Emerging Therapeutic Strategies for Asthma Management

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ABSTRACT

OBJECTIVE: The describe the mechanisms of action of and clinical experience to date with novel asthma drug therapies.

DATA SOURCES: This article is based, in part, on a presentation given by Eli O. Meltzer, MD, at a symposium entitled "New Frontiers in Asthma Management: Biotechnology for Optimal Therapeutic and Economic Outcomes" at the Academy of Managed Care Pharmacy's 15th Annual Meeting and Showcase in Minneapolis, Minnesota, on April 10, 2003.

CONCLUSIONS: Various elements of the pathophysiologic processes involved in allergic asthma, including type 2 helper T lymphocytes, cytokines, and immunoglobulin E (IgE), have been the targets of new drug research. Clinical experience with omalizumab, a humanized anti-IgE monoclonal antibody, is promising.

KEYWORDS: Asthma, Pharmacotherapy, Allergic asthma, Omalizumab

The high prevalence and rates of morbidity and mortality from asthma, despite the availability of evidence-based treatment guidelines and current drug therapies, have spurred research to identify novel asthma interventions with the potential for additional efficacy. Advances in understanding the pathogenesis of asthma have given rise to novel pharmacologic targets.

New therapeutic approaches under investigation target the key elements in the pathogenesis of asthma, including type 2 helper T (Th2) lymphocytes (cells), cytokines, and immunoglobulin E (IgE). The role of the immune system in asthma has been reviewed.¹ Progress, to date, with some of these new investigational therapeutic approaches is described in this article. One of these novel agents, omalizumab, a monoclonal antibody that is specific for IgE, was recently approved by the U.S. Food and Drug Administration (FDA).

Immunomodulators

Because CD4+ T cells are thought to play a key role in the pathogenesis of asthma, keliximab, an anti-CD4+ monoclonal antibody, was developed as a potential asthma therapy.² In a pilot phase I/II study, keliximab reduced T-cell proliferation and improved lung function in patients with corticosteroid-dependent asthma.^{3, 4} Although in this study, there were no serious adverse effects and preliminary results were promising, further evaluation of keliximab for asthma appears to have been discontinued.

Suplatast tosilate is a potential new antiasthma drug that inhibits the Th2 cell cytokines interleukin-4 (IL-4) and interleukin-5 (IL-5) and the production of IgE.⁵ Suplatast tosilate also inhibits the proliferation and infiltration of eosinophils into bronchial tissues.⁵ In 2 clinical studies of patients with mild or moderate asthma, 28 days of oral treatment with suplatast tosilate (300 mg/day) significantly reduced the eosinophil counts in blood and sputum and also airway responsiveness.^{6, 7}

In a multicenter, double-blind, parallel-group trial, 85 patients with moderate-to-severe corticosteroid-dependent asthma (i.e., receiving at least 1,500 µg/day of beclomethasone dipropionate) were randomized to receive suplatast tosilate (300 mg/day) or placebo for 8 weeks.⁸ The corticosteroid dosage remained constant for the first 4 weeks of the study (the add-on phase), but it was reduced by 50% in the final 4 weeks of the study (the steroid-reduction phase).

Pulmonary function and asthma symptom control improved in the suplatast tosilate group during the add-on phase. In the steroid-reduction phase, pulmonary function, asthma symptoms, and beta₂-agonist use deteriorated significantly less in the suplatast tosilate group than in the placebo group.⁸ These findings suggest that suplatast tosilate may prove useful for improving symptom control and reducing corticosteroid requirements in patients with asthma.

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Mediator Antagonists

Numerous mediators contribute to the immune response, and the possibility that antagonists of these mediators might prove useful to treat asthma has been suggested. Tryptase is a potent protease found in large amounts in mast cells. It alters vascular permeability, stimulates mucus secretion, and increases bronchial smooth-muscle cell proliferation and contractility.⁹ In a randomized, double-blind, crossover study of 16 patients with mild atopic asthma, a selective inhibitor of mast cell tryptase known as APC 366, given by inhalation for 4 days, significantly reduced the antigen-induced late asthmatic response.¹⁰ The effects of the active treatment on the early asthmatic response and bronchial hyperresponsiveness were not significantly different from placebo. However, due to toxicity problems, which appear to be specific to APC 366, this drug is no longer being studied for asthma therapy.

