Exploring New Frontiers in Asthma Management
for Optimal Therapeutic and Economic Outcomes

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Supplement

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Exploring New Frontiers in Asthma Management for Optimal Therapeutic and Economic Outcomes

SEAN D. SULLIVAN, PhD, and ELI O. MELTZER, MD

Target Audience

Managed care pharmacists and other health care practitioners

Learning Objectives

Upon completion of this educational program, the participant will be able to

1. discuss recent trends in asthma prevalence and the economic burden of the disease in the United States;
2. define asthma control and characterize the patient with difficult-to-treat asthma;
3. explain the role of atopy, immunoglobulin E (IgE), and the immune system in the pathogenesis of asthma;
4. summarize the diagnosis, classification, and treatment of asthma according to National Asthma Education and Prevention Program guidelines published in 2002; and
5. describe the mechanisms of action and clinical experience to date with novel asthma drug therapies, including the humanized anti-IgE monoclonal antibody omalizumab.

Asthma is a chronic disease that poses a major public health problem in the United States.¹ The incidence, prevalence, and economic burden are increasing at an alarming rate.¹⁻³ In 1998, the economic and social cost of asthma was estimated at \$12.7 billion in the United States, with a disproportionate share of costs borne by the most severely affected individuals.¹ Asthma control, measured by symptom burden, is not optimal in most patient subgroups despite the availability of highly effective pharmacological therapies and evidence-based treatment guidelines.^{4,5}

The first article in this supplement describes recent trends in the prevalence of and morbidity and mortality from asthma in Americans and the impact of the disease on health resource

utilization and costs. Asthma control is defined and the extent to which control is achieved with currently recommended asthma therapies is characterized. Patterns of medication use in patients with asthma who are at high risk for morbidity and mortality are characterized and health resource utilization and morbidity in patients with difficult-to-treat asthma are discussed. Finally, the goals of research efforts to develop new asthma therapies with greater efficacy than those currently available are identified.

The prominent position of inhaled corticosteroids as the preferred therapy for persistent asthma in current guidelines reflects the growing evidence of the important role of inflammation in the pathogenesis of the disease.⁵ The second article in this supplement describes what is currently known about the allergic immunological process and the contribution of various inflammatory cells and mediators to the pathogenesis of asthma. The diagnosis, classification, and treatment of the disease in accordance with National Asthma Education and Prevention Program guidelines published in 2002 are reviewed. Finally, therapeutic issues related to asthma management, including selection of an appropriate inhaled drug delivery system and factors that influence patient adherence and therapeutic effectiveness are discussed.

The third article explores new asthma drug therapies that target various elements in the pathogenesis of asthma. These new approaches to treating asthma have the potential to improve patient outcomes.

REFERENCES

1. Redd SC. Asthma in the United States: burden and current theories. *Environ Health Perspect.* 2002;110(suppl 4):557-60.
2. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma—United States, 1980-1999. *MMWR Surveill Summ.* 2002;51(1):1-13.
3. Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States, 1985-1994. *J Allergy Clin Immunol.* 2000;106:493-99.
4. Bateman ED, Bousquet J, Braunstein GL. Is overall asthma control being achieved? A hypothesis-generating study. *Eur Respir J.* 2001;17:589-95.
5. National Heart, Lung, and Blood Institute. Executive summary of the NAEPP expert panel report: guidelines for the diagnosis and management of asthma—update on selected topics 2002. NIH publication no. 02-5075. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.htm>.

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Asthma in the United States: Recent Trends and Current Status

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ABSTRACT

OBJECTIVE: To describe the prevalence of and morbidity and mortality from asthma in Americans and the impact of the disease on health resource utilization and costs, define asthma control and characterize the extent to which it is achieved with recommended asthma therapies, discuss patterns of medication use in patients with asthma who are at high risk for morbidity and mortality, characterize health resource utilization and morbidity in patients with difficult-to-treat asthma, and identify the objectives of asthma drug therapy research efforts.

DATA SOURCES: This article is based on a presentation given by the author 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: The prevalence of asthma and associated costs has increased in the United States. Patients with asthma that is difficult to treat because of frequent or severe exacerbations, inability to avoid asthma triggers, or the need for multiple drug therapies or complex medication regimens are responsible for a disproportionately large share of health resource utilization and costs. Medication use is less than optimal in many patients with asthma who are at high risk for morbidity and mortality, and asthma control is poor in many patients despite the use of recommended drug therapies. Results of the TENOR Study, a large, 3-year, multicenter, observational cohort study, demonstrated that difficult-to-treat asthma is associated with substantial health resource utilization and morbidity. New asthma drug therapies are needed to improve asthma control, patient adherence to the therapeutic regimen, and quality of life and reduce the incidence of asthma exacerbations, health resource utilization, and costs.

KEYWORDS: Asthma, Cost, Burden of disease, NAEPP guidelines

Asthma affects 17.7 million American adults, including 10.5 million women and 7.1 million men (i.e., the disease affects women in greater numbers than men).¹ The disease also affects approximately 5 million children in the United States.² The prevalence of asthma has more than doubled since 1980, a year when 8.5 million cases were reported.² The increase in asthma prevalence over the past 2 decades has been particularly dramatic in children aged 4 years and younger. In this age group, 0.4 million cases were reported in 1980 and 1 million cases were reported in 1998, representing a 250% increase. Although asthma affects many children and young adults, it also affects elderly Americans.³ However, only about 10% of people with asthma are aged 65 years or older.

Health Resource Utilization and Mortality

Asthma was responsible for 9.3 million physician office visits in the United States in 2000.¹ The disease results in 500,000 hospitalizations⁴ and 5,500 deaths² each year in this country. The rates of emergency department visits, hospitalization, and death are 2 to 3 times higher in African Americans than in white Americans.² The rate of asthma-related emergency department visits by men and women of all races increased during the 1990s (Figure 1), and the increase in rate between 1994 and 1995 was greater in women than in men.⁵ The rate of asthma-related hospitalization began to decrease in the 1990s⁵ (Figure 2), possibly because of improved medication use and the availability of treatment guidelines. Reductions in hospitalizations were observed primarily in white Americans, not in young African Americans. Rates of asthma-related hospitalization, emergency department visits, and deaths in African Americans continue to exceed rates in white Americans.⁶ Between 1979 and 1995, the mortality rate increased by 132%, from 7.2 to 16.7 per million African Americans. The mortality rate increased from 1.4 to 3.9 per million white Americans, an increase of 179% during the same period.

Costs

The costs of asthma increased by about 75% between 1985 and 1994, although the estimated cost per patient with asthma decreased during this period.⁷ The increase in asthma-related costs was lower in children than in adults.

In 1998, the majority (58%) of the costs of asthma were associated with direct medical expenditures (Figure 3).⁸ Indirect costs represented 42% of total asthma-related expenditures, and costs due to lost productivity were the largest component of indirect costs.⁸ Expenditures for medications was the largest component (42%) of direct costs, and medications accounted for a larger percentage of direct costs in 1998 than in 1985, when 30% of direct costs were for medications.^{7,8}

An analysis of national costs and resource utilization data found

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FIGURE 1 Trends in Asthma-Related Emergency Department Use

NCHS, National Hospital Discharge Survey, 1999.

FIGURE 2 Trends in Asthma-Related Hospitalizations

NCHS, National Hospital Discharge Survey, 1999.

FIGURE 3 Distribution of Asthma Costs in 1998^a

1998

Weiss KB, Sullivan SD. *J Allergy Clin Immunol* 2001;107:3-8.

half of all expenditures.⁹ Thus, patients with asthma that is poorly controlled are responsible for a disproportionately large share of costs compared with patients with disease that is well controlled.⁹ Interventions to improve asthma control have the potential to reduce costs.

