CME CREDIT

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Omalizumab: Where does it fit into current asthma management?

ABSTRACT

Omalizumab (Xolair), a monoclonal antibody, is a new agent that blocks the allergic cascade at its primary step. This drug offers substantial promise for patients with moderate-to-severe, persistent allergic asthma that is not well controlled. But due to the cost of the drug, limitations on dosage, and available clinical trial data, it is not a first-line therapy. This review discusses how this drug works, which patients will be candidates for it, and the practical aspects of using it.

KEY POINTS

Omalizumab binds to immunoglobulin E (IgE), a pivotal molecule in the pathogenesis of allergic asthma.

In clinical trials, omalizumab reduced the frequency of asthma exacerbations and the dosage of inhaled corticosteroids needed in moderate-to-severe persistent allergic asthma. It also was beneficial in seasonal allergic rhinitis.

Omalizumab will be most cost-effective in patients with smaller body size, lower IgE levels, and frequent hospitalizations in spite of aggressive multidrug asthma therapy.

OMALIZUMAB (XOLAIR), approved in 2003, is the first monoclonal antibody developed for use in asthma and allergic diseases. It interrupts the allergic cascade at its primary step—the binding of allergen-specific immunoglobulin E (IgE) to mast cells. In contrast, other drugs such as inhaled corticosteroids, antihistamines, and antileukotriene agents act at steps in the cascade after mast cell activation and mediator release.

Thus, omalizumab shows great promise in treating allergic asthma. Clinical trials have shown it can reduce asthma exacerbations and reduce the need for inhaled corticosteroids. But omalizumab is not a first-line agent. As with most bioengineered drugs, it is very expensive. Also, because of current dosage restrictions it may not be used in some patients with larger body size, high IgE levels (ie, > 700 IU/mL), or both.

Currently, omalizumab has approval from the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe persistent allergic asthma in patients older than age 12. However, it has also been studied for use in allergic rhinitis.

This review also discusses the efficacy and safety of omalizumab and offers practical recommendations for its use in clinical practice.

UNMET ASTHMA NEEDS

New and better drugs for asthma are needed. Even though our understanding of asthma has improved in the past 20 years and safe and effective new drugs are available to treat it, asthma is still a serious public health problem,[1] and its prevalence has increased in recent decades.

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This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

In fact, asthma still accounts for approximately 2 million emergency department visits, 500,000 hospitalizations, 14 million missed work days, and 14 million missed school days each year in the United States.[2] Its direct and indirect costs total an estimated $12.7 billion per year.[3] Moreover, asthma claims 4,000 to 5,000 lives each year.[4] Most of these deaths could be prevented with proper management.

There are several potential reasons for these suboptimal outcomes:

- Some patients have poor access to quality health care.
- Some patients develop physiologic resistance to inhaled corticosteroid therapy.[5]
- Inhaled steroids are underutilized. Only 26% of patients with persistent asthma (who should be on inhaled corticosteroids according to national guidelines[6]) are actually taking them.[1] The reasons for this low rate are not entirely clear but probably include patients being unable to obtain their medications and physicians not being aware of which patients need inhaled corticosteroids.
- Patients are not complying with regular use of inhaled corticosteroids. Reasons may include fear of side effects, difficulties with inhaler devices, and cost.

Most asthma deaths could be prevented with proper management

Although omalizumab may be able to address issues of steroid resistance and patient noncompliance (as it is a directly observed therapy), it will be unlikely to fill the needs of patients who suffer asthma morbidity because they have financial difficulty obtaining their medications.

THE ROLE OF IgE IN ALLERGIC ASTHMA

Most experts divide asthma into allergic and nonallergic forms,[7] although some do not make this distinction.[8] A major difference between allergic and nonallergic asthma is the presence of allergen-specific IgE antibodies.

IgE is believed to be pivotal in the pathogenesis of allergic asthma. IgE levels tend to be elevated in people with allergic asthma,[9] and patients with allergic asthma with positive skin-test reactions to a given aeroallergen (a phenomenon known to be IgE-mediated) tend to have exacerbations of asthma when exposed to that aeroallergen.[10]

In addition, the mechanism predominantly responsible for activation of mast cells in the airways of people with allergic asthma is the cross-linking of IgE on the surface of the mast cell by allergens.

In nonallergic (nonatopic) asthma, on the other hand, there are other, IgE-independent pathways that mediate inflammation.[11]

Whether omalizumab will be effective in asthmatic patients with a negative skin test (ie, with nonatopic asthma) but who have elevated IgE levels remains to be determined. At present, the drug has been studied and approved for use only in patients with allergic asthma with both elevated IgE levels and positive inhalent allergies to perennial allergens, documented by either skin testing or radioallergosorbent testing.

