Treatment Options for Asthma: Scientific Review

UC Davis Center for Health Services Research in Primary Care
July 2005
Treatment Options for Asthma: Scientific Review

Prepared for:
CALIFORNIA HEALTHCARE FOUNDATION

Prepared for:
UC Davis Center for Health Services Research in Primary Care

Authors:
Robert Mowers, Pharm.D.
Jesse P. Joad, M.D.

Senior Scientific Editor
Richard L. Kravitz, M.D.

July 2005
Acknowledgments
The authors would like to thank H. William Kelly, Pharm.D. and E. Rand Sutherland, M.D., M.P.H. for their careful review and critique of an earlier draft of this document. Additional thanks are due to Diane Romac, Pharm.D., Jeff King, Pharm.D. and Parag Nene, M.D. for scientific editing; to Wilhelmina Cottman for project management; to Joanne Tang for technical editing; and to the PDIP Scientific Advisory Committee for their consistent guidance and support.

About the Authors
Robert Mowers, Pharm.D., is a managed care pharmacist at the University of California, Davis, Medical Center. Jesse P. Joad, M.D., is a professor and vice chair in the Research Department of Pediatrics, University of California, Davis.

About the Foundation
The California HealthCare Foundation, based in Oakland, is an independent philanthropy committed to improving California’s health care delivery and financing systems. Formed in 1996, our goal is to ensure that all Californians have access to affordable, quality health care. For more information, visit us online (www.chcf.org).

ISBN 1-932064-xx-x
Copyright © 2005 California HealthCare Foundation
**Contents**

4 **I. Description of Condition**
   - Definition
   - Epidemiology and Cause
   - Diagnosis
   - Natural History and Prognosis

6 **II. Nonpharmacologic Therapies**
   - Complementary and Alternative Therapies
   - Over-the-Counter Drug Therapies
   - Immunotherapy
   - Patient Education and Nonpharmacologic Methods for Controlling Asthma

8 **III. Pharmacologic Therapies**
   - Major Treatment Options
   - Index Drug Class: Inhaled Corticosteroids
   - Other Drug Therapies
   - Managing Asthma During Pregnancy

15 **VI. Summary**

17 **Endnotes**
I. Description of Condition

Definition

According to the National Institutes of Health’s National Asthma Education and Prevention Program (NAEPP) expert panel report,

Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

This definition, which was reaffirmed in the 2002 update of the NAEPP report, concurred with the emphasis placed on the importance of airway inflammation in the pathogenesis, pathophysiology, and treatment of asthma.

Epidemiology and Cause

In 2000, more than 11 million persons in the United States had an asthma attack, including 5% of children under the age of 18 years. The rates of hospitalization for asthma have remained stable since 1980 for all age groups, except for children younger than 15 years, in whom the rate has increased. Overall, mortality rates have declined since 1995, but asthma mortality is nearly three times higher in black males than in white males, and 2.5 times higher in black females than in white females.

Diagnosis

The diagnosis of asthma is often made on the basis of a typical history that includes attacks of abrupt dyspnea accompanied by a dry, nonproductive cough and wheezing. In many patients, asthma attacks occur at night. One of the characteristic features of asthma is its reversibility, which can occur spon-
taneously or after treatment. Spirometry is considered the standard for both the diagnosis and evaluation of the severity of asthma as well as for the determination of response to medication. Forced expiratory volume within the first second (FEV1) is the most useful parameter in the evaluation of the asthma patient. Serial measurements of the peak expiratory flow rate with a portable peak flow meter may provide an objective determination of lung function.

Asthma should be differentiated from other upper and lower respiratory tract diseases, including infiltrative lung disease. In older patients, cardiac failure, chronic obstructive pulmonary disease, and airway tumors should be considered in the differential diagnosis.

