Omalizumab, a novel therapy that targets specific steps in the inflammatory cascade of asthma, may benefit the hard-to-treat patient.

IgE-Blocking Therapy for Difficult-to-Treat Asthma: A Brief Review

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ABSTRACT

Purpose. To review the characteristics of difficult-to-treat asthma and describe patients who may benefit from therapy with the recently approved humanized monoclonal anti-immunoglobulin E (IgE) antibody, omalizumab.

Principal findings. Up to 20 percent of patients have difficult-to-treat asthma. These patients consume a disproportionate share of asthma care resources. Clinical and economic outcomes can be improved via improved self-management, increased adherence to prescribed therapy, and better compliance to national asthma treatment guidelines. These patients also may benefit from therapies that directly target mechanisms responsible for persistent airway inflammation and elicit favorable clinical responses.

Conclusions. Effective asthma control remains difficult in a small cohort of patients with persistent, severe airway inflammation. Management strategies that improve asthma control and reduce exacerbations can improve clinical outcomes and minimize health care resource utilization.

Key Words: asthma, asthma management, immunoglobulin E, IgE blockers, omalizumab

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INTRODUCTION

Aggressive management strategies — which include patient education, adherence to prescribed therapies, compliance with national treatment guidelines, and the availability of safe and effective medications — permit the significant majority of asthma patients to lead active, productive lives. Nevertheless, a small cohort of asthma patients experience persistent, difficult-to-treat airway inflammation and remain at increased risk for severe exacerbations. Characteristics of these patients include regular use of high-dose inhaled and systemic corticosteroids, excessive use of rescue medications, poor adherence to therapy, decreased quality of life, and a history of frequent unscheduled office visits, emergency department (ED) visits, and hospitalizations (NIH 2002). These patients also miss a substantial number of work and/or school days as a result of asthma and generally have a poor quality of life (Mannino 2002). Furthermore, disease management in these patients is often complicated by the presence of comorbid conditions such as seasonal allergic rhinitis, atopic dermatitis, various food allergies, and urticaria (Holgate 1998).

Clearly, patients with difficult-to-treat asthma can derive significant benefit from an integrated effort by health care practitioners and health care plans to enhance self management techniques, improve adherence to prescribed therapy, and increase compliance to national asthma treatment guidelines (NIH 2002, NCQA 2002). Additionally, these patients may be candidates for treatment with novel therapies designed to target specific steps in the inflammatory cascade that contribute to persistent airway inflammation.

Prevalence and severity

Nearly 18 million adults in America have been diagnosed with asthma (CDC 2003). Asthma is responsible for 10.4 million unscheduled outpatient medical visits, 1.8 million ED admissions, 465,000 hospitalizations, and approximately 4500 deaths each year in the United States (CDC 2001). Estimates of the distribution of asthma severity among patients vary widely. Fuhlbrigge et al conducted a

survey to quantify the symptom burden and functional impact of asthma and identified 10.7 percent of patients as having an asthma burden consistent with mild-intermittent disease and 77.3 percent with moderate-to-severe persistent disease (Fuhlbrigge 2002). The 1998 Asthma in America Survey indicated that 39.8 percent of patients are classified with mild, intermittent asthma, 22.1 percent with mild persistent, 19.1 percent with moderate persistent, and 19.1 percent with having severe persistent disease (Asthma in America 1998). Despite this variability, it is evident that asthma represents a significant health burden.

Health care resource utilization

In 2000, direct and indirect costs associated with asthma in the United States were estimated to be $12.7 billion (ALA 2002). Direct costs such as hospital and physician services, medications, and diagnostic tests account for 60 percent or $7.62 billion of the total amount spent on asthma care (ALA 2002). Among the variables contributing to the direct costs were hospitalizations (47 percent), medications (30 percent), hospital outpatient visits (15 percent), and ED visits (8 percent) (Headrick 1996). Indirect costs accounted for the remaining $5.08 billion of the total asthma health care expenditure and reflect absence from work, school, and other daily activities and loss of future potential earnings due to premature death (ALA 2002).

Patients with difficult-to-treat disease may represent less than 20 percent of the asthma population (Asthma in America 1998), but it is estimated they consume more than 80 percent of asthma care resources (Smith 1997). The disproportionate use of health care resources and high costs of asthma care by patients with difficult-to-treat asthma has also been reported by others (Godard 2002, Serr-Batlles 1998, Sullivan 2003). The increased cost observed in these patients resulted from a greater number of medications, office/clinic visits, hospitalizations, and emergency services (Smith 1997). High users of health care resources also have the highest risk of asthma-related morbidity and mortality (Weiss 1992, 2000) and lowest degree of asthma-related quality of life (Eisner 2002).