Asthma Control

The National Asthma Education and Prevention Program (NAEPP) goals of therapy for achieving asthma control are listed in Table 1.¹⁰ Many patients with moderate persistent or severe persistent asthma do not achieve control despite the use of the combination controller drug therapies recommended by NAEPP.¹¹ In a study of patients with asthma that was moderate in severity, asthma control was achieved on only about one third of days using an inhaled corticosteroid (ICS) plus a long-acting inhaled beta₂-agonist.¹¹ When a short-acting inhaled beta₂-agonist was added for daytime rescue therapy, control of asthma was achieved on only one half of these days.¹¹

High-Risk Patients

Characteristics of patients at high risk of asthma-related death who were identified in the National Heart, Lung, and Blood Institute's Global Initiative for Asthma are listed in Table 2.¹² The morbidity and mortality for high-risk patients with severe asthma have not decreased despite the introduction of new asthma drug therapies, including long-acting inhaled beta₂-agonists, high-dose ICSs, and leukotriene receptor antagonists. This patient population has an 8- to 16-fold greater risk of dying than other patients with asthma and accounts for a disproportionately large share of health care costs.

An analysis of 4,143 adults with moderate or severe asthma who were at high risk for death was conducted using 1997 to 2001 data derived from the Medstat MarketScan Commercial Claims and Encounters Database of 28,506 patients with asthma and claims in 2000 and 2001.¹³ This database contains the inpatient, outpatient, and outpatient prescription experience of nearly 3 million employed persons and their dependents, early retirees, and Consolidated Omnibus Budget Reconciliation Act (COBRA) beneficiaries covered under a variety of fee-for-service and capitated health plans.¹³ The majority (61%) of the high-risk patients were women, and the mean age was 38 years. Most patients (60%) were covered by a noncapitated insurance plan, and 40% were covered under a capitated plan. Only 0.3% were covered by a Medicare managed care plan. Comorbid allergies and sinusitis were present in more than 40% and nearly 40% of the high-risk patients, respectively.

An analysis of asthma medication use persistence by drug class and controller drugs and treatment adherence to National Heart Lung Blood Institute Guidelines (2002) revealed that the use of ICSs, long-acting inhaled beta₂-agonists, and leukotriene receptor antagonists was observed on only about 30%, 31%, and 55% of days, respectively. The use of these agents is recommended in NAEPP treatment guidelines.¹⁰ The percentage of patients who

that more than 80% of direct costs (e.g., costs for ambulatory care visits, hospital outpatient services and inpatient stays, emergency department visits, physician payments, and medications) were used by 20% of patients.⁹ The estimated annual cost per patient for these high-cost patients exceeded \$2,500, although it was only \$140 for other patients. Hospitalization accounted for more than

received treatment that was consistent with treatment guidelines was determined using 2 scenarios. In the first scenario, appropriate treatment was defined as use of an ICS for at least 50% of the observed time plus use of a long-acting inhaled beta₂-agonist, a leukotriene receptor antagonist, or an oral corticosteroid. Only 24% of high-risk patients received appropriate care using this scenario. In the other scenario, appropriate treatment was defined as the use of any controller medication for at least 50% of the exposure time. Forty-two percent of patients received appropriate treatment when this definition was used. Thus, there is considerable room for improvement in medication use in patients with asthma who are at high risk for death.

The TENOR Study

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is an ongoing 3-year, multicenter, observational cohort study designed to ascertain the impact of asthma that is severe or difficult to treat per physician assessment. Health resource utilization, attendance in the workplace and school, asthma symptoms and quality of life, lung function, and medication use and adverse events were reported.¹⁴ The study cohort comprised 4,756 patients recruited from 283 sites, including the managed care setting, health maintenance organizations, private community practices, and academic medical centers. The TENOR registry contains the largest volume of data compiled to date in this patient population. Because the study is observational, asthma medications and other treatments were given as prescribed by patients' own physicians. The data analysis controlled for the influence of confounding variables.

Subjects were included in the TENOR Study if they had severe or difficult-to-treat asthma in the opinion of their physician, had received care from that provider for at least 1 year, were at least 6 years old, and were able to read and understand English. Patients with mild or moderate persistent asthma were eligible if their disease was considered difficult-to-treat. In addition, patients were included in the study only if they had a history of 2 or more unscheduled care visits for asthma or 2 or more courses of oral corticosteroid therapy within the 12 months before screening or a requirement for large daily dosages of ICSs, at least 5 mg/day of oral prednisone, or 3 or more medications for asthma control at the time of screening. Patients with a history of heavy smoking (i.e., more than 30 pack-years), a primary diagnosis of cystic fibrosis, severe cardiovascular disease (New York Heart Association class II or greater), cancer (except nonmelanoma skin cancer and malignancies that had been "clear" for at least 5 years), a severe psychiatric disorder (except anxiety and depression), significant systemic disease with a life expectancy less than 2 or 3 years, or a history of drug abuse were excluded from the study.

Nearly three fourths (73%) of the patients in the TENOR Study registry were adults (aged 18 years or older), 10% were adolescents (aged 13 to 17 years), and 16% were children (aged 6 to 12 years).¹⁵ The majority (71%) of adults were women, but the numbers of male children and adolescents exceeded the numbers of

TABLE 1 National Asthma Education and Prevention Program Goals of Therapy for Asthma Control¹⁰

- Minimal or no chronic symptoms during the daytime or nighttime
- Minimal or no exacerbations
- No limitations on activities; no school or work missed
- Normal (or near normal) pulmonary function
- Minimal use of short-acting inhaled beta₂-agonists (less than once per day, less than one canister per month)
- Minimal or no adverse effects from medications

TABLE 2 Characteristics of Patients With Asthma at High Risk for Death¹²

- History of severe exacerbations
- Hospitalization or emergency department visit for asthma within the past year
- Current use of or recent discontinuation of systemic corticosteroids
- History of near-fatal asthma requiring intubation and mechanical ventilation
- Excessive dependence on short-acting inhaled beta₂-agonists, especially use of more than one canister of albuterol (or equivalent) monthly
- History of serious psychiatric disease, including depression, or psychosocial problems

FIGURE 4 Physician Assessment of Reasons for Asthma Treatment Difficulty in TENOR Study Patients

female children and adolescents.¹⁵ The majority of patients had moderate or severe asthma in the judgment of their physician (severity was classified based on overall symptoms, nocturnal symptoms, and forced expiratory volume in 1 second (FEV₁) in

FIGURE 5 Health Resource Utilization and Missed Work or School Days by Age in Patients With Difficult-to-Treat Asthma **FIGURE 6** Health Resource Utilization and Missed Work or School Days by Asthma Severity in Patients With Difficult-to-Treat Asthma

accordance with NAEPP guidelines¹⁰). About half of the adolescent and adult patients had severe disease, although only 36% of children in the group aged 6 to 12 years had severe disease. In 96% of all patients, the asthma was judged difficult to treat by physicians because of frequent or severe exacerbations, inability to avoid asthma triggers, the need for multiple drug therapies or complex medication regimens, or a combination of these factors (Figure 4).

Health resource utilization data from the TENOR Study (Figure 5) demonstrate that asthma that is severe or difficult to treat consumes a considerable amount of health care resources for

regular and unscheduled office visits, emergency department visits, and hospitalizations. Nearly 1 in 5 children and adolescents was absent from school because of asthma for at least 1 day in a 2-week period, reflecting substantial morbidity from difficult-to-treat disease. Adult workplace absenteeism was almost as high as school absenteeism in younger patients.

Health resource utilization and workplace and school absenteeism tended to be higher in patients with severe persistent asthma than in patients with moderate or mild persistent asthma (Figure 6). However, these outcome measures did not vary much by FEV₁, demonstrating that FEV₁ is a poor predictor of health resource utilization and morbidity in patients with difficult-to-treat asthma.

Almost all (99%) of patients in the TENOR Study received at least 1 controller medication (e.g., ICSs, long-acting inhaled beta₂-agonists, leukotriene receptor antagonists), 92% of patients received 2 or more controllers, and 56% of patients received 3 or more controllers. The number of controller medications did not substantially affect health resource utilization or workplace or school absenteeism (i.e., adding a second or third controller had little impact). These findings suggest an unmet need in asthma management.