**Natural History and Prognosis**

The natural history of asthma is not well defined. Symptoms in children may improve, and children may become symptom free by early adulthood. Chronic disease may persist in 30% of patients. Asthma can be classified as persistent or acute. Persistent asthma is defined as asthma requiring maintenance treatment. Acute asthma is defined as an exacerbation of underlying asthma requiring urgent treatment. An acute asthma attack may be precipitated by stimuli initiating bronchoconstriction, causing airway hyperresponsiveness and airflow obstruction, with or without increased inflammation. These stimuli, also known as triggers, include the following: allergens (pollens, house dust, animal dander, dust mites, insect parts, fungal spores, and, rarely, foods); irritants (air pollution, tobacco smoke, cold air, strong odors, gastroesophageal reflux); exercise; strong emotional expression (anxiety, fatigue, stress, laughter); and respiratory tract infections. These irritants can trigger severe bronchoconstriction. Cold air, exercise, and strong emotional expression may act as triggers but probably do not cause inflammation. Aspiration of the acid contents of the stomach can result in a persistent cough.

Persistent asthma can be controlled with allergen and irritant avoidance along with medications. If patients do not adhere to the treatment regimen, their activities of daily living may be compromised markedly and life-threatening acute asthma attacks may occur. The most severe asthma cases may require hospitalization despite compliance with maximum doses of chronic medications.

The NAEPP expert panel report lists the following goals for therapy: prevention of chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion); maintenance of “near-normal” pulmonary function; maintenance of normal activity levels (including exercise and other physical activity); prevention of recurrent exacerbations of asthma and minimization of the need for emergency department visits or hospitalizations; provision of optimal pharmacotherapy with minimal or no adverse effects; and meeting of patients’ and families’ expectations of and satisfaction with asthma care. The mainstay of asthma treatment is pharmacologic therapy. However, many nonpharmacologic measures should also be initiated to facilitate successful pharmacologic outcomes.
II. Nonpharmacologic Therapies

Complementary and Alternative Therapies

The use of complementary and alternative medicine for the treatment of asthma is very popular. In a recent review of studies published between June 2002 and September 2003 that deal with complementary and alternative therapies for asthma, the authors evaluated 16 randomized clinical trials and 16 reviews on herbal medicine/phytotherapy, acupuncture, homeopathy, breathing exercises, diet/nutritional therapy, psychotherapy-related techniques, and manual therapy (manipulation, mobilization, chest percussion, shaking, and vibration). Their analysis revealed a lack of data to support the use of homeopathy, air ionizers, manual therapy, or acupuncture for asthma management. In addition, they concluded that the role of antioxidant dietary supplementation is not clearly defined and needs further study, along with other strategies such as breathing or training exercises, to determine if these practices provide an additive role in the current treatment of asthma. They also determined that psychotherapy (e.g., relaxation, hypnosis, biofeedback therapy) has not been shown to be superior to placebo. The authors concluded that use of complementary and alternative therapies places patients at risk of underutilization of conventional (proven) therapies and thus is not recommended as the main treatment in asthma therapy.

Over-the-Counter Drug Therapies

The only over-the-counter medication used specifically for the treatment of asthma is epinephrine, which is available as a metered-dose inhaler. Epinephrine is a mixed alpha-, beta-1-, beta-2- agonist, and works as a bronchodilator (see section on beta-agonists). Although epinephrine is an effective bronchodilator, its unsupervised use must be discouraged, as the potential for adverse effects related to alpha and beta-1 stimulation (e.g., increased heart rate and blood pressure, and palpitations) at normal and high doses limits the safety of epinephrine products. In addition, epinephrine has a short duration of action. Patients should be encouraged to work with their physicians to develop an asthma action plan that includes the use of an inhaled corticosteroid and a beta-2-specific rescue inhaler, instead of relying on self-medication with over-the-counter epinephrine.
Immunotherapy