Support for these findings comes from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. TENOR, a 3-year observational study, enrolled 4,742 patients with severe or difficult-to-treat asthma and who exhibited at least one of the following characteristics: ≥2 unscheduled care visits in the previous year, ≥2 oral corticosteroid bursts in the previous 12 months, chronic daily use of high doses of inhaled or oral corticosteroids, or use of at least three medications to control asthma. TENOR results indicated that patients with severe or difficult-to-treat asthma required more unplanned clinic visits, used ED and inpatient services more frequently, and had a reduced quality of life (Hayden 2002).

Poor control

Avoidance of asthma triggers and proper use of prescribed controller medications leads to sufficient asthma control in the majority of patients. Pharmacotherapy with inhaled corticosteroids (ICS) has emerged as the preferred long-term controller medication because of its beneficial effect on airway inflammation (NHLBI 2002). Nonsteroidal long-term controllers such as leukotriene modifiers and inhaled long-acting beta-agonists have been proposed as alternative and/or adjunctive agents to ICS (NHLBI 2002). Asthma control is compromised by many factors, however, including poor adherence to prescribed therapeutic regimens (Apter 1998, Barr 2002, Schmier 1998, Stoloff 2000), ineffective patient self-management, minimal compliance with treatment guidelines, and poor clinical response to an optimized pharmacologic therapy (Szefler 2002, Malmstrom 1999).

Adherence rates of patients prescribed asthma therapy range from 30 to 70 percent (Bender 1997). It has been noted that fewer than half of all patients prescribed inhaled asthma medications adhere to their prescribed regimens (Apter 1998, Bender 2000, Milgrom 1996). Nonadherence has been associated with increased hospitalization and the need for ED services, detrimental changes in clinical status, and asthma-related mortality (Bender 1997, Milgrom 1996, Schmaling 1998). Conversely, patients who adhere closely to therapy tend to do well clinically (Milgrom 1996). Suissa and colleagues have reported that the hospitalization rate and incidence of asthma-related death are lower in patients who persist with continuous low-dose asthma therapy compared with those who do not (Suissa 2000, 2002).

Educating patients is a cost-effective way to improve asthma outcomes, particularly for patients with difficult-to-treat disease (Cochrane 1996, Trautner 1993). Patients who are knowledgeable about their disease and trained to identify and avoid triggers and monitor warning signs of exacerbations have lower asthma-related morbidity and mortality (Partridge 1995) even without changing the availability, accessibility, or cost of asthma medications (Kotses 1995, Mayo 1990). For example, adult patients who were enrolled in a 7-week self-management training program exhibited significantly fewer asthma symptoms at 1-year follow up (Kotses 1995). Additionally, completion of a self-management training course was associated with a 67 percent reduction in hospital readmissions. Thus, successful completion of an asthma education program appears to be critical to improving asthma control (Mayo 1990).

Asthma treatment guidelines, such as those provided by the National Asthma Education and Prevention Program (NAEPP), are well established and provide physicians, pharmacists, as well as other health care practitioners with a comprehensive, evidence-based guide for the management of the disease (NHLBI 2002). Physician compliance with the NAEPP guidelines is influenced by several factors, including physician training (Doerschug 1999), agreement with the recommendations (Flores 2000), familiarity and training on the guidelines (Doerschug 1999), economic incentives (Homer 1997), and adequate time (Stavish 1998). Although progress has been made in the utilization of guidelines, the 2001 report of the National Committee on Quality Assurance reported that nearly a third of patients enrolled in nongovernment managed care organizations failed to receive recommended asthma medications (NCQA 2002). Clearly, a need exists for continued professional educational regarding the importance of compliance with national asthma treatment guidelines.

Incomplete asthma control may occur even when pharmacotherapy and other interventions are optimized (Milgrom 2003). Significant variability exists in patient response to various long-term controller therapies, particularly when measured in terms of lung function response (Malmstrom 1999, Szefler 2002). Szefler et al observed high variability in response to ICS treatment, as approximately 33 percent of patients failed to show an improvement in FEV_1 following 24 weeks of therapy (Szefler 2002). Similarly, Malmstrom et al observed significant variability in the response to combined therapy with a leukotriene modifier and ICS, as 20 percent of patients enrolled in the trial experienced no effect or even worsening of lung function (Malmstom 1999). While the reasons for inadequate control despite close adherence to recommended therapy remain unclear, in some patients current therapies are insufficient. This suggests that such patients can benefit from therapies to treat airway inflammation with novel mechanisms of action.

