Targeted IgE Therapy for Patients With Moderate to Severe Asthma

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ABSTRACT

It is well established that the proinflammatory cytokine immunoglobulin E (IgE) is a primary contributor to development of allergic airway inflammation following allergen exposure. Recent data suggest that blocking the effects of IgE with omalizumab, a recombinant DNA-derived humanized monoclonal antibody that inhibits the binding of IgE, is an effective strategy for the treatment of asthma, particularly for moderate to severe asthma that is difficult to control with inhaled corticosteroids and traditional controller medications. Targeting specific steps in the inflammatory cascade with omalizumab improves daytime and nocturnal symptom control, reduces exacerbations, and decreases the need for inhaled corticosteroids and beta$_2$ agonists. These benefits, along with improved daily functioning, have resulted in a clinically meaningful improvement in asthma-related quality of life for a substantial number of patients. This paper briefly reviews the contribution of IgE to the development of airway inflammation, discusses the clinical benefits of IgE-blocker therapy, and profiles the patient who stands to benefit from this new and innovative form of therapy.

Key terms: Airway inflammation, asthma, immunoglobulin-E blocker therapy, monoclonal antibody, omalizumab

INTRODUCTION

The proinflammatory cytokine immunoglobulin E (IgE) is an important mediator of allergic reactions and propagates airway inflammation (Fahy 2000). The use of agents that attenuate the inflammatory actions of IgE has emerged as an effective strategy in the treatment of asthma.

One such agent is omalizumab, which is a recombinant DNA-derived humanized monoclonal antibody that inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils and limits the release of mediators of the allergic response.

Pivotal clinical studies have indicated that treatment with omalizumab of patients with poorly controlled moderate to severe asthma has reduced exacerbations, improved nocturnal and daytime symptoms, and reduced the use of inhaled corticosteroids and beta$_2$ agonists. The improvement in asthma control was associated with a decreased incidence of asthma-related hospitalizations and emergency department (ED) visits (Busse 2001a, Solèr 2001, Corren 2003). Omalizumab-treated patients also demonstrated a significant improvement in their daily functioning and overall quality of life (Buhl 2002). This paper briefly examines the extent to which attenuating the effects of airway inflammation with omalizumab therapy improves management of patients with a history of moderate to severe asthma and poorly controlled disease.

IgE and asthma pathophysiology

Asthma is recognized as a disease with allergic triggers that are mediated by IgE. High levels of IgE are associated with inflammation that is typically observed in patients with airway hyperresponsiveness (Bur-

rows 1989) following exposure to a variety of stimuli (Sears 1991, Sunyer 1996). Allergic airway inflammation is initiated when IgE antibodies bound to FcεRI receptors on the surfaces of previously sensitized mast cells or basophils are crosslinked by allergens (Corne 1997, Presta 1994). Allergen-IgE crosslinking results in mast-cell degranulation and the release of a cascade of inflammatory mediators that initiate mucus and edema formation, cellular infiltration, and bronchospasm (Corne 1997). These events, in turn, lead to expression of the classic symptoms of asthma, including wheezing, coughing, and dyspnea (Lemanske 1997).

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The pathologic events associated with IgE-mediated inflammation can be attenuated by preventing the binding of IgE to effector cell membrane receptors with anti-IgE monoclonal antibodies such as omalizumab (Busse 2001b, Corne 1997, Fahy 2000). Initial studies of omalizumab in patients with mild asthma demonstrated that blocking IgE reduced the early bronchoconstrictor response to inhaled allergens (Boulet 1997). MacGlashan (1997) reported that omalizumab therapy produced a 99 percent reduction in serum-free IgE levels, a 97 percent reduction in the density of IgE receptors on the surface of basophils, and a reduction of more than 95 percent in bound IgE found on the surface of these basophils in asthmatic subjects with dust mite allergies. The reduction in bound IgE and in the number of receptors was associated with an approximately 90 percent reduction in allergen-stimulated release of histamine from basophils when stimulated by the presence of specific allergens.

Fahy (1997) reported that blocking the effects of IgE suppressed both early- and late-phase responses to inhaled allergen. Specifically, anti-IgE therapy reduced serum free IgE concentration, increased the dose of allergen needed to provoke an early asthmatic response, and reduced the mean maximal decrease in forced expiratory volume in 1 second (FEV_1) during both the early- and late-phase responses.