Platelet-activating factor (PAF) released from mast cells contributes to the early asthmatic response.² However, in a randomized, double-blind, placebo-controlled, parallel-group study, a PAF antagonist was found to have limited value for treating acute asthma.¹¹

Neuropeptides (e.g., tachykinins, such as substance P) contribute to the late-phase asthmatic response and chronic inflammation.² Tachykinins are produced by dendritic cells, eosinophils, lymphocytes, and other inflammatory cells. They cause mucus secretion and plasma extravasation and stimulate immune cells, effects that are mediated by tachykinin NK-1 receptors. Tachykinins also cause smooth-muscle contraction, which is mediated by NK-2 receptors.¹² Up-regulation of tachykinin receptors and increased airway levels of tachykinins are associated with asthma.¹³ Inhalation of neurokinin A (a tachykinin) in an experimental setting caused bronchoconstriction in patients with asthma.¹⁴ In a double-blind, randomized, crossover study, the selective NK-2 receptor antagonist saredutant (also known as SR 48968) inhibited neurokinin A-induced bronchoconstriction in patients with mild asthma.¹⁴ However, the drug did not have a substantial bronchoprotective effect in another study using an adenosine challenge.¹⁵ Additional experience with kinin antagonists is needed to determine their clinical usefulness for patients with asthma.

Thromboxane A₂ produced by eosinophils and other immune cells causes bronchoconstriction, microvascular leakage, and airway hyperresponsiveness.¹⁶ Thromboxane A₂ synthesis inhibitors have been evaluated for their potential usefulness in treating asthma. Olopatadine (a drug available as an ophthalmic solution for the treatment of allergic conjunctivitis) is a selective histamine H₁-receptor antagonist with inhibitory effects on the release of thromboxanes and other lipid inflammatory mediators from eosinophils. Oral administration of the drug prevented antigen-induced bronchial hyperresponsiveness, airway inflammation, and the immediate and late asthmatic responses to allergen challenge in animals.^{17,18} However, inhibitors of thromboxane synthetase (an enzyme responsible for synthesis of thromboxane A₂) did not reduce methacholine-induced airway hyperresponsiveness in humans with asthma.^{19,20} Additional experience with thromboxane

FIGURE 1 Omalizumab Pharmacokinetics and IgE Responses

Data on file. Genentech, Inc and Novartis Pharmaceuticals Corporation.

A₂ synthesis inhibitors, thromboxane release inhibitors, and thromboxane receptor antagonists is needed before it can be determined if they will have a role in asthma therapy.

Cytokine Modulators

Cytokine modulators that inhibit the action of the key cytokines involved in allergic asthma (especially IL-4 and IL-5) have been explored. Interleukin-5 was studied because it plays a vital role in eosinophil growth, differentiation, and recruitment into the airways.⁹ Humanized anti-IL-5 monoclonal antibodies were developed from murine antibodies, but the results of research in humans have been disappointing. In a randomized, double-blind, placebo-controlled trial, infusion of humanized IL-5 monoclonal antibody significantly reduced the blood eosinophil count after allergen challenge, but it had no significant effect on the late asthmatic response or airway hyperresponsiveness to histamine.²¹