Addressing Unmet Needs in Asthma Management

Asthma is a chronic inflammatory disease that often has an allergic component. Although ICSs are the mainstay of asthma treatment, patient adherence to such therapy is often poor.¹⁶ Asthma symptoms vary in severity over time, but the dosing of ICSs is not always versatile enough to manage symptoms. Poor adherence to and inadequate dosing of ICSs lead to symptoms, increased use of reliever medications, disruption of activities and sleep, and exacerbations that increase health resource utilization and costs. The challenges for researchers and clinicians are to identify new therapies that will target key elements in the pathogenesis of asthma, effectively control symptoms, offer patients convenience, and adverse-effect profiles that promote adherence to the therapeutic regimen, improve patient health status and quality of life, and reduce the incidence of costly exacerbations.

Conclusions

Asthma is an increasingly common and costly health problem in the United States. Patients with severe or difficult-to-treat asthma account for the use of more health resources and a larger share of health care costs than do patients with controlled asthma. Many patients at high risk for morbidity and mortality do not receive treatment consistent with asthma guidelines. Asthma control in these patients is often not achieved with the use of recommended asthma drug therapies. New asthma drug therapies that target the allergic component of asthma and have characteristics that promote patient adherence are needed to reduce the incidence of asthma exacerbations, health resource utilization, and costs.

REFERENCES

- Centers for Disease Control and Prevention National Center for Health Statistics. Fast Stats A to Z: asthma. Available at: <http://www.cdc.gov/nchs/fastats/asthma.htm>. Accessed April 19, 2003.
- Redd SC. Asthma in the United States: burden and current theories. *Environ Health Perspect*. 2002;110(suppl 4):557-60.
- National Heart, Lung, and Blood Institute. NAEPP Working Group Report. Considerations for diagnosing and managing asthma in the elderly. February 1996. NIH publication No. 96-3662. Available at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/as_elder.pdf. Accessed August 15, 2003.
- Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. *J Allergy Clin Immunol*. 2001;107:3-8.
- National Center for Health Statistics. 1999 National Hospital Discharge Survey: Annual Summary with Detailed Diagnosis and Procedure Data. Series 13, No. 151. Available at http://www.cdc.gov/nchs/products/pubs/pubd/series/sr13/160-151/sr13_151.htm. Accessed July 25, 2003.
- Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma—United States, 1980-1999. *MMWR Surveill Summ*. 2002;51(1):1-13.
- Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States, 1985-1994. *J Allergy Clin Immunol*. 2000;106:493-99.
- Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol*. 2001;107:3-8.
- Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med*. 1997;156(3, pt 1):787-93.
- National Heart, Lung, and Blood Institute. Executive summary of the NAEPP expert panel report: guidelines for the diagnosis and management of asthma—update on selected topics 2002. NIH publication no. 02-5075. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.htm>. Accessed August 15, 2003.
- Bateman ED, Bousquet J, Braunstein GL. Is overall asthma control being achieved? A hypothesis-generating study. *Eur Respir J*. 2001;17:589-95.
- National Heart, Lung, and Blood Institute. Global strategy for asthma management and prevention. February 2002. NIH publication no. 02-3659. Available at: <http://www.ginasthma.com/>. Accessed August 15, 2003.
- Sullivan SD, Crown WH, Bresnahan BW et al. Healthcare utilization and expenditures: a study of moderate-to-severe asthma in the United States. *J Allergy Clin Immunol*. 2003;109. In press.
- Hayden ML, Chipps BE, Dolan CM, Johnson C for the TENOR Study Group. Asthma control in patients with severe or difficult-to-treat asthma. Poster presented at: American Thoracic Society meeting; May 2002; Atlanta, GA. *Am J Crit Care Med*. 2002;165(8):A119.
- Dolan CM, Fraher KE, Bleecker E, et al. for the TENOR Study Group. Design and baseline characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) Study—a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol*. In press.
- Jones C, Santanello NC, Boccuzzi SJ, et al. Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. *J Asthma*. 2003;40(1):93-101.

The Role of the Immune System in the Pathogenesis of Asthma and an Overview of the Diagnosis, Classification, and Current Approach to Treating the Disease

ELI O. MELTZER, MD

ABSTRACT

OBJECTIVE: To describe what is currently known about the role of allergy and immunologically active cells and mediators in the airway inflammation associated with asthma; to review the diagnosis, classification, and treatment of the disease in accordance with current National Asthma Education and Prevention Program guidelines published in 2002; and to discuss therapeutic issues related to asthma management.

DATA SOURCES: This article is based on a presentation given by the author 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: Type 2 helper T (Th2) cells, various other cell mediators and cytokines, and immunoglobulin E play important roles in the pathogenesis of asthma. Atopy is an inherited condition characterized by a predominance of Th2 cells and it predisposes to asthma. Objective measures of pulmonary function improve confidence in the diagnosis of asthma and should be used to monitor response to therapy. Asthma severity is often underestimated by patients and physicians, which can lead to inadequate treatment. Inhaled corticosteroids (ICSs) are the preferred maintenance treatment for patients with persistent asthma because these medications are the most potent and effective long-term controller pharmaceutical agents. Addition of a long-acting inhaled beta₂-agonist or a leukotriene modifier to ICS therapy provides added benefit to patients with moderate or severe persistent asthma inadequately controlled by corticosteroids. Choosing an appropriate delivery system for inhaled drug therapies can affect patient adherence and the effectiveness of therapy.

KEYWORDS: Asthma, Immune system, Inhaled corticosteroid therapy, Inhaled beta₂-agonist, Immunoglobulin E

Asthma is a chronic inflammatory disorder of the airways.¹ Inflammation contributes to airway hyperresponsiveness (an exaggerated response to various exogenous and endogenous stimuli), airflow obstruction, and respiratory symptoms that include wheezing, coughing, chest tightness, and shortness of breath.^{1,2} Inflammation may be present even in patients with minimal or no symptoms.²

Airflow obstruction usually is at least partially reversible, spontaneously or with treatment.² Obstruction may be the result of bronchoconstriction, bronchial edema, mucus plug formation, airway wall remodeling, or a combination of these factors.²

Role of the Immune System

Airway inflammation is an immune-mediated process involving inflammatory cells and mediators released by these cells. Airway inflammation is characterized by increased numbers of eosinophils, mast cells, macrophages, and T lymphocytes (T cells) in the mucosa and lumen.² The major trigger of airway inflammation is the allergic response. In persons with atopy (i.e., an inherited predisposition to produce immunoglobulin E [IgE] in response to exposure to common environmental allergens), inhaled allergens deposit on bronchial mucosal tissues where antigen-presenting cells (e.g., dendritic cells) process the allergen and present it to T cells (Figure 1).³ Type 2 helper T (Th2) cells produce interleukin-4, interleukin-5, and other cytokines, resulting in a cascade of effects.³ Interleukin-4 causes B cells to induce formation of IgE specific to the allergen. Some of the IgE binds to the membranes of mast cells and other cells that contain preformed inflammatory mediators (e.g., histamine, tryptase, and lipid mediators, including leukotrienes, prostaglandins, thromboxanes, and platelet-activating factor).³ Subsequent exposure to the allergen causes cross linking of the membrane-bound IgE, degranulation of mast cells, and release of the inflammatory mediators. These mediators contribute to acute-phase symptoms (e.g., wheezing) by causing airway smooth-muscle contraction, vasodilation, and increased vascular permeability and mucus secretion.³

Most patients with asthma also experience a late-phase reaction characterized by airway obstruction and hyperresponsiveness.² These effects are mediated by interleukin-5 and other cytokines that cause inflammatory cells (e.g., eosinophils, basophils, and neutrophils) in the bloodstream to adhere to the vascular endothelium. Diapedesis and cellular infiltration into bronchial tissues follow. The cells contain substances (e.g., basic proteins) that cause epithelial cell damage and disrupt the mucosal lining and also affect blood vessels, resulting in increased vascular permeability

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The Role of the Immune System in the Pathogenesis of Asthma and an Overview of the Diagnosis, Classification, and Current Approach to Treating the Disease

and leakage, edema, and swelling. Airway smooth-muscle hypertrophy and hyperplasia, increased angiogenesis, and collagen deposition (i.e., remodeling) may ensue in patients with chronic inflammation.²

Atopy

Genetics influence the likelihood of developing asthma.² Atopy runs in families and can be measured using allergen skin tests or in vitro assays of total or specific IgE. Atopy during childhood predisposes to asthma.² In a study of newborns followed past the age of 6 years, elevated IgE serum concentrations were a predictor of persistent wheezing at the age of 6 years.⁴

There is an imbalance between type 1 helper T (Th1) cells and Th2 cells in patients with asthma and other atopic diseases (e.g. allergic rhinitis), and Th2 cells predominate in these patients. Type 2 helper T cells predominate in all neonates. Persons without atopy develop a Th1-mediated immune response to allergens as a result of a process referred to as immune deviation.³ By contrast, Th2 cells increase during infancy and childhood in atopic persons. Factors other than genetics that might contribute to atopy (e.g., exposure to allergens) are the subject of controversy.

