

Immunoglobulin E Blockade in the Treatment of Asthma

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Patients with moderate-to-severe asthma often have persistent symptoms despite aggressive pharmacotherapy, enthusiastic patient compliance, and proper technique in using delivery devices. Persistent symptoms have detrimental effects on patients' quality of life and result in a tremendous financial burden because of an increased utilization of health care resources. Guidelines from the National Asthma Education and Prevention Program list symptom prevention, near-normal lung function, and participation in activities (e.g., school, work) as goals of successful asthma therapy. The development of pharmacologic and biologic therapies that target different aspects of airway inflammation will help patients with persistent asthma symptoms achieve these goals. Immunoglobulin E (IgE) is increasingly recognized as a key component of asthma pathophysiology and contributes to both the early- and late-phase inflammatory cascade of the airways by inhibiting allergen-induced activation of mast cells. Both epidemiologic and clinical evidence support the use of IgE blockade for asthma treatment. Omalizumab is currently the only IgE-targeted therapy approved by the United States Food and Drug Administration for asthma treatment. The drug improves symptoms, reduces exacerbations, and improves quality of life in certain patient populations.

Key Words: antiinflammatory asthma, corticosteroids, dosing, immunoglobulin E, IgE, omalizumab.

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Asthma is a chronic inflammatory airway disease characterized by acute episodes of bronchoconstriction that are usually reversible.¹ In the United States, asthma imposes a substantial burden, as approximately 20.5 million Americans (6.2 million persons < 18 yrs of age) reported having asthma in 2004.² Despite advances in pharmacotherapy and asthma management, many patients with moderate-to-severe disease have persistent symptoms, which lead to physician visits, emergency department visits, hospitalizations, and missed work or school days. This situation results in lifestyle limitations and high expenses. In 2004, the total cost related to asthma was approximately \$16 billion.² The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

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(TENOR) 3-year observational study showed that much of the asthma-related morbidity and utilization of health care resources affected patients with moderate-to-severe and/or difficult-to-treat asthma (Figure 1).³

Patient nonadherence and poor inhalation technique are common⁴⁻⁸ and most likely contribute to persistent symptoms. However, the prospective Gaining Optimal Asthma Control (GOAL) study showed that symptoms were uncontrolled in as many as 29% of patients with moderate-to-severe asthma despite aggressive pharmacotherapy, good adherence (virtually 100%), and tightly monitored inhalation techniques.⁹ In such individuals, a variety of comorbid diseases, such as gastroesophageal reflux disease,^{10, 11} thyroid disease,¹² vocal cord dysfunction,¹³ left ventricular dysfunction,¹⁴ and upper airway disease (e.g., seasonal allergies),¹⁵⁻¹⁷ may complicate symptoms of asthma. Triggers, such as respiratory infections (particularly viral infections),^{18, 19} indoor allergens,²⁰ and environmental exposures (e.g., to smoke),²¹ may also aggravate asthma symptoms.

Another notable contributor to persistent symptoms in patients with asthma is a genuine lack of response to pharmacotherapy. Patient characteristics (e.g., genetics, environmental influences) and drug properties (e.g., formulation, delivery system, molecular target) pose considerable and distinctive challenges to the management of asthma symptoms.

Current Approaches to Asthma Therapy

Guidelines from the National Asthma Education and Prevention Program (NAEPP) support compre-

hensive pharmacologic therapy, as a key component of asthma management, to prevent or reverse airway inflammation and to manage acute exacerbations. Other components of management are as follows^{1, 22}:

- Use objective measures of lung function to assess asthma severity and the course of treatment
- Control environmental factors that contribute to disease severity
- Offer patient education that involves the patient, his or her family or caregiver, and clinicians

Goals of successful treatment include the following^{1, 22}:

- Prevent acute and chronic symptoms
- Achieve and maintain near-normal lung function
- Achieve and maintain near-normal participation in activities (e.g., school, work)
- Prevent emergency visits and hospitalizations
- Minimize or eliminate adverse effects of drugs
- Satisfy the patient's expectations for asthma care

A combination approach consisting of the use of reliever drugs to treat acute exacerbations and controller drugs to manage persistent symptoms is the pharmacologic foundation of asthma therapy. Starting and maintaining pharmacotherapy in a stepwise manner is recommended. The steps are based on disease severity, which is classified according to symptoms and lung function.