Interleukin-4 induces the production of IgE and has a variety of other proinflammatory effects.² In a laboratory setting, inhalation of IL-4 led to eosinophil recruitment into the airways and increased airway responsiveness in patients with allergic asthma.²² Soluble IL-4 receptors that sequester IL-4 and interfere with its effects have been developed. In a double-blind, placebo-controlled study,²³ patients with moderate corticosteroid-dependent asthma were randomized to receive a single dose of either 500 µg or 1,500 µg of soluble IL-4 receptor or placebo by nebulizer after discontinuing ICS therapy.²³ Pulmonary function and asthma symptoms were significantly better and beta₂-agonist use was lower in the group receiving the larger dose (1,500 µg) of soluble IL-4 receptor than in the group receiving the smaller dose and the group receiving placebo, despite discontinuing corticosteroid therapy. The active treatment was well tolerated, with no serious adverse events or premature discontinuations because of toxicity.²³ Phase II studies conducted by the manufacturer determined that IL-4 "provided no benefit to the treatment of asthma," and, as a result, the company's resources were redirected toward the devel-

opment of another new investigational antiasthmatic agent.

The efficacy and safety of weekly administration of nebulized soluble IL-4 receptors were demonstrated in a 12-week, randomized, double-blind, placebo-controlled study of 62 patients with corticosteroid-dependent asthma.²⁴ Pulmonary function and asthma symptoms deteriorated in the placebo group but not in the group receiving soluble IL-4 receptor 3 mg/week. The active treatment was well tolerated.²⁴ Although the initial small studies suggested efficacy, further large controlled trials showed that this product provided no significant benefit for the treatment of asthma.

■ New Anti-inflammatory Therapies

Research has addressed various signal transduction pathways involved in the inflammatory cell responses that lead to asthma symptoms. Allergen exposure in patients with asthma may result in the activation of transcription factors in bronchial epithelial cells, resulting in the transcription of genes that encode pro-inflammatory cytokines and adhesion molecules.⁹ Adhesion molecules promote the attachment of inflammatory cells to the vascular lining, which is followed by diapedesis, cellular migration into bronchial tissues, and inflammation. The immunosuppressants cyclosporine and tacrolimus inhibit the activation of transcription factors.⁹ Transcription-factor inhibitors are being investigated; research efforts have been directed toward identifying drug therapies with selective inhibitory action to avoid adverse effects.⁹

Cell adhesion blockers (e.g., alpha 4 integrin antagonists) have been developed for the treatment of asthma and autoimmune diseases.²⁵ Alpha 4 integrins have been the target of research because they interact with cellular adhesion molecules and appear to mediate leukocyte adhesion to the vascular endothelium.²⁵

The protein tyrosine kinase signaling cascade has been a target for drug therapy because it appears to play a prominent role in allergic asthma. Tyrosine kinases are activated when antigen receptors on mast cells and other immune cells are cross-linked.⁹ Mitogen-activated protein (MAP) kinases may then be activated, resulting in the early asthmatic response.⁹ Tyrosine kinase inhibitors prevent antigen-induced activation of mast cells, T and B lymphocytes, and granulocytes, and MAP kinase inhibitors attenuate antigen-induced airway smooth-muscle contraction.⁹ The role that these agents play in treating asthma remains to be determined.

■ Selective Phosphodiesterase Inhibitors

Theophylline is a bronchodilator that has complex actions, including anti-inflammatory or immunomodulatory activity, in patients with asthma.²⁶ The drug is a nonselective inhibitor of phosphodiesterases, enzymes that degrade cyclic 3', 5'-adenosine monophosphate (cAMP).²⁶ Phosphodiesterase (PDE) inhibition increases intracellular cAMP concentrations, relaxes respiratory smooth muscle, and relieves bronchospasm.²⁷ PDE type 4 (one of many phosphodiesterase isoenzymes) is expressed in inflammatory and immune cells.⁹ The anti-inflammatory or immunomodulatory action of theophylline probably is the result of PDE4 inhibition and increased intracellular cAMP levels in inflammatory and

immune cells.⁹ Various selective inhibitors of PDE4 (e.g., the prototype rolipram) have been studied in patients with asthma, but adverse effects (particularly severe nausea and vomiting) have been problematic.^{9,26} Two conformational states for PDE4 were identified, and adverse effects were associated with only one of the 2 conformers.⁹ Second-generation PDE4 inhibitors with lower affinity for that PDE4 conformer and fewer adverse effects have been developed.⁹

In animal studies, the second-generation PDE4 inhibitor cilomilast (also known as SB-207499) attenuated allergen-induced eosinophilia and airway hyperreactivity.²⁸ The drug also prevented bronchospasm in an animal model of exercise-induced asthma.²⁸ In humans with asthma, improvements in lung function were observed in clinical trials of oral cilomilast.²⁹ The drug was well tolerated and did not interact with albuterol or corticosteroids.²⁹ Cilomilast reached Phase II for asthma, but development for this indication has been discontinued.