Diagnosis

Asthma often is diagnosed on the basis of a patient's medical history (Table 1). Asthma should be suspected in patients with a recurrent history of bronchitis, croup, pneumonia, or bronchiolitis. Patients may have been told that they have reactive airway disease in the past to avoid labeling them with a chronic disease, but the term is synonymous with asthma.

Asthma symptoms follow a circadian rhythm (they tend to worsen at night), and they may be absent at the time of assessment despite abnormal pulmonary function. Objective measures of pulmonary function increase the confidence in the diagnosis of asthma.² They also provide a baseline for comparing the response to treatment. The forced expiratory volume in 1 second (FEV1) measured with spirometry provides one measure of pulmonary function. An improvement of at least 12% in FEV1 spontaneously, after inhalation of a bronchodilator or in response to corticosteroid therapy, supports the diagnosis of asthma.²

An improvement in the peak expiratory flow (PEF) rate of at least 15% after inhalation of a bronchodilator or in response to corticosteroid therapy also suggests the diagnosis of asthma.² The PEF rate is a less reliable measure of pulmonary function than FEV1. However, measuring PEF is a practical method for monitoring lung function in the home setting.

Airway hyperresponsiveness to stimuli (a methacholine challenge or an exercise challenge) is another measure of pulmonary function that may help in the diagnosis of asthma in patients with symptoms despite normal FEV1 and PEF values.² These tests sometimes have false positive results, but negative responses often are useful for ruling out asthma. Airway hyperresponsiveness is associated with chronic obstructive pulmonary disease and other

FIGURE 1 Pathways Leading to Acute and Chronic Allergic Reactions

Mackay IR, Rosen FS. *NEJM*. 2001;344(1):30-37

TABLE 1 Components of the Patient Medical History Used to Diagnose Asthma^{1,5}

- Type of symptoms (wheezing, coughing, shortness of breath, and chest tightness)
- Frequency and severity of symptoms
- Factors that provoke or exacerbate symptoms (i.e., triggers, such as upper-respiratory-tract infections, pet dander, and exercise)
- Impact of symptoms on quality of life
- A personal history of allergies or other atopic diseases (e.g., atopic dermatitis)
- A family history of asthma or other atopic diseases
- Response of symptoms to asthma medications
- Required frequency of asthma medication use

TABLE 2 National Asthma Education and Prevention Program Classification of Asthma Severity⁵

Step	Daytime Symptoms	Exacerbations	Nighttime Symptoms	PEF or FEV1 (PEF variability)
4: Severe Persistent	Continual	Frequent; limits activity	Frequent	≤60% (>30%)
3: Moderate Persistent	Daily	≥2 times/week affects activity	>1 night/week	>60% to <80% (>30%)
2: Mild Persistent	>2 times/week but <1 time/day	May affect activity	>2 nights/month	≥80% (20%-30%)
1: Mild Intermittent	≤2 days/week	Brief, with normal lung function and no symptoms between episodes	≤2 nights/month	≥80% (<20%)

FIGURE 2 Asthma Severity Using National Asthma Education Prevention Program Criteria Compared With Physician Perception of Asthma Severity

*Physician perception based on calculation from M/A/R/C, 1995 and MMI's Therapeutic Class Study—Asthma, 1996; NHLBI guidelines based on calculation from Migliara/Kaplan Outcomes study, 1996 and MMI's Therapeutic Class Study—Asthma, 1996.

conditions as well as asthma.²

The diagnosis of asthma is not based on a physical examination of the respiratory system (i.e., auscultation) because wheezing may be absent despite substantial airflow limitation.²

Classification

Asthma severity is classified in one of 4 steps on the basis of daytime and nighttime symptom frequency, duration, and severity; impact on activity levels; exacerbations (clinically important decreases in PEF rate; increases in short-acting inhaled beta₂-agonist use; and pulmonary function (PEF or FEV1 and PEF variability) before treatment (Table 2). Asthma is classified as persistent if symptoms occur more than twice a week and/or nocturnal symptoms occur more than twice a month.⁵

Asthma severity is a continuum, and it may change over time in a particular patient. Moreover, patients may experience exacerbations that vary in severity regardless of how their asthma severity is classified. For example, a patient with mild persistent asthma may experience a severe exacerbation.

Patients tend to underestimate the severity of their asthma. In the Asthma in America Survey of roughly 2,500 patients with asthma, patient self-ratings of asthma severity were compared with the severity classification determined using the National Asthma Education and Prevention Program (NAEPP) criteria (Table 2). A total of 28% of patients with mild persistent, moderate persistent, or severe persistent asthma using the NAEPP criteria reported no symptoms (i.e., they underestimated the severity of their asthma). Seventy-nine percent of patients with asthma that was moderate persistent or severe persistent reported only mild symptoms, and

41% of patients with severe persistent asthma reported only moderate symptoms. This tendency for patients to underestimate the severity of their asthma has serious implications if perceived severity affects the likelihood that patients will seek and use asthma medication (i.e., asthma may be inadequately treated, leading to exacerbations).

Physicians also may underestimate asthma severity. Asthma is estimated to be mild intermittent, mild persistent, moderate persistent, or severe persistent in 33%, 32%, 26%, and 9%, respectively, of the population with asthma (Figure 2), using the NAEPP criteria for classifying severity. However, the results of a study of physician perception of asthma severity revealed that severity was classified by the physicians as mild intermittent in 48% of patients, mild persistent in 16% of patients, moderate persistent in 21% of patients, and severe persistent in 7% of patients (i.e., the percentage of patients with mild intermittent asthma was overestimated and the percentage of patients with mild persistent asthma was underestimated). Extrapolation of these findings suggests that asthma severity is underestimated and inadequately treated in 2.5 million patients with mild persistent asthma.

Treatment

The components of asthma management used to meet the therapeutic goals are patient education and formation of a partnership between the patient and clinician, environmental control measures to reduce allergen exposure, pharmacotherapy, and immunotherapy. Asthma management is almost certain to fail without appropriate patient education. Objective assessment of pulmonary function using spirometry or PEF measurements also is vital to asthma management.²

Proper use of the PEF meter is essential to obtain a meaningful value, and patients should be taught and asked to demonstrate proper use of the device.² Patient counseling should address the importance of knowing one's personal best PEF value as a benchmark for comparison and using the PEF meter periodically to monitor pulmonary function. This counseling should be repeated at regular intervals to reinforce the concepts.

Environmental control measures may prevent or minimize asthma symptoms. Advantages of using environmental control measures include the lack of adverse effects and drug interactions and the safety of the approach for all age groups.

