside the trial ranges (30 to 700 IU per milliliter for patients 12 to 75 years of age).

In clinical practice, there is considerable variability of response to omalizumab therapy. The reasons for this variability have not been established; studies are needed to determine whether

specific characteristics of individual patients may help to predict response.

The clinical trials performed to date have evaluated omalizumab only as adjunctive therapy with inhaled corticosteroids as compared with placebo. They have not evaluated the relative benefit of this agent in comparison with other available therapies, such as leukotriene modifiers or theophylline. Also needed are comparisons with asthma therapies that are available for patients for whom low-dose inhaled corticosteroids do not control the asthma and who need step-up management (i.e., an increased dose of the corticosteroid or the addition of another medication).^{28,29} Furthermore, the clinician should give consideration to the actual clinical relevance of the moderate corticosteroid-sparing effects observed in the trials, even if these reductions were significant, as well as to the substantial improvements noted in placebo groups. Given that the cost of omalizumab is substantially greater than that of conventional asthma therapy, the potential cost-effectiveness of this form of treatment will be important to assess.

The efficacy and safety of omalizumab have not been established for durations of treatment that exceed one year, and it is not known how long clinical effects may persist after therapy is discontinued. Since asthma is a chronic disease, long-term studies, especially in children, are needed to evaluate the effect of serum IgE suppression throughout development; adverse effects may become apparent only with follow-up into adulthood. We know of only one study to date that has been performed exclusively in the pediatric age group.²⁴ Efficacy and safety studies are also needed for geriatric and nonwhite patients.

GUIDELINES

The most recent formal asthma management guidelines of the National Heart, Lung, and Blood Institute were published in June 2003, the same month that omalizumab received FDA approval.²⁹ These guidelines made no recommendation regarding the use of omalizumab, although they did note that "because of the importance of IgE to the pathogenesis of allergic diseases and inflammation, the development of humanized monoclonal antibodies has become a possible treatment."

RECOMMENDATIONS

The patient in the vignette has clinical characteristics consistent with those of the patients in the clinical trials of omalizumab. However, we would recommend careful evaluation of his compliance with his current regimen of medications before making any change in therapy. In addition, because omalizumab is so expensive, we would consider a trial of therapy with a leukotriene modifier or extended-release theophylline. If these measures do not prove effective, we would recommend the addition of omalizumab to his current regimen. His total serum IgE level (436 IU per milliliter) would indicate a dose of omalizumab of 300 to 375 mg subcutaneously every two weeks, depending on his weight. We would observe his response to a stable dose of inhaled corticosteroids for 16 weeks; if he had a substantial reduction in the frequency of exacerbations of asthma, we would then recommend gradual reduction in his inhaled corticosteroids to the lowest dose that still produces consistent asthma control.

No potential conflict of interest relevant to this article was reported.

REFERENCES

- Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89-113.
- Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. *Pediatrics* 2002;110:315-22.
- Castro M, Schechtman KB, Halstead J, Bloomberg G. Risk factors for asthma morbidity and mortality in a large metropolitan city. *J Asthma* 2001;38:625-35.
- Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001;107:3-8.
- Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. *Nat Rev Immunol* 2003;3:721-32.
- Infuhr D, Cramer R, Lamers R, Achatz G. Molecular and cellular targets of anti-IgE antibodies. *Allergy* 2005;60:977-85.
- Maurer D, Fiebiger E, Reininger B, et al. Fcε receptor I on dendritic cells delivers IgE-bound multivalent antigens into a cathepsin S-dependent pathway of MHC class II presentation. *J Immunol* 1998;161:2731-9.
- Owen CE. Anti-immunoglobulin E therapy for asthma. *Pulm Pharmacol Ther* 2002;15:417-24.
- Oettgen HC, Geha RS. IgE regulation and roles in asthma pathogenesis. *J Allergy Clin Immunol* 2001;107:429-40. [Erratum, *J Allergy Clin Immunol* 2001;107:591.]
- Broide DH. Molecular and cellular mechanisms of allergic disease. *J Allergy Clin Immunol* 2001;108:Suppl:S65-S71.
- Presta LG, Lahr SJ, Shields RL, et al. Humanization of an antibody directed against IgE. *J Immunol* 1993;151:2623-32.
- Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6-S11.
- Chang TW. The pharmacological ba-

- sis of anti-IgE therapy. *Nat Biotechnol* 2000; 18:157-62.
14. Hochhaus G, Brookman L, Fox H, et al. Pharmacodynamics of omalizumab: implications for optimized dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003; 19:491-8.
15. 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.
16. 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.
17. Ong YE, Menzies-Gow A, Barkans J, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 2005; 116:558-64.
18. Djukanovic R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004; 170:583-93.
19. MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; 158: 1438-45.
20. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *J Allergy Clin Immunol* 2004; 114:527-30.
21. Prussin C, Griffith DT, Boesel KM, et al. Omalizumab treatment downregulates dendritic cell FcεRI expression. *J Allergy Clin Immunol* 2003; 112:1147-54.
22. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108:184-90.
23. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18: 254-61. [Erratum, *Eur Respir J* 2001; 18: 739-40.]
24. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108:e36.
25. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34:632-8.
26. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60: 309-16.
27. Scientific discussion. (Accessed May 26, 2006, at <http://www.emea.eu.int/humandocs/PDFs/EPAR/Xolair/28009505en6.pdf>)
28. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 2: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Institutes of Health, 1997. (Publication no. 97-4051.)
29. *Idem*. National Asthma Education and Prevention Program Expert Panel Report: guidelines for the diagnosis and management of asthma — update on selected topics 2002. Bethesda, Md.: National Institutes of Health, 2003. (Publication no. 02-5074.)
30. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004; 125:1378-86.
31. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005; 60:302-8.
32. Xolair (omalizumab). San Francisco: Genentech, 2003 (package insert).
33. Hamilton RG, Marcotte GV, Saini SS. Immunological methods for quantifying free and total serum IgE levels in allergy patients receiving omalizumab (Xolair) therapy. *J Immunol Methods* 2005; 303:81-91.
34. Hamilton RG. Accuracy of US Food and Drug Administration-cleared IgE antibody assays in the presence of anti-IgE (omalizumab). *J Allergy Clin Immunol* 2006; 117:759-66.
35. Dacus JJ. Disease of the month: asthma. *PEC Update* 2003; 3:4. (Accessed May 26, 2006, at http://www.pec.ha.osd.mil/Updates/0307web/Aug-Sep_03_Update_Page_4.htm.)
36. Saini SS, MacGlashan DW Jr, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FcεRIα surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol* 1999; 162:5624-30.
37. Food and Drug Administration, Center for Biologics Evaluation and Research. BLA STN 103976/0, review of clinical safety data: original BLS submitted on June 2, 2000 and response to complete review letter submitted on December 18, 2002. Rockville, Md.: Department of Health and Human Services, 2003.
38. Berger W, Gupta N, McAlary M, Fowler-Taylor A. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91:182-8.

Copyright © 2006 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The *Journal's* Web site (www.nejm.org) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronological order, with the most recent first.