Despite evidence to indicate that omalizumab therapy produced a significant reduction in circulating IgE levels, caution should be exercised when interpreting tissue responses to interventions that reduce levels of circulating marker. From symptomatic responses, it does appear logical that blocking IgE receptors on the surface of circulating degranulating target cells is specific and efficacious for allergens. The existence of a correlation between circulating blood effects with specific tissue responses (e.g., lung tissue) remains to be determined, however. If this relationship can be established, it may be possible to develop an omalizumab delivery mechanism that increases available circulating time to partially increase bioavailability to tissue targets. The possibility of locally delivering a greater dose of anti-IgE therapy may have significant advantages, particularly in patients with moderate to severe asthma.

Efficacy and safety

Most patients with asthma have mild to moderate disease that is well controlled with regular use of low-dose inhaled corticosteroids and $beta_2$ receptor antagonists. According to the Asthma in America Survey (1988), however, approximately 19 percent of patients have more severe disease. These individuals remain symptomatic and experience frequent exacerbations despite the chronic use of high-dose inhaled corticosteroids.

Patients who fit this severity classification were selected to participate in two multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials that were designed to assess the effect of IgE blocking therapy with omalizumab on clinical outcomes, including symptoms and effect on the number of exacerbations (Busse 2001a, Solèr 2001). Symptomatic adolescent and adult patients (ages 12–75 years) with moderate to severe allergic asthma were enrolled. The complete eligibility criteria are listed in Table 1 on page 58.

Both studies consisted of a run-in phase, steroid-stable phase, steroid-reduction phase, and a double-blind extension phase. During the run-in phase and prior to randomization, patients were switched from their current inhaled corticosteroids to

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equivalent doses of beclomethasone dipropionate (BDP) and stabilized on this therapy. Omalizumab was administered once or twice monthly via subcutaneous injection, and the dose was adjusted to pretreatment body weight and total serum IgE. A total of 1,071 patients with poorly controlled, moderate to severe asthma were enrolled in the trials.

The primary endpoint of both trials was the number of asthma exacerbations experienced per patient during the steroid-stable and steroid-reduction phases. An exacerbation was defined as an episode that was severe enough to necessitate either a doubling of the baseline BDP dose or a course of systemic corticosteroids, based on the treating physician's clinical judgment following the patient's reporting criteria related to asthma worsening.

This strict exacerbation definition necessitates a comprehensive assessment of asthma control in patients symptomatic on existing asthma therapies. Selected secondary outcomes included corticosteroid requirements, number and frequency of symptoms, rescue-medication use, lung function, and asthma-related quality of life.

Patients with difficult-to-control, moderate to severe asthma who were treated with omalizumab experienced significantly fewer asthma exacerbations per subject compared with patients who received placebo. Additionally, exacerbations were reduced despite significant dose reductions of BDP during the steroid-reduction phase of the trial. Steroid-dose reduction was achieved without precipitating asthma exacerbations, aggravating symptoms, hindering lung function, or increasing the use of rescue medications. Omalizumab also was effective in reducing symptoms, improving FEV_1 and peak expiratory flow, and enhancing asthma-related quality of life (Busse 2001a, Solèr 2001, Buhl 2002). Patients to whom omalizumab was administered also had fewer unscheduled outpatient and ED visits and hospitalizations (Corren 2003). Pooled results of the trials are presented in Table 2.

TABLE 1 Eligibility criteria for inclusion in the pivotal phase 3 clinical trials for omalizumab

Duration of asthma ≥1 year
Positive, immediate responses on skin-prick testing to at least one common allergen
Total serum IgE level ≥30 IU/mL to ≤700 IU/mL
FEV_1 reversibility of >12% within 30 minutes of administration, 90–180 mcg albuterol
Baseline FEV_1 >40% and <80% of predicted
Treatment with 420–840 mcg/day of beclomethasone dipropionate or its equivalent for ≥3 months prior to randomization

FEV1=forced expiratory volume in 1 second,IgE=immunolglobulin E.
SOURCES: BUSSE 2001a, SOLÈR 2001