Asthma medications fall into one of 2 groups: quick relievers and long-term controllers. Quick relievers include short-acting inhaled or oral beta₂-agonists, inhaled ipratropium bromide (an anticholinergic agent), and short courses of oral corticosteroids (slow onset of action >4 hours). These agents are used as rescue agents to treat acute symptoms. Short-acting inhaled beta₂-agonists are the drugs of choice for this purpose. The short-acting inhaled beta₂-agonists are also prescribed to prevent exercise-induced bronchospasm. Increasingly frequent use of a short-acting inhaled beta₂-agonist may indicate the need to initiate or increase long-term controller therapy.⁵

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Long-term controllers include inhaled and systemic corticosteroids, long-acting inhaled and oral β_2 -agonists, inhaled cromones (cromolyn sodium and nedocromil sodium), oral leukotriene modifiers, and oral sustained-release theophylline. These agents are used daily on a long-term basis to maintain control of persistent asthma and prevent exacerbations.

The current NAEPP asthma treatment guidelines (published in 2002) reflect what has been learned in recent years about the pathogenesis of asthma and the comparative efficacy of various drug therapies.⁵ As in the past, the current guidelines recommend a stepwise approach for managing asthma (Figure 3). However, because inhaled corticosteroids (ICSs) are the most potent and effective long-term preventive medications, they are now considered the preferred treatment for patients with persistent asthma (low-, low-to-medium-, and high-dose therapy is recommended for asthma that is mild persistent, moderate persistent, and severe persistent, respectively).⁵ ICSs improve asthma symptoms, pulmonary function, and quality of life and reduce airway hyperresponsiveness, the frequency and severity of exacerbations,² and the need for hospitalization,⁶ short-acting inhaled β_2 -agonists, and oral corticosteroids.⁷ Systemic corticosteroids may be required to control severe persistent asthma.^{2,5}

Current (2002) NAEPP guidelines recommend the use of long-acting inhaled β_2 -agonists in combination with ICSs for patients with asthma that is moderate persistent or severe persistent.⁵ In previous (1997) NAEPP guidelines, increased doses of ICSs were an alternative to adding long-acting inhaled β_2 -agonists for moderate persistent asthma. However, the combination is now recommended because adding the long-acting inhaled β_2 -agonist improves lung function and symptoms and reduces the need for short-acting inhaled β_2 -agonists for quick relief.^{1,5}

Patients should be advised that long-acting inhaled β_2 -agonists are not substitutes for ICSs and should not be used alone or to treat acute symptoms or exacerbations. A large safety study of the long-acting inhaled β_2 -agonist salmeterol xinafoate was terminated early because an interim analysis revealed an increased risk of life-threatening asthma episodes or asthma-related deaths, although these serious adverse events were rare.⁸ The risk appeared to be increased in African-American patients and in patients not receiving ICSs. Nevertheless, the benefits of the long-acting inhaled β_2 -agonists for the asthma population continue to outweigh their risks, according to the U.S. Food and Drug Administration.⁸

Leukotriene modifiers include 2 leukotriene receptor antagonists (montelukast and zafirlukast) and, until recently, zileuton, a leukotriene synthesis inhibitor that acts by interrupting the 5-lipoxygenase pathway.⁹ Zileuton was not widely used because of hepatic toxicity and the need for frequent administration (4 times daily) of large tablets (i.e., patient nonadherence can be a problem).⁹ Current NAEPP guidelines reflect the position of leukotriene modifiers in asthma drug therapy for the first time. Leukotriene modifiers were not among the therapeutic options in

FIGURE 3 Stepwise Approach to Managing Asthma in Adults and Children Older Than 5 Years

ICS = inhaled corticosteroid LABA = long-acting β_2 -agonist;
LTM = leukotriene modifier SR = sustained release.

NIH/NHLBI Guideline Update, June 2002. NIH Publication No. 02-5075

previous NAEPP guidelines because the agents were new and clinical experience with the drugs was insufficient at the time.¹

In the current NAEPP guidelines, leukotriene modifiers are an alternative to ICSs for patients with mild persistent asthma,⁵ although ICSs are preferred because they are more effective for improving FEV1 and reducing the need for hospitalization than leukotriene modifiers.^{10,11} Adding a leukotriene modifier to an ICS is an alternative to an ICS plus a long-acting inhaled β_2 -agonist (the preferred therapy) for patients with moderate persistent asthma³ because the combination of the leukotriene modifier and ICS is more effective for improving FEV1 and reducing nocturnal awakenings and asthma exacerbations than the ICS alone.¹⁰

In previous (1997) NAEPP guidelines, cromones and corticosteroids were alternatives for treating mild persistent asthma, and neither of the 2 therapies was preferred.¹ The position of cromones in current NAEPP guidelines represents a change from previous guidelines because ICSs are now the preferred therapy for mild persistent asthma, and cromones are an alternative.⁵ When an ICS was compared with nedocromil sodium in children aged 5 to 12 years with mild to moderate asthma, the corticosteroid was significantly more effective than nedocromil sodium in improving airway responsiveness and controlling asthma.¹² Cromones also may be used prophylactically before exposure to asthma triggers (e.g., exercise).²

Oral sustained-release theophylline may be used as an alternative to ICSs for mild persistent asthma.⁵ Theophylline also may be used in combination with an ICS for patients with moderate persistent asthma,⁵ although these combinations are less effective than an ICS plus a long-acting inhaled β_2 -agonist, which is the preferred therapy.² The use of theophylline is limited by its adverse effect profile (e.g., nausea, vomiting, tachycardia, nervousness, and insomnia¹³) and the need to monitor serum drug concentrations.

Two approaches may be used for initial drug therapy to gain control of asthma: (1) starting therapy at the step corresponding to

TABLE 3 Key Clinical Activities for
Providing Quality Asthma Care¹⁵

1. Establish asthma diagnosis
2. Classify severity of asthma
3. Schedule routine follow-up care
4. Assess for referral to specialty care
5. Recommend measures to control asthma triggers
6. Treat or prevent comorbid conditions (e.g., rhinitis, sinusitis, gastroesophageal reflux disease, chronic obstructive pulmonary disease, influenza)
7. Prescribe medications according to severity
8. Monitor use of beta₂-agonists
9. Develop a written asthma management plan
10. Provide routine education on patient self-management

the severity of disease and gradually stepping up if control is not achieved, and (2) starting therapy at a step higher than the severity and stepping down once control is achieved. The latter step-down approach is preferred because it provides rapid control.¹

Indications of the need to step up or increase long-term controller therapy in a patient with good previous asthma control include an increase in symptoms, nocturnal awakening because of symptoms, diminished ability to participate in exercise or customary daily activities, daily or increased use of short-acting inhaled beta₂-agonists, reduction in PEF rate by roughly 20% or more, or failure to achieve therapeutic goals.²

Therapeutic Issues

In its 2002 update report, the NAEPP expert panel addressed several therapeutic issues in asthma management, including the question of whether the use of antibiotics in addition to standard treatment improves the outcomes of treatment for acute asthma exacerbations.⁵ Most asthma exacerbations are associated with infection by a respiratory virus.¹⁴ Infections caused by bacteria are infrequent causes of asthma exacerbations.¹⁴ The presence of phlegm in the lungs may reflect mucus associated with asthma or viral infection. Viral infections often resemble bacterial infections. The expert panel determined that the results of clinical trials do not support the use of antibiotics routinely or when suspicion of bacterial infection is low.⁵

The 2002 NAEPP expert panel report also addressed the question of whether the use of a written asthma action plan improves outcomes compared with medical management alone and whether use of an action plan based on PEF rate monitoring improves outcomes compared with a plan based on symptoms.⁵ Insufficient data were available to draw conclusions about the benefits of written action plans or whether plans should be based on PEF monitoring. Nevertheless, written actions plans were recommended by NAEPP as part of an overall effort to educate patients in self-management, especially patients with moderate persistent or severe persistent asthma or a history of severe exacerbations.⁵

Developing a written asthma management plan was one of 10 key clinical activities that are essential for quality asthma care recommended by NAEPP in 2003 (Table 3).¹⁵ In 2002, NAEPP also recommended that PEF monitoring be considered because it may enhance communication between the clinician and patient and increase patient awareness of his or her disease status and control.⁵

In the Asthma in America Survey, there were large discrepancies between patients and physicians in perceptions about whether actions plans had been developed, PEF meter use had been recommended, lung function testing had been performed, follow-up visits had been scheduled, and inhaler use had been demonstrated.¹⁶ Although nearly all physicians thought that a follow-up visit had been scheduled, only 55% of patients were under that impression, a situation that has serious implications because of the need for ongoing monitoring of asthma.