Inhaled Corticosteroids

Inhaled corticosteroids are recommended as

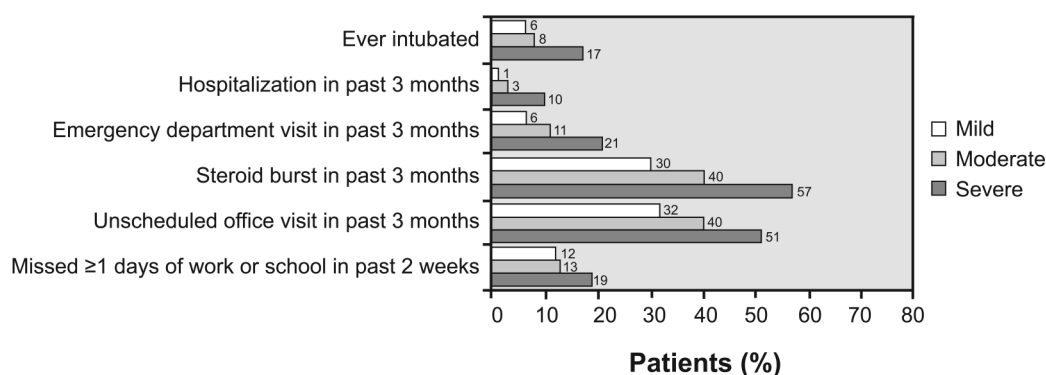


Figure 1. Rates of health care utilization and missed work or school days were higher among patients with moderate-to-severe or difficult-to-treat asthma than among patients with mild asthma in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. Among all severity groups, the χ^2 test yielded $p < 0.05$ for the differences. (Adapted from reference 3 with permission.)

first-line therapy for the long-term control of persistent asthma in adults and children whose disease is mild to severe.²² Inhaled corticosteroids decrease inflammation of the airways,^{23, 24} improve lung function,^{23, 25, 26} reduce asthma-related emergency department visits and hospitalizations,^{27, 28} and reduce mortality due to asthma.^{29, 30} Responses to inhaled corticosteroids vary substantially,³¹ and many patients have persistent asthma symptoms despite upward titration of inhaled corticosteroids to the dosages recommended in the NAEPP guidelines.²² As an alternative, symptoms that persist despite the use of high-dose inhaled corticosteroids may be attributed to the observed plateau in the dose-response curve for inhaled corticosteroids.^{32–36} Meta-analyses demonstrated that most of the clinical benefit of inhaled budesonide was achieved at a dose of 400 µg/day, with maximum clinical effects observed at 1000 µg/day.³⁵ The maximum therapeutic benefit of fluticasone propionate was achieved at 200 µg/day, with nominal clinical benefits observed at doses higher than this.³⁶

Patients with insensitivity to inhaled corticosteroids require higher maintenance doses given earlier and/or more frequent systemic bursts of corticosteroid than those needed for steroid-sensitive patients. Also, patients with severe disease require long-term treatment with high doses of inhaled corticosteroids within the plateau of the clinical response curve. Such patients most likely achieve minimal clinical benefit with high doses of inhaled corticosteroids, yet they are at increased risk for local and systemic adverse effects. Potential local adverse effects include oral candidiasis,³⁷ voice dysphonia, and throat symptoms.³⁸ Systemic absorption due to prolonged use and/or high doses may increase the risk of hip fracture,^{39, 40} vascular changes, cataracts,⁴¹ and potential adrenal suppression.^{42, 43}

Add-On Therapy to Inhaled Corticosteroids for Moderate-to-Severe Persistent Asthma

Long-Acting β_2 -Agonists

The combination of inhaled corticosteroids plus long-acting β_2 -agonists is the preferred first-line treatment for patients with moderate-to-severe persistent asthma.²² However, recent safety data indicate that use of long-acting β_2 -agonists may increase the odds of severe asthma exacerbations and related mortality, particularly in African-Americans.⁴⁴ As a result, the U.S. Food and Drug Administration (FDA) issued a

public health advisory in November 2005 stating that long-acting β_2 -agonists should not be first-line therapy in asthma.⁴⁵ Rather, they should be used only as add-on therapy when other asthma drugs, including inhaled corticosteroids given alone at low-to-medium doses, fail to control symptoms. Adding a long-acting β_2 -agonist provides greater improvements in lung function and symptom control than increasing low-to-medium doses of inhaled corticosteroids.^{9, 46}

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists may be used with inhaled corticosteroids in patients with moderate persistent asthma.²² Many studies have shown that leukotriene receptor antagonists improved lung function, asthma symptoms, and asthma-related quality of life and reduced airway hyperresponsiveness and the need for rescue drugs.^{47, 48} A systematic review of the literature showed that adding leukotriene receptor antagonists to inhaled corticosteroids may be comparable to increasing the dose of inhaled corticosteroids.⁴⁹ However, several meta-analyses of clinical trials indicated that leukotriene modifiers may not provide therapeutic benefit above or in place of that of inhaled corticosteroids in some patients with asthma.^{49–51} Furthermore, a clinical trial of children with mild-to-moderate asthma demonstrated that fluticasone significantly improved clinical outcomes, pulmonary measurements, and inflammatory biomarkers compared with montelukast.⁵² In a systematic review of the medical literature, leukotriene receptor antagonists and long-acting β_2 -agonists decreased asthma exacerbations with similar efficacy when they were added to inhaled corticosteroids.⁵³

Despite these findings, some patients seem to have little response to the addition of this class of drugs, and they remain in need of alternatives for asthma treatment.