The role of immunotherapy (allergy shots) in the treatment of asthma is controversial. A Cochrane review evaluated 75 randomized controlled trials comprising a total of 3506 participants (3188 with asthma), including 36 trials of immunotherapy for allergy to house mites, 20 pollen allergy trials, 10 animal dander allergy trials, two Cladosporium mold allergy trials, one latex trial, and six trials that studied multiple allergens. The meta-analysis showed a reduction in asthma symptoms and medication use, and improvement in bronchial hyperreactivity, following immunotherapy, although between-study heterogeneity was noted. However, the expense, inconvenience, and possibility of adverse effects, including but not limited to fatal anaphylaxis with immunotherapy, must be considered. According to the NAEPP expert panel report, specific immunotherapy may be beneficial in patients when there is clear evidence of an association between symptoms and exposure to an unavoidable allergen to which the patients are sensitive; in patients whose symptoms occur during a major portion of the year and are not perennial; and in those with allergen-triggered asthma not controlled by traditional therapies (e.g., inhaled corticosteroids along with long-acting beta₂-agonists). With the recent Food and Drug Administration approval of omalizumab, specific immunotherapy may be partially replaced by omalizumab therapy (see section on omalizumab).

Patient Education and Nonpharmacologic Methods for Controlling Asthma

Patient education is an essential component of successful asthma management. Patients, families, and health care practitioners need to work together to develop an asthma action plan. These plans should help patients and their families understand the need to institute environmental control strategies to help patients avoid triggers without undue limitations on quality of life. It is important to allow patients to exercise and participate fully in social events.

If animal dander contributes to asthma symptoms, families may need to consider removing the pet from the home. Carpets should be removed from bedrooms. Washing bedding in hot water (>130°F) and using plastic pillow and mattress covers may help patients who are sensitive to dust mites. Lowering the indoor humidity to less than 50% may also be beneficial. If children are sensitive to dust, families should minimize the number of stuffed toys on the bed. Patients who smoke should be encouraged to stop, and adults with children who have asthma should not smoke in the house or car.

Strategies to reduce exposure to environmental allergens have not decreased asthma-related morbidity, and thus their clinical effectiveness is uncertain. Most interventions have focused on removal of a single allergen. However, the recently published Inner City Asthma Study demonstrated that decreasing exposure to indoor allergens (cockroach and dust mite) with an individualized, home-based, comprehensive environmental intervention decreased asthma-associated morbidity among inner-city children.
III. Pharmacologic Therapies

Major Treatment Options

The main therapy for asthma management is prescription pharmacologic therapy, which can be divided into two groups: long-term controllers and “quick-relief,” rescue medications. As inflammation is a major feature of asthma, the most effective controllers are agents that limit inflammation, such as corticosteroids, cromolyn sodium and nedocromil, leukotriene modifiers, and omalizumab. Long-acting inhaled beta_2_ agonists are bronchodilators, do not have anti-inflammatory properties, and should not be used as monotherapy. Methylxanthines are bronchodilators and have mild anti-inflammatory properties, but are rarely used as they are considerably less effective than inhaled corticosteroids and are associated with dose-related toxicities (e.g., tachycardia and other arrhythmias, nausea, vomiting, central nervous system stimulation, seizures). Short-acting beta_2_ agonists are the drugs of choice for rescue medications. Exacerbations that do not respond to beta-agonists require intensification of corticosteroid use (inhaled or systemic). Anticholinergics may be useful as rescue medication in patients who are unable to tolerate short-acting beta_2_ agonists, as well as those with severe exacerbations who are treated in the emergency department or hospital. Anticholinergic agents are substantially less effective than short-acting beta_2_ agonists.

A stepwise approach to asthma therapy, in which the dose and number of medications and frequency of administration are increased or decreased when possible, is used to achieve optimal asthma control.\(^1,2\) Figure 1, from the NAEPP report, demonstrates this stepwise approach.\(^1,2\) Table 1 lists commonly used asthma-related prescription medications and their costs.

Index Drug Class: Inhaled Corticosteroids

Asthma is a chronic inflammatory disorder of the airways. As such, inhaled corticosteroids are the most effective anti-inflammatory agents for the treatment of asthma. Corticosteroids inhibit the inflammatory process at all levels. They inhibit cytokine production and inflammatory cell migration and activation. Additionally, corticosteroid therapy increases the number of beta_2_ receptors, improves the receptor response to beta_2_ stimulation in patients with asthma, and reduces mucus production and hypersecretion. Corticosteroids bind with the
glucocorticoid receptor, and the complex enters the cell nucleus, causing gene activation, which leads to the production of anti-inflammatory mediators and the reduction of proinflammatory mediators. The clinical effects of systemic corticosteroids may be observed 2 to 4 hours after administration in cases of acute asthma exacerbations. The response to inhaled corticosteroids is delayed. In patients with chronic asthma, most patients will notice an improvement in symptoms within the first 2 weeks, with maximal effects seen within 8 weeks.