IgE and the allergic response

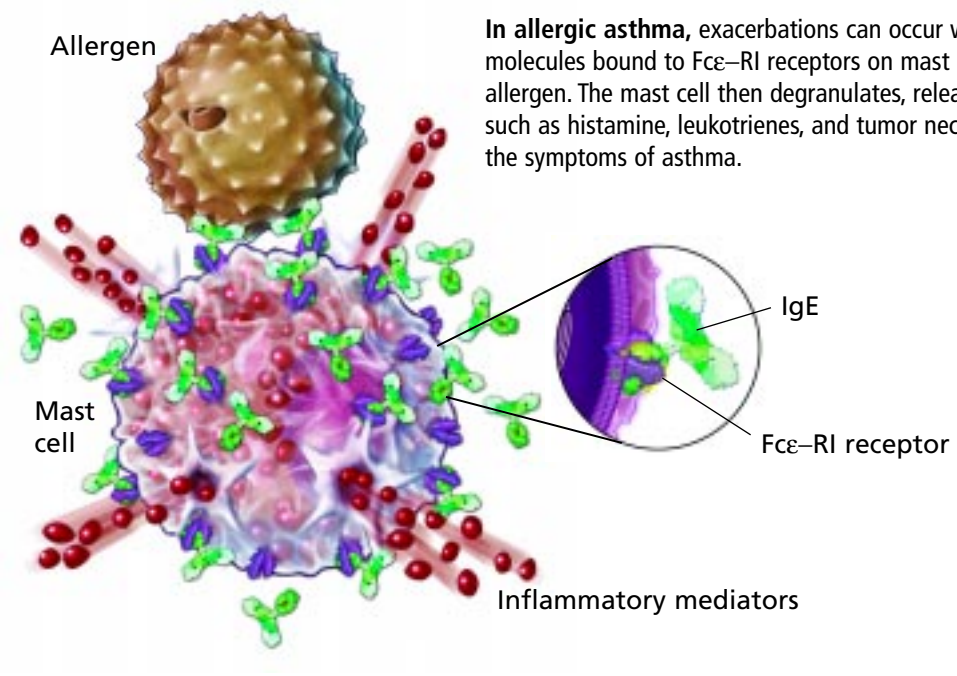
IgE antibodies mediate the allergic response. The putative functional role of IgE in the immune system is to defend against helminths and other parasites. However, given the low prevalence of parasitic infections in the United States, most physicians here are more familiar with IgE's role in mediating allergic reactions in people with rhinitis or asthma.

In allergic disorders, when "naive" B cells encounter an antigen (eg, ragweed) for the first time, they bind it with membrane-bound immunoglobulin M (IgM) on their surface. They then internalize the antigen, degrade it, and present peptide remnants of it "complexed" with major histocompatibility type II molecules to helper (CD4+) T cells.[12]

If these T cells have receptors specific for this allergen, they become stimulated and secrete cytokines, which cause B cells to proliferate. If this proliferation occurs in the presence of interleukin-4 (IL-4) or IL-13, IgM antibodies will then "class-switch" to IgE-type antibodies. These IgE antibodies are then released into the circulation and bind to mast cells and basophils, where they mediate the allergic response.

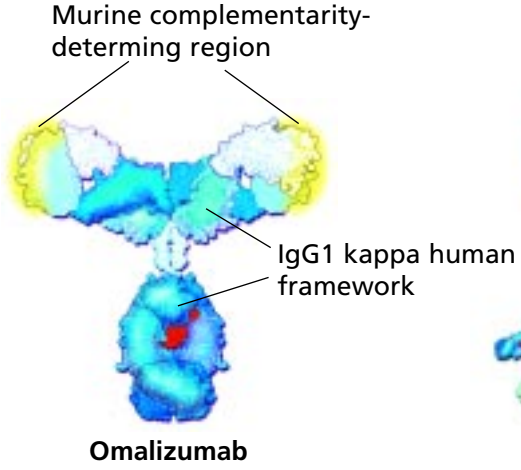
When allergens bind to and crosslink IgE on the surfaces of mast cells and basophils, these cells are activated and release histamine and cytokines such as tumor necrosis factor-alpha. Histamine release can provoke ocular

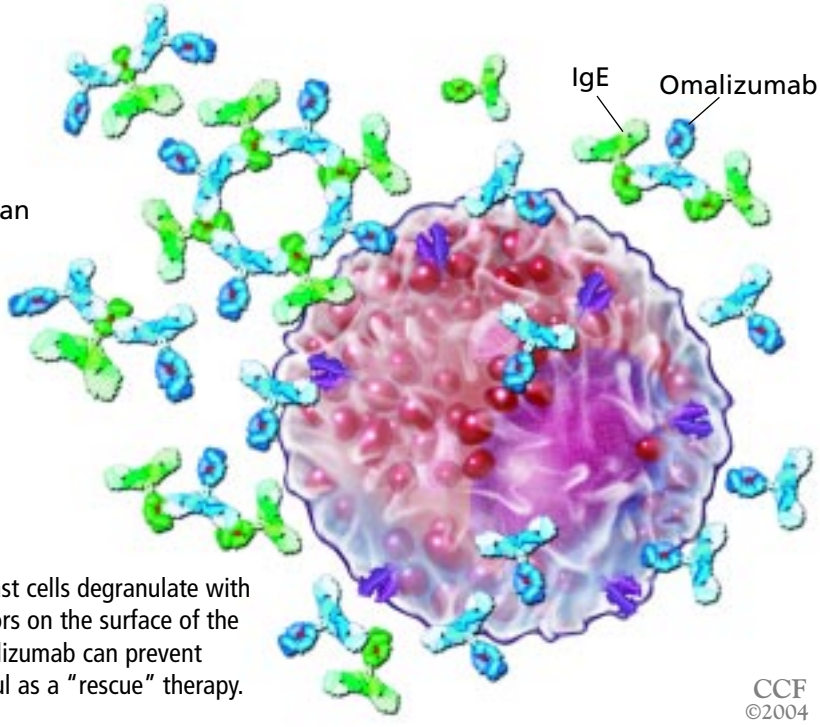
How omalizumab prevents exacerbations of asthma



In allergic asthma, exacerbations can occur when immunoglobulin E (IgE) molecules bound to Fcε–RI receptors on mast cells are cross-linked by an allergen. The mast cell then degranulates, releasing inflammatory mediators such as histamine, leukotrienes, and tumor necrosis factor alpha, which cause the symptoms of asthma.