Roflumilast, another selective PDE4 inhibitor that is more potent than cilomilast in vitro,³⁰ attenuated allergen-induced bronchoconstriction and cellular infiltration into bronchial tissues in animals.³¹ In a placebo-controlled, randomized, double-blind, crossover study, 16 humans with exercise-induced asthma were randomized to receive roflumilast (500 µg/day) or placebo for 28 days.³² At the end of the study, the mean percentage reduction in forced expiratory volume in 1 second (FEV1) after exercise was significantly less in the roflumilast-treated subjects than in the placebo-treated subjects (i.e., exercise-induced asthma was attenuated by roflumilast). The active treatment was safe and well tolerated.³² Studies are continuing with this compound, and complete clinical data, when available, will further define the potential of this drug for the treatment of asthma.

■ Nonselective Immunosuppressants

Various nonselective immunosuppressants that are approved by the FDA for preventing rejection of allogeneic organ transplants, including cyclosporine, sirolimus, mycophenolate mofetil, and tacrolimus, have been explored for the treatment of asthma. But, to date, these agents have not produced a generally favorable risk-benefit profile in human trials. Cyclosporine, a potent immunosuppressant that inhibits the activation of T cells and other inflammatory cells, attenuates the allergen-induced late asthmatic reaction, possibly by inhibiting eosinophils and IL-5 accumulation.³³ Reductions in corticosteroid dosage requirements have been associated with oral cyclosporine use in patients with corticosteroid-dependent asthma.³⁴ Administering cyclosporine by inhalation instead of the oral route to minimize systemic adverse effects (e.g., nephrotoxicity, immunosuppression) is a promising avenue for research.³⁵ Multiple inhaled doses were safe and well tolerated by patients with asthma, with no apparent systemic immunosuppressive activity.³⁵

Sirolimus (rapamycin) and mycophenolate mofetil inhibit allergen-induced proliferation and IL-5 production by peripheral blood mononuclear cells from atopic asthmatic patients.³⁶ These

agents may provide benefits similar to those from cyclosporine but with fewer adverse effects, although comparative clinical trials are needed to verify this theory. Tacrolimus also may prove useful for patients with asthma because it inhibits IL-5 synthesis.³⁷

An analogue of leflunomide, a drug approved by the FDA for the treatment of active rheumatoid arthritis, with greater potency than leflunomide in preventing IgE high-affinity receptor-mediated leukotriene release from mast cells in animals, has been identified.³⁸ This compound prevented airway hyperresponsiveness to methacholine and the recruitment of eosinophils after allergen challenge in animal models.³⁸ The clinical usefulness of the leflunomide analogue in humans remains to be evaluated.

■ Omalizumab

Because IgE plays a central role in allergic asthma and contributes substantially to both the early and late asthmatic responses,⁹ omalizumab, a recombinant DNA-derived humanized monoclonal antibody that is specific for IgE (i.e., anti-IgE monoclonal antibody), has been developed to interrupt the allergic cascade.³⁹ Omalizumab is FDA-approved for use in adults and adolescents (aged 12 years and older) 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 (ICSs).⁴⁰ Omalizumab binds selectively and with high affinity to the FcεRI receptor binding site on free (i.e., unbound) IgE, thereby preventing free IgE from binding to FcεRI receptors on mast cells, basophils, and other cells that contain inflammatory mediators.³⁹ Omalizumab binds to the third domain of the constant region on IgE, regardless of the allergen that elicited formation of the IgE (i.e., binding to IgE is nonspecific for a particular allergen). Administration of omalizumab indirectly reduces the density of FcεRI receptors on cells that contain inflammatory mediators; the lack of stimulation of receptors by free IgE results in a reduction in receptor density.³⁹