Theophylline

Sustained-release theophylline may be used as an add-on or alternative therapy to inhaled corticosteroids at low-to-medium doses, particularly for the prevention of nocturnal asthma symptoms.^{1, 22} Routine monitoring of serum concentrations of theophylline is required because of notable dose-related toxicities, a narrow therapeutic dosing range, and variability in metabolic clearance among individual patients.¹ In the long-term management of

asthma, inhaled corticosteroids have proven more effective than theophylline in terms of decreased airway obstruction, bronchial reactivity, and symptom severity.^{54, 55} However, adjuvant use of slow-release theophylline may allow for reductions in the dosage of inhaled corticosteroids.⁵⁶ Although theophylline is similarly efficacious as leukotriene receptor antagonists,^{57, 58} it consistently demonstrated inferior efficacy compared with salmeterol in terms of increased forced expiratory volume in 1 second (FEV₁) and symptom-free nights.⁵⁹

Rationale for Immunoglobulin E Blockade

Pathophysiology

Immunoglobulin E (IgE) acts at the initial step of the T helper cell type 2–mediated inflammatory cascade (Figure 2), making it an excellent pharmacotherapeutic target.^{60, 61} Inhaled environmental allergens presented by dendritic cells to naïve CD4⁺ T cells in peripheral lymphoid tissues initiate a cascade that culminates in the increased synthesis of allergen-specific IgE by B cells.^{62, 63} This IgE binds to high-affinity IgE receptors (FcεRI) expressed on mast cells and basophils, as well as to low-affinity IgE receptors (FcεRII or CD23) on T cells and B cells.

The half-life of free IgE is considerably shorter (< 1 day)⁶¹ than that of IgE bound to cells (approximately 8 days for basophils).⁶⁴ Long-lasting, cell-bound IgE primes cells for the

allergic response, which occurs in two phases. The early phase occurs within minutes of repeat exposure to an antigen. The antigen binds and induces cross-linking of adjacent FcεRI receptors, triggering degranulation of mast cells and the immediate release of preformed proinflammatory mediators such as histamine, leukotrienes, prostaglandins, and tryptase.^{61, 63} Activated mast cells subsequently synthesize and secrete cytokines, interleukins, tumor necrosis factor-α, and leukotrienes *de novo*. The early reaction results in a rapid onset of mucosal edema formation, mucus production, vasodilation, plasma exudation, and constriction of bronchial smooth muscle. In general, the early response resolves in 1–2 hours.

A late-phase response occurs 4–8 hours later and persists for as long as 24 hours.⁶³ Mast-cell mediators derived from the early phase promote an increased secretion of cytokines and chemokines, enhancing the binding and presentation of allergen by dendritic cells to memory T cells and by boosting inflammation mediated by T helper cells type 2. With increased expression of endothelial cell adhesion molecules, this process facilitates the recruitment of inflammatory cells (including eosinophils) into the airways, which further release inflammatory mediators and proteases. The late response is associated with increased airway hyperresponsiveness to histamine, methacholine, and various airway irritants.

In addition to starting the allergic cascade, IgE

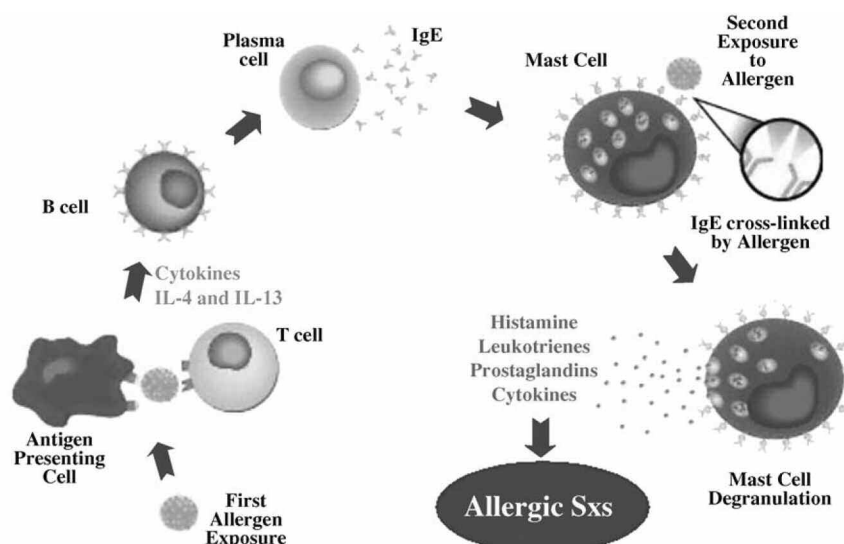


Figure 2. Immunoglobulin E (IgE) and the allergic cascade. IL = interleukin; Sxs = symptoms. (Adapted from reference 60 with permission.)