A review of inhaled corticosteroids was issued in 2005 by the RTI-UNC Evidence-based Practice Center in conjunction with the Oregon Evidence-based Practice Center’s Drug Effectiveness Review Project (DERP). The DERP report concluded that “most efficacy studies provide fair evidence that, at equipotent doses administered through comparable delivery devices, ICSs [inhaled corticosteroids] do not differ in their ability to control asthma symptoms and reduce the need for additional rescue medication.” In addition, the authors of the report noted that there is insufficient evidence to conclude that any one inhaled corticosteroid is superior to another for patients of a specific age group, ethnic group, or sex.

A 2003 review by Kelly was concordant with the DERP report, concluding that “there is currently no evidence to support differences in efficacy when [inhaled corticosteroids] are administered at equipotent doses.” Earlier publications by Kelly list the relative anti-inflammatory potency of inhaled corticosteroids in the following rank order: flunisolide = triamcinolone acetonide < beclomethasone dipropionate < budesonide < fluticasone propionate. We agree with the findings of the DERP report, that, at equipotent doses administered through comparable delivery devices, inhaled corticosteroids do not differ in their ability to control asthma symptoms or to reduce the need for additional rescue medication. Different inhaled corticosteroids vary in potency. However, potency differences can be overcome by increasing the dose of corticosteroid administered, and equipotent doses provide comparable efficacy. Of note, the delivery device and pharmacokinetic differences among inhaled corticosteroids have a larger effect on clinical efficacy than do the relative potencies. The 2002 NAEPP expert panel update provides information (Table 2) on inhaled corticosteroid doses with approximately equivalent efficacy, based on relative potency and delivery as well as numerous clinical trial results.

The systemic adverse effects of inhaled corticosteroids are influenced by potency and bioavailability. Inhaled corticosteroids have a favorable side-effect profile (minimal growth reduction in children, less adrenal suppression, and minimal bone mineral density reduction) owing to the high topical-to-systemic ratio of these products compared with oral corticosteroids. The topical adverse effects of oral candidiasis and hoarseness can be decreased by using a valved holding-chamber type of spacing device to administer the inhaled corticosteroid, as well as by mouth washing after inhalation. Systemic availability of beclomethasone dipropionate and flunisolide, which can be absorbed from the gastrointestinal tract, may also be decreased with the use of valved holding chambers. In contrast, fluticasone propionate and budesonide are minimally absorbed orally. None of the inhaled corticosteroids are absolutely interchangeable on a microgram or per puff basis, as a result of differences in potency, delivery, and pharmacokinetics. In general, for most patients, twice-daily dosing is adequate for controlling asthma symptoms.
The 2005 DERP report noted that the overall incidence of adverse events is similar among inhaled corticosteroids and that discontinuation rates because of adverse events do not differ markedly within this class of medications. In addition, the report investigated whether specific adverse events (including osteoporosis, growth retardation, acute adrenal crisis, cataracts, and ocular hypertension) are related to inhaled corticosteroid use, and concluded that the evidence of an association between inhaled corticosteroids and osteoporosis is “mixed.” Of four studies that measured fractures, two found no increase in risk whereas the others reported a slight dose-dependent increase in the risk of fractures in patients treated with inhaled corticosteroids. Similarly, there was mixed evidence regarding growth retardation with inhaled corticosteroid use. The report found insufficient evidence to draw conclusions about a higher risk of acute adrenal crisis with this class of medications. It was also noted that the risk of cataracts increases with “higher doses, longer duration of treatment, and older age” and that there is also a dose-related increase in the risk of ocular hypertension and open-angle glaucoma with inhaled corticosteroid use. Of note, no study compared the risk of developing cataracts, ocular hypertension, or open-angle glaucoma with any one inhaled corticosteroid versus another.