New therapies

Current pharmacotherapy decreases airway inflammation and provides symptomatic relief, but it does not entirely suppress the underlying disease (Milgrom 2003). As more is learned about the role of the immune system and inflammatory processes in asthma pathology, new targets for intervention are being identified and tested. Emerging biologic agents target specific steps in the disease pathogenesis and offer the promise of therapies that modify the natural history of the disease. Areas under research include anti-immunoglobulin E (IgE) antibodies, monoclonal antibodies targeted against Th2 cytokines and mediators, and cytokine modulators. With the exception of the IgE-blocker omalizumab, these experimental therapies are several years away from potential use in regular clinical practice. Currently, no data comparing the cost-effectiveness of these agents to more conventional therapies exist.

IgE and the allergic inflammatory cascade

IgE is the initiator of the inflammatory cascade in the airways that produces the classic early- and late-phase airway response to an inhaled allergen. Airway inflammation is initiated when an inhaled allergen forms a crosslink with a mast cell or basophil-bound IgE. Linking of the allergen and receptor-bound IgE provokes mast cell/basophil degranulation and release of inflammatory mediators including histamine, prostaglandins, and leukotrienes. Together, these mediators are responsible for mucosal edema and smooth muscle contraction that are characteristic of the early asthma response (Fahy 1997).

Omalizumab is a recombinant, humanized, monoclonal anti-IgE antibody that binds to the portion of the circulating IgE recognized by the high-affinity IgE receptor on the surface of the mast cell or basophil. Formation of omalizumab-IgE complexes reduces, in a dose-dependent manner, the amount of free IgE available to crosslink with an allergen, minimizes effector cell activation, and greatly attenuates release of inflammatory mediators (Boulet 1997).

Treating poorly controlled asthma with IgE blockers

The safety and efficacy of omalizumab was tested in two 28-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials that enrolled 1,071 patients with moderate-to-severe persistent asthma that was poorly controlled on daily ICS therapy (Busse 2001, Soler 2001). Patients randomly received either placebo or omalizumab via subcutaneous injection every 2 or 4 weeks. During the initial 16 weeks of the trial, both omalizumab and a constant dose of ICS were administered. During the subsequent 12 weeks, the ICS dose was tapered while the dose of omalizumab remained constant. Results of both studies indicated that addition of omalizumab to ICS significantly (P=.006) reduced the frequency of asthma exacerbations compared to ICS treatment alone. Omalizumab therapy also reduced the ICS requirement by 30 to 50 percent — a result that was significantly greater (P=.001) than the ICS reduction that was noted with placebo. Additionally, omalizumab (P=.0067) delayed the time to first exacerbation (P=.004), reduced the proportion of patients experiencing one or more exacerbations, resulted in improvement from baseline in FEV_1, reduced rescue $beta_2$-agonist use, improved daytime and nocturnal asthma symptom scores (Busse 2001, Soler 2001),

and improved asthma-related quality of life (Buhl 2002).

Omalizumab was generally well tolerated in all clinical studies and no serious drug-related adverse events were reported (Busse 2001, Soler 2001). There was also no evidence of antibodies to omalizumab or formation of antibody complexes. The most serious adverse reactions occurring in clinical studies with omalizumab were malignancies (0.5 percent in omalizumab vs. 0.2 percent in placebo) and anaphylaxis (<0.1 percent). The most frequent adverse events were observed at similar rates in omalizumab-treated and control patients and included injection-site reaction (45 percent), viral infections (23 percent), upper respiratory tract infection (20 percent), sinusitis (16 percent), headache (15 percent), and pharyngitis (11 percent).

TABLE 1 Omalizumab indication

Indication	Adults and adolescents (>12 years of age) with moderate-to-severe persistent asthma, who have a positive skin test or in vitro reactivity to perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.
Limitations	• Omalizumab should not be administered to patients who have experienced a severe hypersensitivity reaction to the drug. • Refer to package insert for complete safety information.

SOURCE: Omalizumab prescribing information. Genentech Inc. and Novartis Pharmaceutical Corp. 2003.

Omalizumab administration

Omalizumab 150 to 375 mg is administered subcutaneously every 2 or 4 weeks. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment; and body weight (kg). Doses above 150 mg are divided among more than one injection site. Full dosing information is available in the product insert. Omalizumab is for single-use only, contains no preservatives, and should be prepared using sterile water for injection (United States Pharmacopoeia). The lyophilized product takes 15 to 20 minutes to dissolve.