enhances inflammation at several points, resulting in responses to allergen exposure that are more robust and prolonged. In addition, IgE increases the number of FcεRI receptors on mast cells.^{65, 66} When it is bound to FcεRI, IgE prevents receptor degradation.⁶⁷ It also enhances cellular expression of low-affinity FcεRII receptors.⁶⁸ In turn, mediators derived from IgE-activated mast cells can direct IgE synthesis,^{65, 66, 69} resulting in a positive feedback loop that augments the allergic response.

Epidemiology

In the past, asthma was classified as extrinsic when a clear symptomatic trigger could be identified or as intrinsic when the cause was unknown. A landmark epidemiologic study in 1989 demonstrated that serum IgE levels were correlated with the prevalence of asthma.⁷⁰ The investigators concluded that IgE-mediated inflammation was present to some degree in nearly all patients with asthma.

High total serum IgE levels are correlated with asthma symptoms, bronchial hyperresponsiveness to allergens,^{71–73} increased disease severity (particularly in young patients), visits to emergency department, and hospitalizations.^{3, 74} However, low serum IgE levels do not help in ruling out an allergen-mediated response, as IgE levels considerably overlap between patients with and those without atopy.^{75–78} For example, total IgE levels were elevated in approximately 20% of patients without atopy, whereas total IgE levels were normal in approximately 35–50% of people with allergic rhinitis.⁷⁹ The high prevalence of IgE-mediated (allergic) asthma makes IgE a prime target for therapeutics.

Omalizumab

The broad scope and the integral role of IgE in the initiation and persistence of airway inflammation in asthma make it an obvious pharmacotherapeutic target. Omalizumab is the only IgE-targeted therapy currently available. As a recombinant, humanized monoclonal antibody, omalizumab selectively binds free IgE but not IgE bound to FcεRI.⁸⁰ Omalizumab-IgE complexes cannot interact with FcεRI receptors. Without cell-bound, IgE-mediated antigen cross-linking, activation of mast cells and basophils cannot occur. Omalizumab also indirectly down-regulates the expression of FcεRI receptors on basophils,^{81, 82} mast cells,⁸³ and dendritic cells.⁸⁴ Thus, it may attenuate future allergic responses

to allergens.

Approved for use in the United States in 2003, omalizumab is indicated for the treatment of moderate-to-severe persistent asthma in adults and adolescents aged 12 years or older who have a positive skin-test result or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.⁸⁵ In October 2005, omalizumab was approved for use in Europe.

Efficacy

Several double-blind, placebo-controlled, phase III clinical trials demonstrated a clear role for omalizumab in the management of moderate-to-severe IgE-mediated asthma. In two pivotal 28-week trials, 1071 patients aged 12 years or older were given beclomethasone dipropionate for 4–6 weeks followed by placebo or omalizumab.^{86, 87} Omalizumab was administered for 16 weeks while the beclomethasone dipropionate dose was maintained, for 12 weeks while the beclomethasone dipropionate dose was reduced, and for 4 weeks while the lowest effective dose of beclomethasone dipropionate was maintained.

In one study, significantly fewer patients had an asthma exacerbation when omalizumab was administered than when placebo was given (14.6% vs 23.3%, $p=0.009$ for the steroid-stable phase; 21.3% vs 32.3%, $p=0.004$ for steroid-reduction phase).⁸⁶ In addition, exacerbations/patient decreased when patients were treated with omalizumab versus placebo (0.28 vs 0.54, $p=0.006$ for the steroid-stable phase; 0.39 vs 0.66, $p=0.003$ for the steroid-reduction phase). The other study yielded similar results.⁸⁷ Omalizumab reduced the number of exacerbations by 58% during the steroid-stable phase and by 52% during the steroid-reduction phase compared with placebo (both $p<0.001$). In both studies, symptoms of asthma and the use of rescue drugs were significantly reduced in omalizumab-treated patients compared with placebo-treated patients, and modest improvements in pulmonary function were observed.