Omalizumab, a monoclonal antibody, binds the same domain on the IgE molecule that would otherwise attach to the Fcε–RI receptor. The resulting complexes (trimers and hexamers) therefore cannot bind to mast cells.





As a result of omalizumab therapy, fewer mast cells degranulate with allergen exposure. The number of Fcε–RI receptors on the surface of the mast cell is also indirectly down-regulated. Omalizumab can prevent exacerbations of asthma; however, it is not useful as a "rescue" therapy.

FIGURE 1

TABLE 1

Omalizumab at a glance

Pronunciation and nomenclature: oh-mah-LYE-zoo-mab: li=immunomodulatory, zu=humanized, mab=monoclonal antibody

Mechanism: Humanized monoclonal antibody that binds human IgE and prevents it from attaching to mast cells and basophils

Indications: Moderate or severe persistent asthma that has not responded well to inhaled corticosteroids and long-acting beta-agonists

Side effects: Urticaria in 2%–3% of patients; anaphylaxis in 0.01%–0.1%

Route and frequency: Subcutaneous, monthly or every 2 weeks depending on the dose

Dose: 0.016 mg × body weight (kg) × IgE level (IU/mL)

Cost: Varies on the basis of dose needed, but will average about $12,000 per year

Omalizumab is given by subcutaneous injection in monthly doses

and nasal itching, sneezing, and rhinorrhea in the upper airway, bronchospasm in the lower airway, and hypotension when circulating systemically.[13] Tumor necrosis factor-alpha, when released from mast cells in the airway of a patient with asthma, attracts T cells and eosinophils into the airways.

HOW DOES OMALIZUMAB WORK?

Omalizumab, a recombinant humanized monoclonal antibody, binds free (unbound) IgE in the serum regardless of allergen specificity. The bound IgE cannot bind to the high-affinity IgE Fcε-RI receptors on mast cells and basophils because omalizumab binds to the same region on the IgE molecule that the Fcε-RI receptor does (FIGURE 1).

Omalizumab is given by subcutaneous injection in monthly doses (TABLE 1). When given in sufficient doses, omalizumab can reduce free IgE levels by up to 98%.[14] Total IgE levels (which include both free and bound IgE) actually increase slightly during therapy, because omalizumab-bound IgE has a slower rate of clearance than free IgE.[14] At present, commercially available assays for IgE measure only total IgE and therefore are not useful after a patient has received omalizumab.

In addition, omalizumab decreases the density of Fcε-RI receptors on basophils by more than 95%.[15] This reduction in turn decreases the basophils' ability to degranulate in response to an allergen. Omalizumab-bound allergen-specific IgE may also act as a "sponge" to soak up allergen that the body encounters.

HOW WELL DOES IT WORK?

A number of studies have demonstrated the efficacy of omalizumab in treating asthma and allergic rhinitis

Studies in asthma

TABLE 2 summarizes the major studies of the efficacy of omalizumab in asthma.[14,16–20] To enter these studies, patients had to have perennial allergic asthma as defined by positive skin-test responses to perennial allergens (from dust mites, cats, dogs, or, in the study by Busse et al,[14] cockroaches). They also had to have an IgE level between 30 and 700 IU/mL (children with levels up to 1,300 IU/mL were also included) and to have asthma inadequately controlled by inhaled corticosteroids. (The normal range for IgE varies with age but is always less than 100 IU/mL at our laboratory.)

Busse et al[14] randomly assigned 525 "severe allergic asthmatics requiring daily inhaled corticosteroids" to receive placebo or omalizumab subcutaneously. The patients had persistent airflow obstruction despite moderate doses of inhaled corticosteroids but were not using long-acting beta-agonists. This profile is similar to that of many patients seen in primary care practice.

The dose of inhaled corticosteroids was held constant for 16 weeks, and then was tapered during an additional 12 weeks. The primary outcome measures were the number of asthma exacerbations during each phase.

During the steroid-stable phase, 14.6% of patients in the omalizumab group had asthma exacerbations vs 23.3% in the placebo group ($P = .009$). The omalizumab group continued to have fewer exacerbations during the steroid-reduction phase (21.3% vs 32.3%; $P = .004$).