Omalizumab therapy also elicits clinically significant improvements in asthma-related quality of life as measured by the widely used Juniper Asthma Quality of Life Questionnaire (AQLQ), which reflects aspects of the disease and treatment that are of greatest importance to asthma patients (Juniper 1993). Omalizumab-treated patients who were enrolled in the phase 3 trials experienced improvements that were observed across all domains (Activities, Symptoms, Emotions, Environmental Stimuli) of the AQLQ (as measured by a 0.5-point change in the AQLQ score). The benefits of omalizumab include reduced symptom frequency and improved activity limitation scores (Buhl 2002). It is important for clinicians and policymakers to understand that exacerbation reduction, improvement in FEV_1, and that improvement in symptom scores translate into improved quality of life in a substantial number of omalizumab-treated patients.

Adverse events that were observed in the pivotal phase 3 clinical trials occurred with similar frequency in both the omalizumab- and placebo-treated groups, and no serious drug-related adverse events were reported (Busse 2001a, Solèr 2001). The most serious drug-related adverse events noted in all patients receiving omalizumab included anaphylaxis and malignancies.

Only three cases of anaphylaxis have been reported, two of which occurred during the first injection of omalizumab and one of which occurred at week 7 of the clinical trial. No cases have been observed beyond week 7. Each case occurred 90 minutes to 2 hours after administration of omalizumab, was treated aggressively, and had a favorable outcome.

Malignant neoplasms (excluding nonmelanoma skin cancers) occurred in 16 of 4,127 patients exposed to the drug and 2 of 2,236 controls.

The majority of tumors occurred within 6 months of treatment, and nearly all were solid tumors. Given that the solid tumors emerged so shortly after the initiation of therapy, it is highly unlikely that omalizumab was a causative factor in these developments.

There is also no evidence of a dose response in the occurrence of tumors; high doses of omalizumab were not more likely than lower doses to be associated with malignancy, and there was no evidence of a time-dependent association with malignancy. Data from the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) database indicate that the expected prevalence of malignancy in the general population through the course of 1 year is approximately 5 percent; an incidence rate identical to the prevalence seen in omalizumab-treated patients (Pickle 1999).

Interestingly, the control group had an unexpectedly low incidence of malignancy (much lower, in fact, than would be expected in the general population), whereas the omalizumab group had an incidence that was identical to that expected in the general population. Even with subgroup analysis, such as the incidence rate of breast cancer in the omalizumab group versus the general population, the incidence rate was identical. Thus, it appears highly unlikely that omalizumab was responsible for induction of the neoplasms, although long-term studies will be undertaken to further demonstrate its safety.

Asthma severity and resource utilization

Patients with poorly controlled asthma consume a disproportionate percentage of overall health care costs compared with the majority of asthma patients. This observation is supported by a population-based study of asthma patients who participated in the National Medical Expenditure Survey. In this study, only 20 percent of patients surveyed were considered to have difficult-to-treat asthma. Nonetheless, this small minority of patients generated more than 80 percent of the total direct costs associated with treatment of the disease (Smith 1997). Further support for the close relationship between asthma severity and use of health care resources comes from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, which reported that patients with severe and/or difficult-to-treat asthma have the highest rate

TABLE 2 Pooled results of phase 3 omalizumab clinical trials

Outcome	Omalizumab n=769	Placebo n=638	Change relative to placebo
Asthma exacerbations			
Steroid stable	74*	143	↓50%
Steroid reduction	100*	164	↓40%
ICS dose reduction	83%*	50%	↑67%
100% ICS withdrawal	43%*	20%	↑115%
Albuterol use (puffs/day)	2.00*	3.67	↓46%
Nocturnal symptom score	0.36*	0.83	↓56%
AROQL score	29%*	17%	↑71%
Health care utilization			
Asthma hospitalizations	3*†	15	↓83%
Asthma-related ED visits	8†	15	↓56%
Urgent office visits	102*†	138	↓39%

*P<.05 vs. placebo.

†Number of patients requiring health care services out of the total number of patients in either the omalizumab or placebo groups.

AQLQ=Asthma Quality of Life Questionnaire, ICS=inhaled corticosteroids.