These phase III trials were followed by 24-week, double-blind extension studies during which randomized treatment and the previously established lowest effective dose of beclomethasone dipropionate were maintained.^{88, 89} In both studies, treatment with omalizumab maintained long-term reductions in asthma exacerbations/patient compared with placebo; results were 0.60 versus 0.83 ($p=0.023$)⁸⁸ and 0.48 vs 1.14 ($p<0.001$).⁸⁹

Two groups of investigators examined the effects of omalizumab as add-on therapy to inhaled corticosteroids and other controller drugs.^{90, 91} One group conducted an open-label, randomized, multicenter, parallel-group study in which they evaluated 312 adults or adolescents aged 12–73 years with moderate-to-severe IgE-mediated asthma and poorly controlled symptoms (defined as at least one emergency department visit/hospitalization and at least one additional course of oral corticosteroids because of asthma in the last year).⁹⁰ All but one patient were receiving NAEPP step 3 or 4 best standard care. Adolescents were receiving inhaled beclomethasone dipropionate or its equivalent at a minimum dose of 400 µg/day; adults were receiving inhaled beclomethasone dipropionate or its equivalent at a minimum dose of 800 µg/day. In addition, 77.9% of patients were taking long-acting β_2 -agonists, and 21.2% required systemic corticosteroids during the study. Some patients were treated with omalizumab in addition to their best standard care. Compared with best standard care alone, omalizumab plus best standard care reduced the number of incidents related to asthma deterioration/patient-year (9.76 vs 4.92, $p<0.001$), the mean number of clinically significant asthma exacerbations/patient-year (2.86 vs 1.12, $p<0.001$), symptoms scores (0.7 vs 6.5, $p<0.001$), and the use of rescue drugs (20.7% vs 41.4% subjects who required a rescue drug < 1 day/wk, $p<0.001$). Modest improvements in FEV₁ were also observed with omalizumab plus best standard care.

The other group performed the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) study to examine patients with severe persistent asthma in whom symptoms were uncontrolled despite step 4 therapy (high-dose inhaled corticosteroids and long-acting β_2 -agonists) recommended in the Global Initiative for Asthma (GINA).⁹¹ The INNOVATE trial was a randomized, double-blind, parallel-group multicenter study of 419 patients who were given omalizumab for 28 weeks in addition to their current therapy. Compared with placebo, omalizumab reduced the number of clinically significant asthma exacerbations, which were defined as a worsening of symptoms that required treatment with systemic corticosteroids (0.68 vs 0.91, $p=0.042$). In addition, omalizumab reduced by 50% the rate of severe asthma exacerbations (defined as a peak expiratory flow or FEV₁ $< 60\%$ of the patient's personal best that required treatment with systemic corticosteroids)

compared with placebo (0.24 vs 0.48, $p=0.002$). Visits to the emergency department were also reduced more with omalizumab than with placebo (0.24 vs 0.43, $p=0.038$), as were morning peak expiratory flow and asthma symptom scores.

The results of these two studies highlighted the benefits of omalizumab as add-on therapy in patients who still had symptoms although they received the most aggressive and current best standard care.^{90, 91}

Steroid-Sparing Effects

Omalizumab significantly reduced the dose of inhaled corticosteroids required to maintain control of asthma symptoms. Investigators conducted a phase II, dose-ranging, multicenter, randomized, placebo-controlled trial of 317 patients with moderate-to-severe IgE-mediated asthma who required inhaled corticosteroids, oral corticosteroids, or both.⁹² In the second phase of the study (12 wks), the patients' original steroid regimen was maintained while high- or low-dose omalizumab, 5.8 or 2.5 µg/kg per nanogram of IgE/ml, respectively, was administered.

Asthma symptom scores significantly improved with both the high dose ($p=0.008$) and the low dose ($p=0.005$) compared with baseline. The improvements were maintained during an 8-week steroid-reduction phase. About 38% of patients taking placebo were able to reduce their dose of inhaled corticosteroids by at least half, compared with 51% ($p=0.07$) and 49% ($p=0.12$) of patients taking the high and low doses of omalizumab, respectively. Inhaled corticosteroids were completely discontinued in 12% of patients in the placebo group versus 18% ($p=0.27$) and 23% ($p=0.048$) in the high- and low-dose groups, respectively.

For patients who required oral steroids at baseline, the mean reduction in the dose of oral corticosteroids was 0% in patients treated with placebo compared with 50% ($p=0.045$) and 65% ($p=0.11$) in patients taking high and low doses of omalizumab, respectively. Doses of oral steroid were reduced by at least 50% in 78% ($p=0.04$) of patients given the high dose and in 57% ($p=0.23$) of patients given the low dose compared with the placebo group (33%). Oral steroids were stopped altogether in more patients taking high- or low-dose omalizumab than in patients taking placebo (33% [$p=0.38$] and 43% [$p=0.15$], respectively, vs 17%).