A secondary outcome of this study was the

TABLE 2

Summary of studies of efficacy of omalizumab in asthma

FIRST AUTHOR	AGE RANGE	NO. OF PATIENTS*	IgE RANGE (IU/ML)†	FEV1‡	RESULTS§
Busse[14]	12–75	268/257	30–700	40–80%	**Steroid-stable phase:** Exacerbations in 14% vs 23% ($P = .009$) **Steroid-reduction phase:** Exacerbations in 21% vs 32% ($P = .004$)
Holgate[16]	Not available	126/120	19–1,055	63–66%	**Steroid-stable phase:** Better "total asthma symptom score" vs placebo group **Steroid-reduction phase:** 60% vs 50% reduction in inhaled corticosteroid dose in favor of omalizumab ($P = .003$)
Milgrom[17]	11–50	212/105	40–1,785	50–90%	**Steroid-stable phase:** Asthma symptom score (0 [best] to 7 [worst]) 2.87 in both treatment groups vs 3.1 in control group ($P < .05$ for both comparisons) **Steroid-reduction phase:** Symptom score 2.7 in both high-dose and low-dose groups vs 2.9 in placebo group ($P = .048$ and .14 for high-dose and low-dose groups vs placebo, respectively)
Milgrom[18]	6–12	225/109	30–1,300	> 60%	**Steroid-stable phase:** 35% of omalizumab vs 25% of placebo patients had an asthma exacerbation (P not significant) **Steroid-reduction phase:** Inhaled corticosteroids were completely withdrawn in 55% of omalizumab group vs 39% of placebo group ($P = .004$)
Finn[19]	12–75	268/257	30–700	40–80%	**Steroid-stable phase:** Score on asthma quality-of-life questionnaire (1 [worst] to 7 [best]) increased by 0.93 points in treatment group vs 0.66 points in placebo group ($P < .01$) **Steroid-reduction phase:** Scores increased 0.97 points in treatment group vs 0.7 points in placebo group ($P < .01$)
Soler[20]	12–76	274/272	30–700	40–80%	**Steroid-stable phase:** Treated patients had 0.28 exacerbations per patient vs 0.6 for placebo ($P < .001$) **Steroid-reduction phase:** Treated patients had 0.36 exacerbations per patient vs 0.75 for placebo ($P < .001$)

*Active treatment group/placebo group
†Range of total serum levels of immunoglobulin E, IU/mL
‡Range of baseline forced expiratory volumes in 1 second (% of predicted), except for the study of Holgate et al[16]: mean of 63% in the active treatment group and 66% in the placebo group.
§All comparisons are with omalizumab 0.016 mg/kg body weight/IU/mL IgE concentration, except for the study of Milgrom et al,[17] which compared omalizumab 0.014 mg/kg/IU/mL, omalizumab 0.006 mg/kg/IU/mL, and placebo

mean reduction in the dose of inhaled corticosteroids: 75% in the treatment group vs 50% in the placebo group ($P < .001$).

Milgrom et al[17] randomized 317 patients with moderate or severe persistent asthma to receive either placebo, omalizumab in a high dose (5.8 µg per kg of body weight per ng of IgE per mL; see **HOW TO CALCULATE THE DOSE**, below), or omalizumab in a low dose (2.5 µg/kg/ng/mL). Subcutaneous injections were given every 2 weeks for the next 20 weeks. For the first 12 weeks the inhaled corticosteroid dose was held constant. Then for the next 8 weeks an attempt was made to decrease the dose of inhaled corticosteroid.

The primary outcome was the patient's score on a 7-point asthma symptom scale, with 7 representing the most severe symptoms. All three groups began the study with a mean score of 4.0.

At the end of the study, the scores were 2.7 in both of the treatment groups and 2.9 in

the placebo group (P = .048 for the comparison between the placebo group and the high-dose group). This difference of 0.2 points may appear small, but the treatment groups were taking less inhaled corticosteroid than the placebo group.

Other studies also showed a statistically significant improvement in indices of quality of life with omalizumab.[21] Significantly more patients receiving omalizumab vs placebo were able to discontinue inhaled or oral corticosteroids.

Together, these studies clearly document that patients receiving omalizumab had from 35% to 50% fewer exacerbations of asthma while reducing their doses of inhaled corticosteroids—a clinically important effect.

Studies in more-severe asthma

Patients in these studies were for the most part on moderate-dose inhaled corticosteroids alone, without any other controller therapy, whereas patients in clinical practice who will be candidates for this drug will likely be on a high-dose inhaled corticosteroid plus a long-acting beta-agonist.

Cost of omalizumab: $5,196 to $25,980 per year

At present it is unclear if the clinically meaningful benefit observed in asthma patients on moderate-dose inhaled corticosteroids will also occur in sicker patients on high-dose inhaled corticosteroids and long-acting beta-agonists—the population at which omalizumab will be most directed.

Holgate et al[16] performed a study in 250 patients who were using an inhaled corticosteroid in high doses (fluticasone, average dose > 1,300 μg/day). Patients were randomized to receive either omalizumab or placebo. The primary outcome was the percentage dose reduction in inhaled fluticasone.

This study did demonstrate a larger decrease in inhaled corticosteroid usage in the treatment group than in the placebo group. There were also fewer asthma exacerbations in the treatment group, but the trend did not reach statistical significance, as the study was not powered to examine this outcome.

Studies in children

Omalizumab is FDA-approved only for patients age 12 and older. Two studies[18,22] examined its efficacy in patients as young as age 6; their results suggest that it will be equally effective in younger patients.