Omalizumab is a humanized murine monoclonal antibody that was created by grafting the variable sequence of a murine antibody onto the constant IgG1 kappa human framework. The murine sequence is only 5% of the product, and it is hidden from the immune system when omalizumab binds to IgE. Therefore, antiomalizumab antibodies are not elicited because they are recognized as human.⁴² Omalizumab also does not activate complement. Furthermore, omalizumab does not cross-link cell-bound IgE. Consequently, anaphylaxis is highly unlikely.⁴²

Omalizumab forms small, biologically inert complexes with free IgE. In pharmacokinetic studies, serum concentrations of unbound IgE decreased dramatically within 1 hour after subcutaneous administration of omalizumab (Figure 1).⁴² Serum concentrations of total IgE increased because of the formation of complexes with omalizumab. In asthma patients, the omalizumab serum elimination half-life averaged 26 days.⁴⁰ The changes in serum concentrations of IgE were reversible after discontinuing omalizumab. There was no rebound increase in unbound IgE above the baseline value after stopping the drug. Commercially

TABLE 1 Omalizumab Dosages for Patients With Asthma

Baseline IgE (IU/mL)	Body weight (kg)							
	20-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-150
>30-100	150	150	150	150	150	150	150	300
>100-200	150	150	300	300	300	300	300	450
>200-300	150	300	300	300	450	450	450	600
>300-400	300	300	450	450	450	600	600	
>400-500	300	450	450	600	600	750	750	
>500-600	300	450	600	600	750			
>600-700	450	450	600	750				
>700-800	450	600	750					
>800-900	450	600	750					
>900-1,000	600	750						
>1,000-1,100	600	750						
1,100-1,200	600							
>1,200-1,300	750							

Doses ≤300 mg per 4-week interval are administered once/4 weeks subcutaneously

Doses >300 mg per 4-week interval are split into two equal doses administered every 2 weeks (i.e., 600 mg total = 300 mg every 2 weeks)

available IgE assays do not differentiate between bound and unbound IgE, so it is not possible to measure unbound IgE after omalizumab administration.

In 15 subjects, the density of FcεRI receptors on basophils in peripheral blood decreased from a median of approximately 220,000 receptors per basophil before intravenous treatment with anti-IgE monoclonal antibody to a median of 8,300 receptors per basophil after 3 months of treatment.⁴³ These findings demonstrate that omalizumab administration down-regulates expression of FcεRI receptors.

In 8 subjects with a wheal-and-flare response to allergen skin testing, omalizumab treatment significantly reduced the size of the wheal formed in response to 2 subsequent skin tests using the same allergen after approximately 90 days and 180 days of omalizumab treatment (compared with the baseline wheal size in skin testing performed before omalizumab treatment).⁴⁴

In a randomized, double-blind, placebo-controlled, parallel group study, the effects of 9 weeks of anti-IgE monoclonal antibody treatment on bronchial responses to inhaled allergen challenges were assessed in a laboratory setting in 19 patients with allergic asthma.⁴⁵ The reduction from baseline in FEV1 after allergen challenge was significantly attenuated by treatment with anti-IgE monoclonal antibody in both the early phase (i.e., the first hour after allergen challenge) and the late phase. In the group receiving anti-IgE monoclonal antibody treatment, the eosinophil influx into sputum associated with allergen challenge was blunted after 9 weeks of treatment (i.e., the percentage of eosinophils in sputum did not increase markedly in response to allergen challenge after anti-IgE treatment as it had before anti-IgE treatment). These findings suggested that anti-IgE monoclonal antibody therapy might be useful for patients with allergic asthma.