These early data suggested that omalizumab

may be particularly beneficial in patients with severe asthma requiring oral steroids for symptom control, who are at increased risk for systemic adverse events.^{92, 93}

A double-blind, randomized, placebo-controlled trial evaluated patients with severe IgE-mediated asthma who required fluticasone 1000 µg/day or more to control symptoms.⁹⁴ Almost half of the patients were concomitantly taking long-acting β_2 -agonists. Patients were treated with either omalizumab or placebo. The dose of fluticasone was maintained for 16 weeks and then reduced for 16 weeks. Doses of fluticasone were reduced more in patients who received omalizumab than in those who received placebo (reductions of 57.2% vs 43.3%, $p=0.003$). Doses of fluticasone were reduced by at least 50% in more omalizumab-treated patients than placebo-treated patients (74% vs 51%, $p=0.001$). Patients taking omalizumab maintained or improved asthma control and needed fewer rescue drugs despite the substantial reductions in their dose of fluticasone.

Significant reductions in doses of inhaled corticosteroids were also observed in the pivotal phase III trials and in their extension phases.^{86–89}

Pooled Meta-Analyses

Pooled meta-analyses of the initial and subsequent clinical trials supported the efficacy of omalizumab in treating patients with moderate-to-severe asthma. One analysis included 254 patients at high risk for serious asthma-related morbidity and mortality from three studies.⁹⁵ Another was an examination of three trials and 1405 patients (including 1071 subjects ≥ 12 yrs).⁹⁶ Yet another was based on data from seven clinical studies of the effect of add-on omalizumab therapy in patients with severe persistent asthma.⁹⁷ When used as add-on therapy, omalizumab significantly reduced the rate of total emergency department visits for asthma by 47% compared with controls ($p<0.0001$).⁹⁷ In all three pooled analyses, omalizumab significantly reduced the rate of asthma exacerbations compared with controls.

Quality of Life

Data from the pivotal phase III studies and their extension phases were analyzed in two studies to specifically assess the effects of omalizumab on asthma-related quality of life, as measured by using the Asthma Quality of Life Questionnaire (AQLQ).^{98, 99} In both studies,

treatment with omalizumab led to statistically significant and clinically meaningful (≥ 0.5 -point) improvements in AQLQ scores. Improvements were observed in the overall score as well as in all four domains of the AQLQ after the steroid-stable, steroid-reduction, and extension phases (Figure 3).

Pooled analysis of these studies with 948 patients was conducted to determine the specific AQLQ items that led to the observed differences in AQLQ scores between omalizumab and placebo groups.¹⁰⁰ These differences included reductions in waking with asthma symptoms in the morning, in being awakened at night with symptoms, in limitations affecting the overall range of activities, in the fear of not having drugs available, and in symptoms associated with dust exposure.

A recent meta-analysis combining data from published clinical trials with unpublished clinical study reports showed that omalizumab-treated patients with moderate-to-severe asthma were 1.6–2.0 times more likely than placebo-treated patients to improve their AQLQ scores by at least 1 point.¹⁰¹ Several studies described earlier in detail also showed that omalizumab significantly improved asthma-related quality of life.^{91, 92, 94}

Patients' Assessments of Effectiveness

Researchers from the pivotal phase III studies also reported how patients and physicians rated

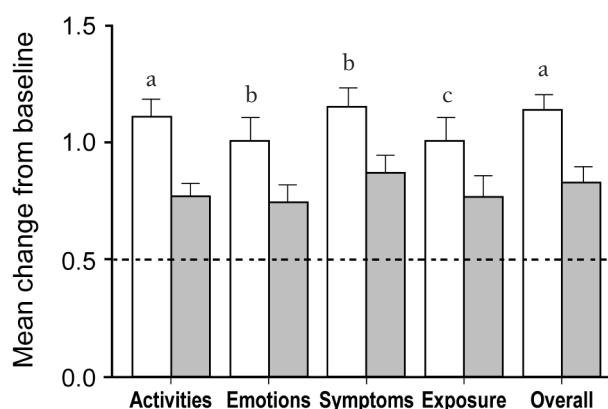


Figure 3. In a 1-year, double-blind trial, adjusted mean changes in asthma-related quality of life significantly improved among patients treated with omalizumab (white bars) compared with those given placebo (gray bars). Scores were based on patients' responses on the Juniper Asthma Quality of Life Questionnaire at the end of an extension phase. An increase of at least 0.5 point from baseline (dotted line) signified a clinically significant improvement. ^a $p<0.001$; ^b $p<0.01$; ^c $p<0.05$. (Adapted from reference 98 with permission.)

the treatment effectiveness of omalizumab. After 28 weeks of therapy, 61–70% of patients receiving omalizumab rated treatment effectiveness as good (marked improvement in asthma) or excellent (complete control of asthma) compared with only 38–40% of patients receiving placebo.^{86, 98} Physicians' ratings of treatment effectiveness were 53–70% and 33–40% for omalizumab and placebo, respectively. In each study, the higher ratings for the omalizumab group were statistically significant compared with those for the placebo group ($p < 0.001$).