Anti-inflammatory effect

Because the emphasis in the management of asthma has shifted toward preventing inflammation and its putative result, airway remodeling, it is important that asthma therapies demonstrate anti-inflammatory activity.

Given that mast cell activation causes inflammation by release of cytokines such as tumor necrosis factor-alpha and IL-4, and that omalizumab prevents mast cell activation (at least via IgE-dependent mechanisms), it is conceivable that omalizumab exerts substantial anti-inflammatory activity.

Fahy et al[23] randomized 19 asthma patients to receive intravenous omalizumab or placebo. Patients who received omalizumab had a significant attenuation of the early- and late-phase responses to allergen inhalation challenge, and had significantly lower sputum eosinophil counts after treatment compared with patients who received placebo.

Silkoff et al[24] showed that exhaled nitric oxide (a marker of airway inflammation in asthma) is suppressed by omalizumab as compared with placebo.

The studies suggest that omalizumab has anti-inflammatory properties and that it may ultimately influence remodeling.

IS OMALIZUMAB COST-EFFECTIVE?

Biologic agents tend to be expensive to produce. The wholesale acquisition cost of omalizumab (ie, the price the pharmacy pays) is $433 for one 150-mg vial.[21]

The dosage of omalizumab depends on the patient's body weight and IgE level (see below). Therefore, a small patient with a slightly elevated IgE level might require only one vial per month, at a wholesale cost of $5,196 per year. A larger patient with an IgE level of 600 IU/mL could require as many as five vials per month, at a cost of $25,980 per year.

Given that patients with severe asthma incur costs of as much as $12,813 per year for their asthma care (primarily for medications and hospitalizations),[25] omalizumab is most likely to be cost-effective if it is used in

patients who consume a disproportionate amount of economic resources.

Hospitalizations account for a large part of the expense of asthma care. One emergency department visit with subsequent hospitalization for asthma was estimated to cost $3,102 in 1997 dollars.[26] Omalizumab has been shown, in a pooled analysis of three multicenter trials, to prevent 92% of hospitalizations when compared with placebo.[27] Therefore, this drug is most cost-effective if given to patients who are hospitalized two or more times a year despite multidrug asthma therapy.

The major clinical trials of omalizumab all required that patients have IgE-mediated sensitivity to perennial allergens such as cat, dog, or dust mite allergens. No studies of this therapy have been done in patients with pure seasonal asthma. Omalizumab may be cost-effective for a significant proportion of these patients with seasonal asthma, as it will not need to be given year-round.

EFFICACY IN SEASONAL ALLERGIC RHINITIS

Multiple studies have shown omalizumab to be effective in IgE-mediated allergic rhinitis.[28–31] This efficacy may be particularly relevant to its use in asthma because most patients with asthma have allergic rhinitis, either in clinical or subclinical form,[32] and because treatment of allergic rhinitis improves clinical outcomes in asthma.[32]

The emerging view suggests that allergic rhinitis and asthma are similar pathophysiologic processes but in different locations. Therefore, when treating patients for allergic asthma with omalizumab, clinicians will often be concomitantly treating allergic rhinitis.

Adelroth et al,[28] in a double-blind trial, randomized 536 patients between 12 and 75 years of age with at least a 2-year history of ragweed-induced allergic rhinitis to receive omalizumab (300 mg, 150 mg, or 50 mg) or placebo every 3 weeks (if their IgE levels were between 151 and 700 IU/mL) or every 4 weeks (if their IgE levels were between 30 and 150 IU/mL).

The main outcome measures were the self-assessed daily nasal symptom severity score, which ranged from 0 (no symptoms) to 3, and the frequency of rescue antihistamine use.

The nasal symptom scores were significantly lower with the 300-mg dose than with placebo (0.75 vs 0.98 respectively; $P = .002$). Patients in the 300-mg and 150-mg groups used rescue antihistamines less frequently than did patients on placebo (12% and 13% of the days for the 300-mg and 150-mg groups vs 21% of the days for patients on placebo). Had patients in all groups been required to use the same amount of oral antihistamine, the difference in symptom level between the treatment and placebo groups would likely have been larger.

Nayak et al[33] found omalizumab to significantly improve rhinitis-specific quality of life.

SAFETY OF OMALIZUMAB

More than 4,000 patients have received omalizumab in placebo-controlled trials, and no serious adverse effects have consistently appeared.

Urticaria. In the trial by Milgrom et al,[17] urticaria developed in 8 (7.5%) of 106 patients in the high-dose group, 6 (5.7%) of 106 patients in the low-dose group, and 3 (2.9%) of 105 patients in the placebo group. In a similar trial in children,[18] urticaria developed in 9 (4%) of 225 omalizumab-treated patients and 1 (0.9%) of 109 placebo-treated patients. However, in the study by Busse et al,[14] urticaria was noted in 1.5% of treated patients and 3.1% of placebo patients.

Omalizumab may cause urticaria in a small percentage of patients, but the urticaria tends to be mild and happens only with the first infusion, suggesting that it is not IgE-mediated. In most instances, patients continue to tolerate the drug well.

Anaphylaxis. Three patients in whom no other allergic trigger could be found have experienced anaphylaxis during treatment with omalizumab. None of these patients required admission to an intensive care unit. This incidence represents less than 0.1% of patients treated.