The DERP report also investigated the safety of inhaled corticosteroid use during pregnancy. Two studies found no marked differences in gestational age, birth weight, and length between infants whose mothers had used inhaled corticosteroids and those whose mothers had not.

Other Drug Therapies

Beta₂-Agonists
Beta₂-agonists can be divided into short-acting agents for rescue (albuterol, bitolterol, pirbuterol, terbutaline, and levalbuterol) and long-acting agents or “controllers” (salmeterol and formoterol). Beta₂-agonists can also be used prophylactically for exercise-induced asthma.

Beta₂-agonists are the most effective bronchodilators. They cause smooth muscle relaxation, mast cell membrane stabilization, and skeletal muscle stimulation. Adverse effects include tachycardia, skeletal muscle tremor, hypokalemia, and headache. The inhalation route is generally preferred over the oral route (tablets or solution) because it causes fewer adverse effects. With spacers and masks, parents can safely administer inhaled beta₂-agonists to the majority of children and avoid the adverse effects associated with the oral route.

Short-Acting Beta₂-Agonists
As stated earlier, epinephrine is not recommended because of its potential for excessive cardiac stimulation at higher doses. The most frequently used short-acting beta₂-agonist is albuterol, since the other agents have not been shown to be clinically superior and are also more costly.

All beta₂-agonists exist as mixtures (50:50) of two enantiomers or mirror images of one another. It is postulated that the S enantiomer is responsible for producing more of the adverse effects and that the R enantiomer is responsible for bronchodilation. Therefore, a new formulation without the S enantiomer is now available (levalbuterol). However, studies have not demonstrated a substantial decrease in adverse effects with levalbuterol when compared with albuterol. Lötvall et al compared local bronchodilating and systemic pharmacodynamic effects of albuterol and levalbuterol with placebo, and found that levalbuterol and albuterol had similar potency ratios for local (FEV₁) and systemic (heart rate) effects. The safety of albuterol appears to be similar to that of levalbuterol. At this time, published reports do not demonstrate advantages of levalbuterol over albuterol.
There are many devices available for delivering short-acting beta_2-agonists to asthma patients. These include chlorofluorocarbon (CFC)–propelled pressurized metered-dose inhalers, CFC-free propelled pressurized metered-dose inhalers, and breath-activated inhalers. A recent meta-analysis of 118 randomized clinical trials did not find a clinical difference between standard CFC metered-dose inhalers and other handheld devices, concluding that the least expensive device that the patient is able to use should be the first agent (device) considered.

A systematic review found that there is no advantage in using inhaled short-acting beta_2-agonists on a regular basis as compared with using them on an as-needed basis to relieve asthma symptoms. At the same time, the authors also provided reassurance that regular use of short-acting beta_2-agonists is not associated with a “clinically meaningful deleterious effect on the main indicators of asthma control.”

The key issues with short-acting beta_2-agonists are as follows: albuterol is the most cost-effective short-acting beta_2-agonist; if patients are using more than one canister a month, anti-inflammatory medication should be initiated or intensified; and regularly scheduled daily use is not recommended.

**Long-Acting Beta_2-Agonists**

Long-acting beta_2-agonists include salmeterol and formoterol. Neither of these agents is indicated in the management of acute symptoms or exacerbations of asthma as they provide long-term control of asthma, and salmeterol has a slower onset of action (15 to 30 minutes) as compared with 2 to 5 minutes for albuterol. Although formoterol has a similar onset of action as albuterol, its relative costs and dry-powder inhaling system do not provide a cost-effective or convenient as-needed therapy. Both long-acting beta_2-agonists are useful in preventing symptoms, especially nocturnal or exercise-induced bronchospasm. Tachycardia, skeletal muscle tremor, and hypokalemia are the main adverse effects at standard doses. Some patients find it difficult to fall asleep if these agents are administered just before bedtime.

There are no data to suggest that salmeterol or formoterol are clinically different when used for the long-term control of asthma.