Patient Adherence

A study of adherence to asthma pharmacologic therapy over a 13-week period in 24 patients aged 8 to 12 years who received ICSs and short-acting beta₂-agonists by pressured metered-dose inhaler (pMDI) found that the rate of compliance with the corticosteroids was 13.7% for patients who experienced asthma exacerbations and 68.2% for patients without exacerbations, a difference that is significant.¹⁷ Compliance was measured both electronically, using a device attached to the pMDI, and with diary cards filled out by the child or a parent, although neither the subjects nor their parents were aware of the electronic monitoring. The electronic device revealed that 58% of prescribed corticosteroid doses were taken, with only 31% of prescribed doses taken on time. By contrast, the diary cards suggested that 95% of prescribed doses were taken as directed. Thus, poor asthma control may reflect patient nonadherence, even in patients who report taking their medications as prescribed because some patients exaggerate the extent to which they are compliant.

Effectiveness

The effectiveness of long-term controller therapy in patients with asthma may differ from the efficacy demonstrated in clinical trials because of patient nonadherence, which usually comes less into play in clinical trials. Factors that can affect adherence to the therapeutic regimen include route of administration, type of delivery system for inhaled drug therapies, administration frequency, adverse effects, cost, and patient education (e.g., understanding of proper inhalation technique, the medication regimen, and the importance of adherence).

Immunotherapy

Allergen immunotherapy is effective for reducing symptoms of allergic asthma and should be considered for patients with demonstrable evidence of specific IgE to clinically relevant allergens. The decision to initiate allergen immunotherapy depends on the extent to

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which symptoms can be reduced by allergen avoidance and medications and the amount, type, and adverse effects from pharmacotherapy.¹⁸

In a meta-analysis of 20 randomized, placebo-controlled, double-blind trials of allergen immunotherapy for asthma, the combined odds of symptomatic improvement from immunotherapy for any allergen was 3.2.¹⁹ The odds of reduction in bronchial hyperactivity were 6.8. In studies of immunotherapy for mites, the odds of reduction in medication requirements were 4.2. The mean predicted improvement in FEV1 from any immunotherapy was 7.1%.¹⁹

Conclusions

Asthma is often the result of an allergic cascade involving antigen presentation by dendritic cells to Th2 cells, which predominate in atopic individuals. Mast cells, eosinophils, and various other inflammatory cells; interleukins and other cytokines; and IgE appear to play key roles in this cascade. Asthma should be diagnosed on the basis of a patient medical history, but objective measures of pulmonary function can confirm the diagnosis and monitor response to therapy.

Although asthma severity is classified in one of 4 categories, severity is a continuum and it changes over time in an individual. Patients and physicians tend to underestimate asthma severity, which can lead to inadequate treatment and exacerbations. Current NAEPP guidelines reflect what has been learned recently about the greater efficacy of ICSs compared with leukotriene modifiers and cromones and the benefits of using corticosteroids in combination with long-acting inhaled beta₂-agonists for moderate persistent and severe persistent asthma. The route of administration, type of delivery system for inhaled drug therapies, administration frequency, adverse effects, cost, and patient education can affect patient adherence to and the effectiveness of pharmacotherapy. Immunotherapy is a valuable option in patients with a significant allergic component to their asthma.

REFERENCES

1. National Heart, Lung, and Blood Institute. *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2*. Washington, DC: U.S. Department of Health and Human Services; 1997. NIH publication no. 97-4051.
2. National Heart, Lung, and Blood Institute. Global strategy for asthma management and prevention. February 2002. NIH publication no. 02-3659. Available at: <http://www.ginasthma.com/>. Accessed August 15, 2003.
3. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med*. 2001;344:30-37.
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995;332:133-38.
5. National Heart, Lung, and Blood Institute. Executive summary of the NAEPP expert panel report: guidelines for the diagnosis and management of asthma—update on selected topics 2002. NIH publication no. 02-5075. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.htm>. Accessed August 15, 2003.
6. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol*. 2001;107:937-44.
7. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med*. 1995;332:868-75.
8. U.S. Food and Drug Administration. Study of asthma-drug halted. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01192.html>. Accessed April 24, 2003.
9. McEvoy GK, ed. Zileuton. In: *AHFS Drug Information* 2003. Bethesda, MD: American Society of Health-System Pharmacists; 2003:3705-06.
10. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med*. 1999;130:487-95.
11. Stempel DA, Pinto L, Stanford RH. The risk of hospitalization in patients with asthma switched from an inhaled corticosteroid to a leukotriene receptor antagonist. *J Allergy Clin Immunol*. 2002;110:39-41.
12. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med*. 2000;343:1054-63.
13. McEvoy GK, ed. Theophyllines. In: *AHFS Drug Information* 2003. Bethesda, MD: American Society of Health-System Pharmacists; 2003:3487-93.
14. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics—2002. *J Allergy Clin Immunol*. 2002;110(suppl 5):141-219. Available at: <http://www2.us.elsevierhealth.com/scripts/om.dll/serve?action=searchDB&searchDBfor=iss&id=jai021105b>. Accessed August 15, 2003.
15. Williams SG, Schmidt DK, Redd SC, Storms W. National Asthma Education and Prevention Program. Key clinical activities for quality asthma care: recommendations of the National Asthma Education and Prevention Program. *MMWR Recomm Rep*. 2003;52(RR-6):1-8. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr5206.pdf>. Accessed May 4, 2003.
16. Asthma in America executive summary. Washington, DC: Schulman, Ronca, Bucavalas, Inc., and Glaxo Wellcome Inc.; October 1998.
17. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol*. 1996;98(6, pt 1):1051-57.
18. Joint Task Force on Practice Parameters. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2003;90(suppl 1):1-40.
19. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med*. 1995;151:969-74.

Emerging Therapeutic Strategies for Asthma Management

SEAN D. SULLIVAN, PhD, and ELI O. MELTZER, MD

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 μ g/day to 840 μ g/day of beclomethasone dipropionate in the United States study and 500 μ g/day to 1,200 μ g/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.

REFERENCES

1. Boushey HA. New and exploratory therapies for asthma. *Chest*. 2003;123(suppl 3):439S-445S.
2. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med*. 2001;344:30-37.
3. Kon OM, Sihra BS, Loh LC, et al. The effects of an anti-CD4 monoclonal antibody, keliximab, on peripheral blood CD4+ T-cells in asthma. *Eur Respir J*. 2001;18:45-52.
4. Kon OM, Sihra BS, Compton CH, Leonard TB, Kay AB, Barnes NC. Randomised, dose-ranging, placebo-controlled study of chimeric antibody to CD4 (keliximab) in chronic severe asthma. *Lancet*. 1998;352:1109-13.
5. Matsumoto K, Hayakawa H, Ide K, et al. Effects of suplatast tosilate on cytokine profile of bronchoalveolar cells in allergic inflammation of the lung. *Respirology*. 2002;7:201-07.
6. Yoshida M, Aizawa H, Inoue H, et al. Effect of suplatast tosilate on airway hyperresponsiveness and inflammation in asthma patients. *J Asthma*. 2002;39:545-52.
7. Horiguchi T, Tachikawa S, Handa M, et al. Effects of suplatast tosilate on airway inflammation and airway hyperresponsiveness. *J Asthma*. 2001;38:331-36.
8. Tamaoki J, Kondo M, Sakai N, et al. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. Tokyo Joshi-Idai Asthma Research Group. *Lancet*. 2000;356:273-78.
9. Wong WS, Koh DS. Advances in immunopharmacology of asthma. *Biochem Pharmacol*. 2000;59:1323-35.
10. Krishna MT, Chauhan A, Little L, et al. Inhibition of mast cell tryptase by inhaled APC 366 attenuates allergen-induced late-phase airway obstruction in asthma. *J Allergy Clin Immunol*. 2001;107:1039-45.
11. Gomez FP, Marrades RM, Iglesias R, et al. Gas exchange response to a PAF receptor antagonist, SR 27417A, in acute asthma: a pilot study. *Eur Respir J*. 1999;14:622-26.
12. Joos GF, Germonpre PR, Pauwels RA. Neural mechanisms in asthma. *Clin Exp Allergy*. 2000;30(suppl 1):60-65.
13. Joos GF, Pauwels RA. Tachykinin receptor antagonists: potential in airways diseases. *Curr Opin Pharmacol*. 2001;1:235-41.