ADAPTED FROM BUHL 2002, BUSSE 2001a, CORREN 2003, SOLÈR 2001

of health care utilization compared with patients with mild asthma (Hayden 2002).

In addition, these patients have the highest frequency of hospitalization as well as a history of intubation, despite above-average adherence rates to medication regimens utilizing multiple standard-of-care medications (Hayden 2002). These data suggest that targeting the small cohort of asthma patients who account for the largest proportion of asthma care costs is critical. Aggressive management strategies incorporating conventional therapy that is supplemented with new and innovative therapies may have the potential to reduce avoidable morbidity and, in turn, decrease the economic burden that these patients place on the health care system.

No formal cost-effectiveness analyses are yet available for omalizumab, either in place of or in addition to common asthma-management medications such as inhaled corticosteroids. It is unlikely that this agent will prove to be cost-effective if prescribed for a broad population of asthma patients. Because of its proven ability to improve symptom control and reduce exacerbations in patients with difficult-to-treat disease, however, omalizumab has the potential to be cost-effective if it reduces the need for emergency or inpatient care, a primary driver of the overall cost of asthma care.

A *post hoc* analysis of three omalizumab clinical trials was conducted to determine the benefits of IgE-blocker therapy in 254 patients considered to be at high risk (defined as having either a history of hospitalization or ED visit in the previous year, or prior intubation for asthma) (Holgate 2001). Results of the analysis indicated that omalizumab reduced the asthma exacerbation rate by 56 percent in these patients and prevented exacerbations in approximately 17 out of every 100 patients during the steroid-stable phase of the trials.

By comparison, the reduction in asthma exacerbation rate for the entire cohort of 1,412 patients with moderate or severe allergic asthma was 41 percent. The analysis also revealed that 5.7 patients need to be treated with omalizumab to maintain 1 patient exacerbation-free. Two (4.5 percent) of 44 patients in the omalizumab group and 6 (12 percent) of 49 patients in the placebo group who had a history of hospitalization within the previous year were rehospitalized (Holgate 2001).

Appropriate use of omalizumab therapy

Many patients with asthma achieve reasonable symptom control with combinations of inhaled corticosteroids, long-acting inhaled beta$_2$ agonists, leukotriene modifiers, or other available agents. Yet asthma control may be elusive in some patients with moderate to severe disease, even when therapy with traditional agents is optimized. Omalizumab is indicated for use in adults and adolescents (≥12 years old) 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 inhaled corticosteroids (Xolair 2003).

Writing on behalf of an expert panel that was convened to provide recommendations on the integration of IgE-blocker therapy into the National Asthma Education and Prevention Program guidelines (NAEPP 1997, 2002), Rosenwasser and Nash (2003) suggested that due to the need for subcutaneous administration, cost, and narrow indication, omalizumab, while promising, should not be used in large numbers of asthma patients. Rather, its use should be targeted toward patients who have asthma with a documented allergic component and who experience frequent exacerbations, have a history of high health care resource utilization, and a poor record of adherence to therapy, and in whom therapy may be complicated by IgE-mediated comorbidities such as allergic rhinitis.

Omalizumab also should be evaluated in the treatment of patients who require unacceptably high doses of oral or inhaled corticosteroids and those who are suffering from steroid-induced side effects. Other patients who may benefit from omalizumab therapy include those who require directly observable therapy due to a history of poor adherence that is complicated by psychiatric disorders or psychosocial problems, and those with imperfect effort or poor technique that limits the effectiveness of inhaled medications.

SUMMARY

Patients with poorly controlled moderate to severe asthma may fail to achieve optimal asthma control despite use of multiple standard of care medications. These patients experience persistent symptoms, frequent exacerbations, reduced productivity, and impaired quality of life. They also account for the use of a disproportionate share of health care resources. Omalizumab, the first IgE blocker approved for the treatment of moderate to severe asthma, inhibits the development of airway inflammation and minimizes exacerbations, reduces

symptoms, decreases asthma-related hospitalizations and ED visits, and improves asthma-related quality of life. Omalizumab offers patients with a history of poor asthma control a new therapeutic option that can reduce the clinical and social burden of asthma.

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