The omalizumab dose required to achieve an unbound IgE serum concentration less than 10 IU/mL was higher in patients with a high baseline serum concentration of IgE than in patients with a low baseline level. The omalizumab dosage also depends on body weight (Table 1). In patients with allergic asthma, omalizumab doses are given subcutaneously every 2 weeks or 4 weeks,

FIGURE 2 Exacerbations per Patient During the Steroid-Reduction Phase^{46,47}

Busse W. et al. *J Allergy Clin Immunol.* 2001;108:184-90;
Soler M. et al. *Eur Respir J.* 2001;18(2):254-61.

FIGURE 3 Comparison of Hospitalization Rates*

*Pooled analysis of 3 studies.

n=1,071 adults, 334 children; P<0.01.

Corren J. et al. *J Allergy Clin Immunol.* 2003;111:87-90.

depending on patient weight and baseline IgE levels. The sustained protection provided by once or twice monthly dosing may improve patient adherence.

Clinical Studies

Two pivotal randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of omalizumab were conducted in adult and adolescent patients (aged 12 to 75 years) with moderate to severe allergic asthma; one study took place in the United States and the other study was an international study.^{46,47} In both studies, patients were eligible to participate if they had asthma that had been diagnosed at least 1 year earlier and disease that had been stable for at least 1 month. An improvement in FEV1 of at least 12% in response to an inhaled bronchodilator in spirometric tests to a perennial allergen (i.e., reversible airway disease), evidence of antigen sensitization (positive results in a prick skin test or radioallergosorbent test), and an IgE level of 30-700 IU/mL were required at the time of screening. Patients also were required to have residual symptoms and an FEV1 value that was 40% to 80% of the pre-

dicted value despite the use of ICSs (the equivalent of 420 µg/day to 840 µg/day of beclomethasone dipropionate in the United States study and 500 µg/day to 1,200 µg/day of beclomethasone dipropionate in the international study).

All subjects were switched to beclomethasone dipropionate, and the dosage was optimized during a 4- to 6-week run-in phase. Subjects were randomized to receive omalizumab or standard-of-care therapy with an ICS during a 16-week stable-steroid phase. The corticosteroid dosage was reduced by 25% every 2 weeks to the lowest amount required for asthma control in a subsequent 12-week steroid-reduction phase during which omalizumab or placebo was continued. Dosing of omalizumab was the same for both studies. Patients received 150 mg or 300 mg every 4 weeks or 225 mg, 300 mg, or 375 mg every 2 weeks. All doses were based on baseline unbound IgE serum concentration and body weight, and all injections were given subcutaneously.

The primary efficacy endpoint in both pivotal studies was the frequency of exacerbations defined as the need for the physician to double the dosage of the ICS that had been established in the run-in phase or administer a course of corticosteroids orally or intravenously.^{46,47} Physician evaluation was precipitated by an asthma attack requiring urgent medical care; a more than 50% increase from baseline in the use of rescue medication, nocturnal awakening requiring rescue medication, or a peak expiratory flow (PEF) rate 80% or less of the baseline value on at least 2 of 3 consecutive days; a PEF rate less than 50% of the personal best value; or an FEV1 value 80% or less of the baseline value in a patient with any other of these criteria.

In the 525 subjects participating in the U.S. study, the mean number of exacerbations per patient during the stable-steroid phase was 48% lower in the omalizumab group than in the placebo group (0.28 versus 0.54), a difference that is significant.⁴⁶ In the 546 subjects participating in the international study, the mean number of exacerbations per patient during the stable-steroid phase was 0.28 in the omalizumab group and 0.66 in the placebo group, representing a 58% reduction with the active treatment.⁴⁷

In the steroid-reduction phase, significant decreases in exacerbations per patient by 41% in the U.S. study and 52% in the international study were observed with the active treatment compared with placebo (Figure 2).^{46,47}

The time to first exacerbation was significantly longer with omalizumab than placebo.⁴⁸ First exacerbations often occurred around the time of corticosteroid dosage reduction.