14. Van Schoor J, Joos GF, Chasson BL, Brouard RJ, Pauwels RA. The effect of the NK2 tachykinin receptor antagonist SR 48968 (saredutant) on neurokinin A-induced bronchoconstriction in asthmatics. *Eur Respir J*. 1998;12:17-23.
15. Kraan J, Vink-Klooster H, Postma DS. The NK-2 receptor antagonist SR 48968C does not improve adenosine hyperresponsiveness and airway obstruction in allergic asthma. *Clin Exp Allergy*. 2001;31:274-78.
16. Minoguchi K, Adachi M. Thromboxane A2 synthase inhibitor and receptor antagonist. *Nippon Rinsho*. 2001;59:1986-91 [article in Japanese].
17. Ohmori K, Ishii H, Sasaki Y, Ikemura T, Manabe H, Kitamura S. Effects of KW-4679, a new orally active antiallergic drug, on antigen-induced bronchial hyperresponsiveness, airway inflammation and immediate and late asthmatic responses in guinea pigs. *Int Arch Allergy Immunol*. 1996;110:64-72.
18. Ohmori K, Hayashi K, Kaise T, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. *Jpn J Pharmacol*. 2002;88:379-97.
19. Gardiner PV, Young CL, Holmes K, Hendrick DJ, Walters EH. Lack of short-term effect of the thromboxane synthetase inhibitor UK-38,485 on airway reactivity to methacholine in asthmatic subjects. *Eur Respir J*. 1993;6:1027-30.
20. Peccini F, Dottorini ML, Casucci G, Mezzasoma AM, Sorbini CA, Tantucci C. Ineffectiveness of a four-week treatment with the thromboxane synthetase inhibitor, imidazole salicylate, in reducing airway hyperresponsiveness to methacholine in asthmatics. *Monaldi Arch Chest Dis*. 1997;52:130-37.
21. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet*. 2000;356:2144-48.
22. Shi HZ, Deng JM, Xu H, et al. Effect of inhaled interleukin-4 on airway hyperreactivity in asthmatics. *Am J Respir Crit Care Med*. 1998;157(6, pt 1): 1818-21.
23. Borish LC, Nelson HS, Lanz MJ, et al. Interleukin-4 receptor in moderate atopic asthma: a phase I/II randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 1999;160:1816-23.
24. Borish LC, Nelson HS, Corren J, et al. Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. *J Allergy Clin Immunol*. 2001;107:963-70.
25. Jackson DY. Alpha 4 integrin antagonists. *Curr Pharm Des*. 2002;8:1229-53.
26. Torphy TJ. Phosphodiesterase isozymes: molecular targets for novel anti-asthma agents. *Am J Respir Crit Care Med*. 1998;157:351-70.
27. McEvoy GK, ed. Theophyllines. In: *AHFS Drug Information* 2003. Bethesda, MD: American Society of Health-System Pharmacists; 2003:3487-93.
28. Billah MM, Cooper N, Minniccozi M, et al. Pharmacology of N-(3,5-dichloro-1-oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinoline carboxamide (SCH 351591), a novel, orally active phosphodiesterase 4 inhibitor. *J Pharmacol Exp Ther*. 2002;302:127-37.
29. Gienbycz MA. Cilomilast: a second generation phosphodiesterase 4 inhibitor for asthma and chronic obstructive pulmonary disease. *Expert Opin Investig Drugs*. 2001;10:1361-79.
30. Hatzelmann A, Schudt C. Anti-inflammatory and immunomodulatory potential of the novel PDE4 inhibitor roflumilast in vitro. *J Pharmacol Exp Ther*. 2001;297:267-79.
31. Bundschuh DS, Eltze M, Barsig J, Wollin L, Hatzelmann A, Beume R. In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor. *J Pharmacol Exp Ther*. 2001;297:280-90.
32. Timmer W, Leclerc V, Birraux G, et al. The new phosphodiesterase 4 inhibitor roflumilast is efficacious in exercise-induced asthma and leads to suppression of LPS-stimulated TNF-alpha ex vivo. *J Clin Pharmacol*. 2002;42:297-303.
33. Khan LN, Kon OM, Macfarlane AJ, et al. Attenuation of the allergen-induced late asthmatic reaction by cyclosporin A is associated with inhibition of bronchial eosinophils, interleukin-5, granulocyte macrophage colony-stimulating factor, and eotaxin. *Am J Respir Crit Care Med*. 2000;162(4, pt 1): 1377-82.
34. Evans DJ, Cullinan P, Geddes DM. Cyclosporin as an oral corticosteroid sparing agent in stable asthma. *Cochrane Database Syst Rev*. 2001;(2): CD002993.
35. Rohatagi S, Calic F, Harding N, et al. Pharmacokinetics, pharmacodynamics, and safety of inhaled cyclosporin A (AD1628) after single and repeated administration in healthy male and female subjects and asthmatic patients. *J Clin Pharmacol*. 2000;40:1211-26.
36. Powell N, Till S, Bungre J, Corrigan C. The immunomodulatory drugs cyclosporin A, mycophenolate mofetil, and sirolimus (rapamycin) inhibit allergen-induced proliferation and IL-5 production by PBMCs from atopic asthmatic patients. *J Allergy Clin Immunol*. 2001;108:915-17.
37. Mori A, Suko M, Nishizaki Y, et al. IL-5 production by CD4+ T cells of asthmatic patients is suppressed by glucocorticoids and the immunosuppressants FK506 and cyclosporin A. *Int Immunol*. 1995;7:449-57.
38. Malaviya R, Uckun FM. Leflunomide metabolite analogue alpha-cyano-beta-hydroxy-beta-methyl-N-[3-(trifluoromethyl)phenyl]propenamide inhibits IgE/FcepsilonRI receptor-mediated mast cell leukotriene release and allergic asthma in mice. *Am J Ther*. 2001;8:309-16.
39. Boushey HA Jr. Experiences with monoclonal antibody therapy for allergic asthma. *J Allergy Clin Immunol*. 2001;108(suppl 2):S77-S83.
40. Xolair [package insert]. San Francisco, CA: Genentech, Inc.; 2003.
41. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med*. 2001;164(8, pt 2):S6-S11.
42. Data on file at Genentech Inc, San Francisco, CA, and Novartis Pharmaceuticals Corporation, East Hanover, NJ.
43. MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol*. 1997;158:1438-45.
44. Togias A, Corren J, Shapiro G, et al. Anti-IgE treatment reduces skin test (ST) reactivity [abstract]. *J Allergy Clin Immunol*. 1998;101:S171. Abstract 706.
45. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med*. 1997;155:1828-34.
46. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184-90.
47. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18:254-61.
48. Nelson H, Fick R, Fowler-Taylor A, et al. Increased time to first asthma exacerbation seen in Xolair-treated patients compared with placebo [abstract]. *Ann Allergy Asthma Immunol*. 2001;86:98. Abstract P17.
49. Buhl R, Hanf G, Soler M, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J*. 2002;20:1088-94.
50. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol*. 2003;111:87-90.
51. Holgate S, Bousquet J, Wenzel S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin*. 2001;17:233-40.
52. National Heart, Lung, and Blood Institute and the National Asthma Education and Prevention Program. *Guidelines for the Diagnosis and Management of Asthma*. Expert Panel Report 2. Pub. No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; 1997.
53. Rosenwasser LJ, Nash DB. Incorporating omalizumab into asthma treatment guidelines: consensus panel recommendations. *P&T*. 2003; 28:400-14.