Effects on Inflammatory Markers

Omalizumab had significant effects on various inflammatory markers, a finding that confirmed the central role of IgE in inflammation and asthma. Compared with placebo, omalizumab given for 16 weeks significantly decreased levels of the proinflammatory mediator interleukin-13, the release of histamine, the area of wheal reactions to skin pricks with three allergens, and the peripheral eosinophil count (all $p < 0.01$).¹⁰² In 43 patients with mild-to-moderate asthma, omalizumab administered for 16 weeks reduced sputum eosinophils by 74% compared with 18% for placebo ($p < 0.001$).¹⁰³ Numbers of interleukin-4-positive cells and CD3⁺, CD4⁺, and CD8⁺ T cells were also reduced more in omalizumab-treated patients than in others.

Omalizumab may reduce eosinophil counts by means of apoptosis. A study of isolated peripheral eosinophils from 19 patients with IgE-mediated asthma demonstrated that omalizumab significantly increased levels of the apoptotic marker annexin V ($p = 0.004$ vs placebo).¹⁰⁴

In an *in vitro* study, omalizumab and budesonide similarly reduced the levels of tumor necrosis factor- α , tumor growth factor- β , and interleukin-4 secreted by human bronchial epithelial cells.¹⁰⁵ Repeat skin allergen challenges in patients with IgE-mediated asthma who were treated with omalizumab resulted in a progressive reduction in both early- and late-phase skin reactions, with changes greater than that observed with placebo.¹⁰⁶ Of importance, this study also showed that the effect of omalizumab in the late phase (63% reduction) was greater than its effect in the early phase (24% reduction, $p = 0.009$).

Safety

An updated and detailed analysis of the safety of omalizumab included 12 controlled, phase IIb–III clinical trials and more than 5243

patients.¹⁰⁷ Omalizumab therapy was generally well tolerated and associated with a favorable safety profile similar to that of placebo. Headaches, viral or upper respiratory tract infections, sinusitis, and pharyngitis were observed in patients taking omalizumab and controls. Such events were not surprising, as patients evaluated in the safety analysis had IgE-mediated asthma, seasonal or perennial allergic rhinitis, or atopic dermatitis. Also, injection-site reactions similarly occurred in the omalizumab and control groups. Three deaths that occurred in omalizumab-treated patients were not deemed to be related to the study drug.^{107, 108}

Malignancies

Slightly more malignant neoplasms were observed in 20 omalizumab-treated patients (25 neoplasms [0.48%]) than in five control patients (five neoplasms [0.22%]).^{107, 108} The increased occurrence of malignancies in omalizumab-treated patients was deemed not to be due to the study drug for several reasons.¹⁰⁷ First, malignancies were diagnosed in the first 26 weeks of treatment. Second, an expert panel of oncologists who blindly reviewed each case concluded that the malignancies existed before the study and that they were either unrelated (22 neoplasms) or remotely related (three neoplasms) to the study drug. Third, the tumors in omalizumab-treated patients varied in type. Fourth, according to data from the Survey of Epidemiology and End Results from the National Cancer Institute, the rate of malignancies in the control patients was lower than normal and may have been stochastically influenced. Finally, the rate of malignancy in the omalizumab-treated patients was similar to that of the general population of patients with asthma and/or allergies.

Anaphylaxis and Antibodies Against Omalizumab

Three omalizumab-treated patients and one control patient had anaphylaxis during the above-mentioned study.¹⁰⁷ Two anaphylactic reactions in omalizumab-treated patients were deemed to be related to the study drug. No complications associated with reduced levels of circulating IgE or antibodies against omalizumab were observed.¹⁰⁷

On July 3, 2007, the FDA added a boxed warning to the labeling of omalizumab addressing the risk of anaphylaxis occurring after administration of any dose of the drug, even when no reaction occurred with earlier doses.¹⁰⁹

Table 1. Dosing Information for Omalizumab Administered by Subcutaneous Injection to Patients Aged 12 Years or Older with Asthma⁸⁵

Pretreatment Serum IgE Level (IU/ml)	Body Weight (kg)			
	30–60	61–70	71–90	91–150
Dose (mg) Administered Every 4 Weeks				
30–100	150	150	150	300
101–200	300	300	300	—
201–300	300	—	—	—
Dose (mg) Administered Every 2 Weeks				
101–200	—	—	—	225
201–300	—	225	225	300
301–400	225	225	300	UNK ^a
401–500	300	300	375	UNK ^a
501–600	300	375	UNK ^a	UNK ^a
601–700	375	UNK ^a	UNK ^a	UNK ^a

IgE = immunoglobulin E; UNK = unknown.

^aAdditional studies are needed to determine the optimal dose in these patients.

Dosing and Administration

Patients with asthma require therapy that is customized to alleviate their specific symptoms. Consultation with an asthma specialist is recommended when therapy is indicated.