The ICS dosage reduction achieved in the omalizumab group was significantly greater than that in the placebo group in both pivotal studies.^{46,47} In the U.S. study, the dosage was reduced by 75% in the omalizumab group and 50% in the placebo group.⁴⁶ Corresponding values in the international study were 83% and 50%.⁴⁷ The percentage of patients who were able to discontinue the ICS was significantly greater in the omalizumab group (40%) than in the placebo group (19%) in the U.S. study.⁴⁶ Corresponding figures in the international study were 43% and 20%, a difference that is significant.⁴⁷

Statistically significant improvements in daytime and nocturnal symptoms and FEV1 were observed with omalizumab therapy compared with placebo, despite reductions in ICS and rescue beta₂-agonist use.⁴⁷ (The FDA concluded that there was only a small effect on rescue medication use and no remarkable effect on lung function, and between-treatment-group differences in symptom scores were of uncertain clinical meaning.) Another key consideration in asthma therapy is quality of life, and one study showed that patients treated with omalizumab were more likely to achieve clinically significant improvements in asthma-related quality of life.⁴⁹ In this study, almost 70% of patients and investigators rated treatment with omalizumab as “excellent/good” compared with about 40% of patients who received placebo.⁴⁹

Using a study design similar to the other 2 trials, a separate randomized, double-blind, placebo-controlled, parallel-group study evaluated omalizumab in 350 adults and adolescents aged 12 to 75 years with severe allergic asthma controlled by inhaled fluticasone 1,000 µg/day to 2,000 µg/day (n=250) or oral corticosteroids plus inhaled fluticasone (n=100). If initiated before the study, patients were allowed to remain on inhaled long-acting beta-agonist therapy. The primary endpoint in the study was reduction in ICS dose; the PEF rate number of asthma exacerbations was a secondary endpoint. Dosing of omalizumab was the same as the other 2 trials. For the primary endpoint, the reduction from baseline in ICS dose was 60% in the omalizumab group and 50% in the placebo group ($P=0.003$). Subjects were able to cease use of ICS, which occurred with 21% of patients on omalizumab and 15% on placebo. In the oral corticosteroid subgroup, there were no significant differences between groups in reduction from baseline in oral steroid dose or in subjects able to discontinue use of ICS. There were no significant differences between groups in either the steroid-stable phase or the steroid-reduction phase in subjects with one or more exacerbations. There were no notable intertreatment group differences in lung function tests.

Health Care Utilization

Long-term data from 3 multicenter, randomized, double-blind, placebo-controlled phase III studies of omalizumab in adults and adolescents aged greater than 12 years (n=1071) and children aged 6 to 12 years (n=334) with allergic asthma who required ICS therapy were pooled to determine the impact of the drug on health care utilization.⁵⁰ During the 1-year study period, 767 patients were treated with omalizumab and 638 patients were treated with placebo.⁵⁰ The rate of unscheduled, asthma-related outpatient visits was significantly lower for the omalizumab-treated group than for the placebo group (102/767 visits versus 138/638 visits) as were emergency-room visits (8/767 versus 15/638). More important, hospitalizations for asthma-related problems were significantly lower in patients receiving omalizumab (8/767) than in those receiving placebo (15/638) (Figure 3).⁵⁰

High-Risk Patients

A meta-analysis was conducted of 3 randomized, double-blind,

TABLE 2 Adverse Events in Omalizumab-Treated Patients⁴⁰

Adverse Event*	Omalizumab n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Athralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritis	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

* Adverse events that occurred $\geq 1\%$ more frequently in patients receiving omalizumab than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature dictionary.

placebo-controlled studies of omalizumab (including the 2 pivotal trials) with a total of 1,412 patients with moderate or severe allergic asthma.⁵¹ A subgroup of 254 of these patients were identified who were at high risk for asthma-related morbidity and mortality as defined by a history of asthma-related hospitalization or an emergency department visit within the past year or an intubation for asthma at any time in the past. Omalizumab reduced the asthma exacerbation rate by 56% in the 254 high-risk patients compared with placebo in the stable-steroid phase. The reduction in asthma exacerbation rate for the entire group of 1,412 patients with moderate or severe allergic asthma was 41%.