Continuing Education

Exploring New Frontiers in Asthma Management for Optimal Therapeutic and Economic Outcomes

Date: _____

In order to receive CE credit for this program, you must complete this form and the Program Evaluation form in addition to completing the posttest with a score of at least 70% (forms may be photocopied). Please mail all materials to the **Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314**. To receive credit, these forms must reach the Academy of Managed Care Pharmacy by December 1, 2005. CE certificates will be mailed to your address (below) as soon as possible after receipt of the Record of Completion and Program Evaluation forms and the posttest is graded and successful completion is determined.

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☐ I verify that I have completed the program and posttest for "Exploring New Frontiers in Asthma Management for Optimal Therapeutic and Economic Outcomes."

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Member Type: ☐ Active ☐ Supporting Associate ☐ Student ☐ Nonmember

Posttest Answers:

	A	B	C	D
1.	☐	☐	☐	☐
2.	☐	☐	☐	☐
3.	☐	☐	☐	☐
4.	☐	☐	☐	☐
5.	☐	☐	☐	☐

	A	B	C	D
6.	☐	☐	☐	☐
7.	☐	☐	☐	☐
8.	☐	☐	☐	☐
9.	☐	☐	☐	☐
10.	☐	☐	☐	☐

	A	B	C	D
11.	☐	☐	☐	☐
12.	☐	☐	☐	☐
13.	☐	☐	☐	☐
14.	☐	☐	☐	☐
15.	☐	☐	☐	☐

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Continuing Education

Exploring New Frontiers in Asthma Management for Optimal Therapeutic and Economic Outcomes

Please indicate the correct answers on the Record of Completion.

1. Which of the following trends was observed in the United States in the 1990s?
 - a. The prevalence of asthma began to decrease.
 - b. The rate of asthma-related emergency department visits began to decrease.
 - c. The rate of asthma-related hospitalization began to decrease.
 - d. The rate of asthma-related mortality began to decrease.
2. Which of the following was the largest component of asthma-related costs in the United States in 1998?
 - a. Hospital inpatient care
 - b. Indirect costs
 - c. Medications
 - d. Physician services
3. Which of the following factors was identified as a reason for difficulty in treating asthma in the TENOR Study?
 - a. Failure to prescribe a controller medication
 - b. The need for multiple medications
 - c. The high cost of health care
 - d. Lack of access to health care
4. Which of the following statements about patients with severe asthma who are at high risk for asthma-related morbidity and mortality and their share of health care costs is correct?
 - a. They make up a small percentage of the patient population and account for a small share of health care costs.
 - b. They make up a small percentage of the patient population and account for a large share of health care costs.
 - c. They make up the majority of the patient population and account for a small share of health care costs.
 - d. They make up the majority of the patient population and account for a large share of health care costs.
5. Which of the following statements about the role of atopy and the immune system in asthma is correct?
 - a. Th1 cells predominate at birth in all persons, but an imbalance with a predominance of Th2 cells, a Th2-mediated immune response, and a predisposition to asthma develop later in persons with atopy because of immune deviation.
 - b. Neither Th1 cells nor Th2 cells predominate at birth, but an imbalance with a predominance of Th2 cells, a Th2-mediated immune response, and a predisposition to asthma may develop later in patients exposed to certain allergens.
 - c. Th2 cells predominate at birth and later in life only in persons with atopy, who develop a Th2-mediated immune response and a predisposition to asthma.
 - d. Th2 cells predominate at birth in all persons, but an imbalance with a predominance of Th1 cells and a Th1-mediated immune response develops later in persons without atopy because of immune deviation.
6. Which of the following is most reliable for confirming the diagnosis of asthma?
 - a. Chest auscultation
 - b. A methacholine challenge test
 - c. Spirometry
 - d. The peak expiratory flow rate
7. Which of the following therapeutic regimens is preferred for long-term control of moderate persistent asthma in adults according to the NAEPP expert panel in its 2002 update report?
 - a. An inhaled corticosteroid plus a long-acting inhaled beta₂-agonist
 - b. An inhaled corticosteroid or a long-acting inhaled beta₂-agonist
 - c. An inhaled corticosteroid or a cromone or theophylline
 - d. An inhaled corticosteroid or a leukotriene modifier or theophylline
8. Which of the following statements about the accuracy of patient and physician perceptions of asthma severity is correct?
 - a. Patients tend to estimate it accurately if they are taught to use a PEF meter properly.
 - b. Physicians and patients tend to overestimate it, which could result in toxicity from excessive drug therapy.
 - c. Physicians and patients tend to underestimate it, which could result in asthma exacerbations from inadequate treatment.
 - d. Physicians tend to overestimate it and prescribe excessive drug therapy, resulting in toxicity and patient nonadherence.
9. Which of the following factors does not affect patient adherence to a therapeutic regimen?
 - a. Administration frequency
 - b. Patient administration
 - c. Manufacturing processes
 - d. Route of administration

10. Which of the following symptoms would indicate the need to increase long-term controller therapy in a patient with good previous asthma control?
- Decrease use of short-acting inhaled β_2 -agonists
 - Achievement of therapeutic goals
 - Uninterrupted sleep
 - Diminished ability to participate in customary daily activities
11. Which of the following investigational asthma therapies is a selective PDE4 inhibitor?
- Omalizumab
 - Roflumilast
 - Saredutant
 - Suplatast tosilate
12. Which of the following elements of allergic asthma is targeted by omalizumab?
- Th2 cells
 - Cytokines
 - IgE
 - Inflammatory mediators
13. Which of the following is the target of keliximab?
- IL-4
 - IL-5
 - IgE
 - CD4+ T cells
14. Which of the following is the mechanism of action of alpha 4 integrins?
- Cell adhesion inhibition
 - MAP kinase inhibition
 - PDE4 inhibition
 - Tyrosine kinase inhibition
15. Which of the following nonselective immunosuppressants has been administered by inhalation to patients with asthma without any apparent evidence of systemic immunosuppression?
- Cyclosporine
 - Mycophenolate mofetil
 - Sirolimus
 - Tacrolimus

Exploring New Frontiers in Asthma Management for Optimal Therapeutic and Economic Outcomes

Participant's name: _____ Date: _____

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

Scale For Questions 1-5

- 1 = Not at all
2 = Not very well
3 = Somewhat well
4 = Well
5 = Very well

Scale For Questions 6 and 7

- 1= Poor
2= Fair
3= Good
4= Very good
5= Excellent

Using the scale above for questions 1-5, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Using the scale above for questions 6 and 7, please indicate the number that best expresses your opinion.

Objectives:

1. discuss recent trends in asthma prevalence and the economic burden of the disease in the United States;
2. define asthma control and characterize the patient with difficult-to-treat asthma;
3. explain the role of atopy, immunoglobulin E (IgE), and the immune system in the pathogenesis of asthma;
4. summarize the diagnosis, classification, and treatment of asthma according to National Asthma Education and Prevention Program guidelines published in 2002; and
5. describe the mechanisms of action and clinical experience to date with novel asthma drug therapies, including the humanized anti-IgE monoclonal antibody omalizumab.

6. What is your overall rating of this program? _____

7. How would you rate the pertinence of this program material to your practice? _____

8. To what degree was there promotional bias (check one):
- a. Not at all _____
 - b. Somewhat _____
 - c. A great deal _____

9. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)

1	2	3	4	5
No change				Significant change

10. Please indicate the length of time it took to complete this program: (circle selection)

Hours:	1	2	3	
Minutes:	0	15	30	45

11. Please rate the difficulty factor for completing this CE program:
(circle selection) Easy Moderate Difficult

12. Please rate your willingness to recommend this program to colleagues: (circle selection)
- Very willing Willing Not willing

13. Please indicate which venue you prefer for obtaining continuing education: (circle selection)
Written monograph	Slides	Videos	Internet-based

Live sessions Other: _____

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