Table 1 shows the dose-determination chart for omalizumab, which is based on body weight and on serum total IgE levels measured before treatment.⁸⁵ After subcutaneous administration, omalizumab is slowly absorbed. Maximum serum concentrations are reached in 7–8 days, with an absolute bioavailability of 62% and a serum half-life of approximately 26 days. Serum levels of free IgE are reduced in a dose-dependent manner within an hour of administration, and a decrease in serum free IgE levels of more than 96% is achieved within 1 hour after the first dose and maintained between doses.

Measuring IgE levels after the administration of omalizumab is not informative. Total serum IgE levels increase after the first dose as the result of the formation of omalizumab-IgE complexes, and the elimination kinetics of these complexes from circulating whole blood are slower than those of free IgE. If a patient interrupts and resumes treatment within 1 year after the start of therapy, dosages should be based on serum IgE levels recorded before the initial administration. Additional studies are needed to determine the optimal dose and frequency of administration in patients with IgE levels above 700 mg/dl. In these patients, the recommended high-end dose of omalizumab 375 mg given every 2 weeks (Table 1)⁸⁵ may be insufficient to saturate circulating free IgE.

Many patients with moderate-to-severe persistent asthma whose disease is refractory to NAEPP-recommended pharmacotherapy may be candidates for omalizumab. Allergen testing with an in vitro test or skin test should be the first step in determining the patient's suitability for omalizumab. Starting omalizumab therapy requires the commitment of the patient and the health care team. Therefore, care must be taken to maximize therapy and check adherence to the medical regimen.

Once- or twice-monthly injections with initial close follow-up and commitment to a trial of at least 6 months are standard for patient selection. Doses greater than 150 mg can be administered at more than one injection site to limit the amount injected at a single location. Patients should be monitored for potential anaphylaxis, for clinically significant changes in their body weight that require dosage adjustments, and for reductions in high doses of concomitantly prescribed inhaled corticosteroids. Frequent reinforcement and close monitoring of clinical outcomes should make assessment of this therapy relatively straightforward. After sufficient time has passed, reevaluation of therapy is warranted.

Cost

Omalizumab is more expensive than other controller drugs,¹¹⁰ although it may be cost-effective in patients with severe asthma who frequently utilize health care resources even as they receive therapies recommended in asthma-management guidelines.^{111, 112}

The aim of a retrospective economic analysis of

the 52 weeks of treatment during the pivotal phase III clinical trials was to determine the direct cost of treatment (in 2003 dollars) from the perspective of a third-party payer.¹¹² Mean treatment costs were higher in patients given omalizumab than in those given placebo. These costs were mainly due to the acquisition of omalizumab. However, the overall cost for other asthma-related utilization of health care resources (e.g., hospitalizations, emergency department visits, and unscheduled office visits) were reduced when patients were treated with omalizumab. The cost-effectiveness of omalizumab may have been underestimated because of the study methods and because of potential underestimation of hospital costs, placebo and protocol effects, and emergency care.¹¹³

A more recent study in Sweden, based on efficacy data from the INNOVATE study, analyzed the cost-effectiveness of omalizumab in 419 subjects.¹¹⁴ The Markov model used in the economic analysis projected lifetime costs and described benefits in terms of quality-adjusted life-years. The model included the assumption that all patients had a risk of exacerbation every 2 weeks and a risk of death due to a clinically significant severe asthma exacerbation. For model imputation, life expectancy and cost data were obtained from the Pharmaceutical Benefits Board of Sweden, and resource utilization and/or utilities data were obtained from both the INNOVATE trial and an observational study in the United Kingdom. Costs used in the model included those related to drugs, routine care, exacerbations, and added years of life.

Compared with standard treatment, add-on omalizumab had an additional lifetime cost of 42,754 (~ \$58,943 US), with 0.762 additional quality-adjusted life-year. About 85% of the increase in quality-adjusted life-years was derived from life extension, and 15% was due to improved quality of life. Give the assumptions used in the model, these data suggest that omalizumab may provide clinically beneficial cost offsets in patients with severe asthma who have uncontrolled symptoms despite receiving GINA-recommended standard treatment.

Conclusion

Despite the availability of effective drugs and excellent treatment guidelines, many patients with moderate-to-severe asthma continue to have symptoms. Because IgE plays a prominent role in

the initiation and perpetuation of chronic airway inflammation, blockade of IgE with omalizumab improves symptoms, reduces exacerbations, and improves quality of life in appropriate patients. The GINA guidelines updated in October 2005 incorporated anti-IgE therapy into its treatment recommendations.^{115, 116} Before omalizumab therapy is started, patients should be referred to an asthma specialist to ensure optimal management of their disease. Care includes not only stepwise pharmacotherapy according to asthma-management guidelines but also patient education, optimal environmental control, and management of comorbidities like allergic rhinitis, sinusitis, and gastroesophageal reflux disease.

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