Clinical utilization of omalizumab

As described in Table 1, omalizumab is indicated for adults and adolescents (≥12 years of age) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. A panel of asthma experts convened by Genentech and Novartis created a practical treatment guide that specifically addressed gaps in the current NAEPP recommendations, particularly for patients with moderate persistent asthma and severe persistent asthma and who have a history of frequent, severe exacerbations and poor asthma control (Milgrom 2003, Rosenwasser 2003).

Consistent with the current NAEPP guidelines (NHLBI 2002), the panel's primary recommendations include completion of a comprehensive asthma evaluation and the implementation of a patient-education program. In addition, as illustrated in Table 2, the panel suggests initiating omalizumab therapy in three groups of patients including those remaining symptomatic on a combined regimen of moderate doses of ICS plus an inhaled long-acting inhaled beta$_2$ agonist or leukotriene modifier, patients currently controlled on high-dose inhaled or oral corticosteroids, and nonadherent patients requiring directly observable therapy (Rosenwasser 2003). The panel agreed that patients with IgE-mediated comorbidities such as rhinitis or atopic dermatitis also might benefit from IgE-blocking therapy.

Because of the need for subcutaneous administration, cost, and narrow indication, biologic therapies such as omalizumab, while promising, currently are not recommended for use in large numbers of asthma patients. Rather, their use should be targeted toward those patients who have asthma with a documented allergic component and who experience frequent exacerbations, a history of high health care resource utilization, a poor record of adherence to therapy, and in whom therapy may be complicated by IgE-mediated comorbidities. Therapy with this and other biologic agents remains costly when compared with existing therapies but may be cost-effective if targeted at the most appropriate patients. A thorough description of the cost-effectiveness of omalizumab will be revealed through further investigation.

Potential disease-modifying properties of omalizumab

The potential for omalizumab to be a disease-controlling agent is an unproven yet intriguing notion. The question of the duration of therapy that is required to achieve disease modification — and the degree to which disease progression can be halted or prevented — merits ongoing research. One study has provided a theoretical basis for predicting a disease-modifying property of omalizumab in at least some patients with allergic asthma. MacGlashan and colleagues demonstrated that receptor density on the surface of cir-

TABLE 2 Administering omalizumab for moderate-to-severe persistent asthma

National Asthma Education and Prevention Program recommended therapy	Expert panel recommends considering omalizumab for patients with the following characteristics
• Preferred treatment: - High-dose inhaled corticosteroids AND - Long-acting inhaled beta$_2$-agonists AND, if needed, - Corticosteroid tablets or syrup long term (2 mg/kg/day; generally do not exceed 60 mg/day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.) • Preferred treatment: - Low-to-medium dose inhaled corticosteroids and long-acting beta$_2$-agonists • Alternative treatment (listed alphabetically): - Increase inhaled corticosteroids within medium-dose range OR - Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline	• Diagnosis of moderate-to-severe persistent asthma • Patient ≥12 years of age • Evidence of reversible disease (e.g., ≥12 percent improvement in FEV$_1$ with at least a 200 mL increase or ≥20 percent improvement in peak expiratory flow) • IgE level: 30 to 700 IU/mL • Evidence of specific allergic sensitivity by positive skin test or blood test for specific IgE • Patient inadequately controlled, despite at least medium dose of inhaled corticosteroids for at least 3 months in combination with a trial of long-acting inhaled beta$_2$ agonist or leukotriene modifier • Patient requires systemic corticosteroids or high-dose inhaled corticosteroids to maintain adequate control • Patient requires directly observable therapy due to history of poor adherence with prescribed therapy

SOURCE: ROSENWASSER 2003

culating basophils was decreased from a median of 220,000 receptors per basophil to approximately 8,300 receptors per basophil in patients treated with omalizumab, after 3 months of therapy (MacGlashan 1997). Durability of this change was not studied. If future studies confirm and extend this finding to mast cells and determine durability, IgE-blocker therapy would have far-reaching clinical potential for allergic asthma and possibly other IgE-mediated diseases.

SUMMARY

Up to 20 percent of asthma patients experience persistent symptoms and frequent exacerbations, have poor clinical outcomes, and generate the highest aggregate costs associated with asthma care. Implementation of aggressive asthma management strategies that improve adherence to prescribed therapy and increase self-management in conjunction with the appropriate drug therapy has the potential to minimize symptoms, reduce exacerbations, improve asthma-related quality of life, and lessen the need for health care resources. Emerging biologic therapies, such as omalizumab, target specific steps in the underlying disease and can enhance asthma control in patients with difficult-to-treat asthma. Further study should define a clear role for this medication in asthma therapy, including its potential as a disease-modifying agent and its cost-effectiveness.

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