Nevertheless, in view of the risk of anaphylaxis, it is recommended that this medication be given in the office of a physician capable of treating anaphylaxis and that patients

Allergic rhinitis and asthma may be similar processes in different locations

should be observed for a period of time before leaving the office.

Malignancy. The product label for omalizumab notes that it poses a possible increased risk of malignancy. Malignancies occurred in 0.5% of patients on active treatment and 0.2% of patients on placebo in the studies that were submitted to obtain FDA approval. Because these studies were conducted over less than 1 year, a shorter period than that in which oncogenesis is usually observed, and because the tumors involved various and seemingly unrelated organs, there is reason to doubt that these tumors were caused by the drug.

Further postmarketing surveillance in progress will provide more definitive data on whether a causal relationship exists between malignancy and omalizumab.

WHICH ASTHMA PATIENTS ARE CANDIDATES FOR OMALIZUMAB?

The FDA has approved omalizumab for use in patients who have all of the following criteria:

- Moderate or severe persistent allergic asthma
- Age greater than 12 years
- Symptoms despite inhaled corticosteroid therapy
- A serum total IgE level between 30 and 700 IU/mL (Unless the IgE level exceeds 30, there is too little substrate for the omalizumab to bind. The IgE level should not exceed 700 IU/mL, as the volume of the omalizumab injection needed will likely be too large.)
- A positive result on skin-prick testing or radioallergosorbent testing with at least one perennial (ie, always-present) allergen.

Omalizumab is not a first-line therapy for asthma

HOW TO CALCULATE THE DOSE

The monthly dose of omalizumab (in milligrams) is calculated as 0.016 × body weight in kg × the IgE level in IU/mL: thus, a 67-kg patient with an IgE level of 700 IU/mL would require 0.016 × 67 × 700 = 750 mg per month.

Owing to the volume of the injection, doses of omalizumab larger than 300 mg per month must be given in divided doses every 2 weeks. Therefore, this hypothetical patient should get 375 mg subcutaneously every 2 weeks. Since omalizumab is concentrated to 150 mg/1.2 mL, each 375-mg dose would be delivered in approximately 2.5 mL subcutaneously.

Even so, some patients who are very large or who have very high IgE levels or both may not be able to receive omalizumab because the calculated dose would be too large to be given in two subcutaneous injections per month. At present, omalizumab is not recommended for patients requiring more than 750 mg per month according to the above formula.

Omalizumab has not been well studied at doses above 750 mg per month and is not FDA-approved above this dose. This is primarily because using doses greater than 750 mg per month would be cost-prohibitive (see above discussion) and would require more than two injections per month because technical issues limit how much this drug can be concentrated.

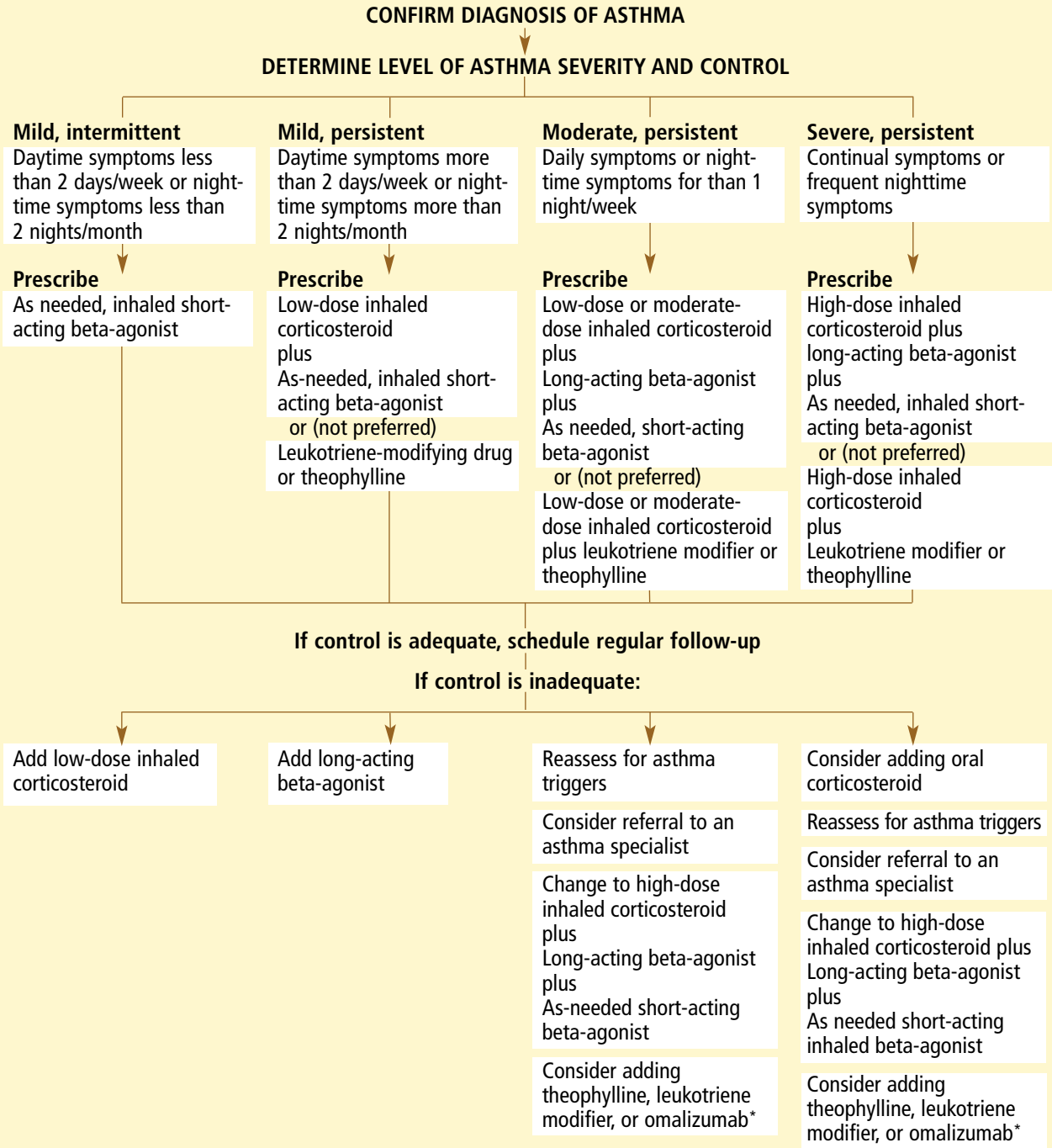
The dosing formula described above, if used correctly, will lead to prescribing enough omalizumab to bind over 98% of the free IgE in most patients.[14] Therefore, there is no need to monitor IgE levels after prescribing this drug, and in fact, as mentioned above, there is no commercially available assay that measures free IgE levels.