When the high-risk patients were stratified by baseline FEV1, omalizumab reduced the asthma exacerbation rate by 28%, 50%, and 66% for an FEV1 that was high (80% of the predicted value or higher), intermediate (61% to 79% of the predicted value), or low (60% of the predicted value or less), respectively, compared with placebo.⁵¹ Although the benefit was greatest in the group with the lowest FEV1 value at baseline, the exacerbation rate after omalizumab treatment was similar regardless of the baseline FEV1 level. This suggests that the level of the FEV1 is not the only indicator for omalizumab use.

Nocturnal and total symptoms, PEF rate, and asthma quality of life improved to a significantly greater extent with omalizumab treatment than with placebo treatment in high-risk patients.⁵¹ Two (4.5%) of 44 patients in the omalizumab group and 6 (12%) of 49 patients in the placebo group who had a history of hospitaliza-

tion within the previous year were rehospitalized.⁵¹

Extrapolation of the data from the meta-analysis suggests that omalizumab can prevent asthma exacerbations in 17 additional patients for every 100 patients treated (NNT=17), and about 50% of potential exacerbations are prevented by omalizumab treatment.⁵¹ The number of patients who need to be treated with omalizumab to maintain 1 patient exacerbation-free is 5.7.

Safety

Omalizumab was well tolerated in clinical studies. The adverse reactions most commonly observed in patients treated with omalizumab included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%) (Table 2).⁴⁰ Injection-site reactions occurred at a rate of 45% in omalizumab-treated patients compared with 43% in placebo-treated patients. Severe injection-site reactions were reported for 12% omalizumab subjects compared with 9% for control subjects.

The most serious adverse reactions, which occurred in clinical studies with omalizumab, were malignancies (0.5% in omalizumab versus 0.2% in placebo). The observed malignancies in omalizumab-treated patients were of heterogeneous tumor cell types commonly associated with long latency. Exposure interval for 12 of the patients was less than 6 months, and exposure interval was less than 1 year for 6 patients. Anaphylaxis occurred in <0.1% of patients treated with omalizumab.

Reductions in platelet count initially were a cause for concern during omalizumab clinical trials. Further assessments revealed that the incidence of small reductions in platelet count during clinical trials was comparable with omalizumab and placebo. Larger reductions occurred infrequently in both treatment groups, but the incidence initially appeared to be about twice as high in patients treated with omalizumab as in patients treated with placebo. Therefore, FDA requested additional long-term safety data before approving omalizumab. Subsequent study evaluations have not documented that omalizumab increases the risk of bleeding or reduction in the numbers of platelets.

Consensus Panel Recommendations

A consensus panel of experts in the management of asthma was convened by the manufacturer of omalizumab to make recommendations as to how to best incorporate IgE blocker therapy into the current National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma.⁵² According to the guidelines, asthma is classified into the following 4 categories: (1) mild intermittent, (2) mild persistent, (3) moderate persistent, or (4) severe persistent. The consensus panel recommended that IgE blocker therapy be considered for patients with moderate to severe persistent asthma.⁵³ The specific recommendations for IgE blocker therapy in this category are as follows:

- patient aged at least 12 years;
- evidence of reversible disease

- IgE level ≥ 30 IU/mL (range 30 IU/mL to 700 IU/mL)⁴⁰;
- evidence of specific allergic sensitivity (i.e., positive skin test or blood test for IgE);
- condition is inadequately controlled despite medium dose of ICSs for at least 3 months in combination with a trial of long acting inhaled beta₂-agonists or a leukotriene modifier;
- systemic corticosteroids or high-dose ICSs are required to maintain adequate asthma control⁴⁰;
- as directly observable therapy in patients who are not adherent to prescribed therapy.

Conclusion

A wide variety of targeted asthma therapies are in development to target different aspects of the pathophysiologic mechanisms involved in asthma. Which of these therapies or combinations of therapies will be most effective for treating asthma will be an unfolding picture as the results of additional clinical research become available. The results of clinical research with omalizumab suggest that it holds significant promise in the treatment of moderate-severe asthma.

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