Omalizumab is not a first-line therapy for asthma and is intended for use only in patients who, despite optimal medications taken regularly, do not achieve the goals of asthma management. Therefore, it will usually be used as add-on therapy for patients who are already on two or three drugs for asthma (FIGURE 2). It is classified as a preventive therapy and does not have any known benefit during an acute asthma exacerbation.

There is no evidence to suggest that tachyphylaxis occurs with prolonged use of omalizumab, although data are limited regarding its long-term use. Continued safety and efficacy has been reported when omalizumab treatment was given for two consecutive seasons for seasonal allergic rhinitis.[34]

For asthma patients who satisfy the above-described criteria for use, omalizumab should be considered for patients in any of the following categories:

Omalizumab in an algorithm of asthma care



*__Criteria for use of omalizumab__ (all must be present)

- IgE level 30–700 IU/mL
- Skin test or radioallergosorbent test positive for at least one perennial allergen
- Age > 12 years
- Poor asthma control on low-or moderate dose inhaled corticosteroid plus long-acting beta-agonist or leukotriene modifying drug
- Patient's calculated dose of omalizumab < 750 mg

FIGURE 2

- Dependent on oral steroids
- On multiple-drug asthma therapy (eg, inhaled steroids combined with a long-acting beta-agonist, a leukotriene modifier drug, or theophylline) with persistent and significant symptoms or reversible airflow obstruction as measured by spirometry.
- Have had adverse effects from corticosteroids, or are at increased risk for them.

TOPICS FOR FUTURE RESEARCH

Although omalizumab has been studied in more than 4,000 patients with asthma or allergic rhinitis, a number of questions remain.

- *What are it's long-term effects?* Studies are ongoing.
- *Will it be effective in nonatopic asthma?* Given that IgE is produced locally in the airways of people with nonatopic asthma, whether omalizumab will have salutary effects in this population remains to be seen.
- *Will it prevent airway remodeling?* Since this agent has anti-inflammatory properties, it will be of great importance to gauge whether it prevents either the long-term loss of lung function or airway remodeling that some patients with asthma experience.[35,36]
- *Will it facilitate immunotherapy?* Some patients with asthma or allergic rhinitis currently receive allergen vaccines ("allergy shots"). Occasionally, patients receiving immunotherapy exhibit a tendency for serious IgE-mediated (anaphylactic) reactions. Such patients may be unable to advance the dose of immunotherapy injections to therapeutic levels. Omalizumab, by decreasing the severity or frequency of these reactions, may enable these patients to achieve therapeutic ("maintenance") doses of immunotherapy.
- *Will it be beneficial in severe asthma?* The major clinical studies with omalizumab primarily included patients on inhaled corticosteroids and short-acting beta-agonists. In these patients it clearly showed additive benefit, but due to cost considerations it will tend to be used primarily in patients with the most severe asthma.

However, these patients are usually on inhaled corticosteroids, long-acting beta-agonists, short-acting beta-agonists, and often a leukotriene modifier. It remains to be clearly demonstrated that patients on all four of these drugs will experience the same level of improvement in their asthma symptoms and quality of life.

- *Can it be used in other allergic diseases?* Omalizumab may ultimately be helpful in all allergic disorders in which IgE is mechanistically involved. A potential role for anti-IgE therapy in food allergy has been studied.[37]

REFERENCES

1. **Adams RJ, Fuhlbrigge A, Guilbert T, Lozano P, Martinez F.** Inadequate use of asthma medication in the United States: results of the asthma in America national population survey. J Allergy Clin Immunol 2002; 110:58–64.
2. **Mannino D, Homa D, Akinbami L, Moorman J, Gwyn C, Redd S.** Surveillance for asthma—United States, 1980–1999. MMWR March 29, 2002/51(SS01):1–13.
3. **Weiss K, Sullivan S.** The health economics of asthma and rhinitis. Assessing the economic impact. J Allergy Clin Immunol 2001; 107:3–8.
4. **Minino A, Arias E, Kochanek K, Murphy S, Smith B.** Deaths: Final Data for 2000. National Vital Statistics Report. Sept 16, 2002 Vol 50, No 15.
5. **McGeehan M, Busse WW.** Refractory asthma. Med Clin North Am 2002; 86(5):1073–1090.
6. **National Asthma Education and Prevention Program-Expert Panel Report 2.** Guidelines for diagnosis and management of asthma. J Allergy Clin Immunol 2002; 110:S141–S219.
7. **Novak N, Bieber T.** Allergic and nonallergic forms of atopic diseases. J Allergy Clin Immunol 2003; 112:252–262.
8. **Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG.** Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989; 320:271–277.
9. **Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD.** Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991; 325:1067–1071.
10. **Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL.** Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol 1986; 78:590–600.
11. **Mehlhop PD, van de Rijn M, Goldberg AB, et al.** Allergen-induced bronchial hyperreactivity and eosinophilic inflammation occur in the absence of IgE in a mouse model of asthma. Proc Natl Acad Sci USA 1997; 94:1344–1349.
12. **Janeway CA, Travers P, Walport M, Schlomchik M.** Immunobiology—The Immune System in Health and Disease, 5th ed. New York: Garland Publications, 2001:343–344.
13. **Kaliner M, Shelhamer JH, Ottesen EA.** Effects of infused histamine: correlation of plasma histamine levels and symptoms. J Allergy Clin Immunol 1982; 69:283–289.
14. **Busse W, Corren J, Lanier B, et al.** Omalizumab, anti-IgE recombinant humanized monoclonal antibody for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108:184–190.
15. **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; 158:1438–1445.
16. **Holgate S, Bousqet J, Wenzel S, et al.** Omalizumab improves disease control in patients at high risk of serious asthma related morbidity and mortality [abstract]. Am J Respir Crit Care Med 2002;165:A187.
17. **Milgrom H, Fick R, Su J, et al.** Treatment of allergic asthma with monoclonal anti-IgE antibody. N Engl J Med 1999; 341:1966–1973.
18. **Milgrom H, Berger W, Nayak A, et al.** Treatment of childhood asthma

with anti-immunoglobulin E antibody. Pediatrics 2001; 108:E36.
19. **Finn A, Gross G, van Bavel J, et al.** Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. J Allergy Clin Immunol 2003; 111:278–284.
20. **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; 18:254–261.
21. **Personal Communication.** David Zito, clinical specialist, Genentech.
22. **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; 91:182–188.
23. **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; 160:1023–1027.
24. **Silkoff P, Milgrom H, Tran Z, et al.** Exhaled nitric oxide (ENO) and anti-inflammatory effects of a recombinant humanized monoclonal antibody to IgE (RHUMAB-E25) in pediatric asthma [abstract]. Chest 2000; 118:101S.
25. **Cisternas M, Blanc P, Yen I, et al.** A comprehensive study of the direct and indirect costs of adult asthma. J Allergy Clin Immunol 2003; 111:1212–1218.
26. **Stanford R, McLaughlin T, Okamoto LJ.** The cost of asthma in the emergency department and hospital. Am J Respir Crit Care Med 1999; 160:211–215.
27. **Corren J, Casale T, Deniz Y, Ashby M.** Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003; 111:87–90.
28. **Adelroth E, Rak S, Haatela T, et al.** Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000; 106:253–259.
29. **Casale T, Condemi J, LaForce C, et al.** Effect of omalizumab on symptoms of seasonal allergic rhinitis. JAMA 2001; 286:2956–2967.
30. **Casale T, Bernstein IL, Busse W, et al.** Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997; 100:110–121.
31. **Casale T, Condemi J, Miller S, et al.** Anti-IgE (omalizumab) in the treatment of seasonal allergic rhinitis (SAR). Ann Allergy Asthma Immunol 1999; 82:A32.
32. **Togias A.** Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol 2003; 111:1171–1183.
33. **Nayak A, LaForce C, Rowe M, et al.** RhuMAb-E25 improves quality of life in patients with seasonal allergic rhinitis (SAR) [abstract]. J Allergy Clin Immunol 1999; 103:S49.
34. **Casale TB, Condemi J, Bernstein JA, et al.** Safety of re-administration of rhuMAb-E25 in seasonal allergic rhinitis (SAR) [abstract]. Ann Allergy Asthma Immunol 2000; 84:A70.
35. **Hudon C, Turcotte H, Laviolette M, Carrier G, Boulet LP.** Characteristics of bronchial asthma with incomplete reversibility of airflow obstruction. Ann Allergy Asthma Immunol 1997; 78:195–202.
36. **Brown PJ, Greville HW, Finucane KE.** Asthma and irreversible airflow obstruction. Thorax 1984; 39:131–136.
37. **Leung DYM, Sampson HA, Yunginger JW, et al.** Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003; 348:986–993.

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