There is good evidence that monotherapy with beta_2-agonists (short-acting or long-acting) is inferior to inhaled corticosteroids as maintenance treatment in persistent asthma. However, it has also been shown that in patients already taking low-to-moderate doses of inhaled corticosteroids, adding a long-acting beta-agonist improves symptoms and lung function more than does increasing the dose of inhaled corticosteroids. Hence, long-acting beta_2-agonists should not be used as single agents in place of anti-inflammatory therapy. Rather, they should be added to a patient’s medical regimen when low-to-medium doses of inhaled corticosteroids do not control asthma symptoms.

**Anticholinergic Agents**

Ipratropium can reverse cholinergically mediated bronchospasm. It does not block exercise-induced bronchospasm or modify bronchospasm due to antigens. Ipratropium works by competitively inhibiting the muscarinic cholinergic receptors. Ipratropium has a limited role in the treatment of asthma because multiple mediators produce bronchospasm in asthma. Ipratropium can be an alternative rescue medication for patients with intolerance to beta_2-agonists; however, it has a slower onset of action. Ipratropium produces additive bronchodilation with beta_2-agonists in severe asthma and is a safer bronchodilator than theophylline products.

One systematic review found that in children, adding multiple doses of inhaled ipratropium bromide to an inhaled beta_2-agonist (fenoterol or salbutamol) reduced hospital admissions by an average of 25% in children with moderate or severe exacerbations. The authors concluded that “using [inhaled anticholinergics and beta_2-agonists]...
nists] together improves outcomes for children with severe asthma attacks, although there is not enough evidence about effects for children with mild or moderate attacks."

Another systematic review, of anticholinergic agents for adults with chronic asthma, found that although treatment with anticholinergic agents was better than placebo, "the size of the effect was rather small." In addition, the review concluded that adding an anticholinergic agent to a short-acting beta₂-agonist did not result in a substantial benefit. The authors, however, did express concerns about the quality of the studies and did not exclude the possibility that there may be subgroups of patients who derive some benefit from anticholinergic agents as add-on treatment. They also noted that the role of long-acting anticholinergic agents (e.g., tiotropium bromide) in asthma has yet to be established.

Ipratropium has a larger role in the management of non–asthma chronic obstructive pulmonary disease (e.g., emphysema, chronic bronchitis), where the bronchospasm is primarily mediated by cholinergic stimulation. Of note, ipratropium may be the treatment of choice for bronchospasm due to beta-blockers.

**Cromolyn and Nedocromil**

Both cromolyn and nedocromil have been suggested for use in children so as to avoid the use of inhaled corticosteroids and their possible adverse effects. Both agents stabilize mast cell membranes and inhibit the activation and release of mediators from eosinophils. The therapeutic response is slow; it takes 4 to 6 weeks of therapy to determine the maximal benefit. The NAEPP expert panel report lists cromolyn and nedocromil as options for the treatment of asthma in adults and children; however, inhaled corticosteroids remain the preferred treatment.

**Leukotriene Modifiers**

Leukotrienes are released from mast cells, eosinophils, and basophils. They cause the smooth muscles to contract, as well as increase vascular permeability, increase mucus secretions, and attract inflammatory cells in the airway. Zileuton is a 5-lipoxygenase pathway inhibitor, whereas zafirlukast and montelukast are leukotriene receptor antagonists. Leukotriene receptor antagonists improve lung function modestly when used as monotherapy in adults and children with mild or moderate persistent asthma. Ducharme reviewed 13 randomized clinical trials (12 involving adults and one involving children) of antileukotrienes versus inhaled corticosteroids as single-agent treatment in patients with mild or moderate asthma. Leukotriene receptor antagonists were compared with inhaled corticosteroids at a daily dose equivalent to 400 to 450 lg of beclomethasone dipropionate. Patients treated with leukotriene receptor antagonists were 60% more likely to suffer an exacerbation requiring systemic corticosteroids. Inhaled corticosteroids (at doses equivalent to 400 lg/d of beclomethasone dipropionate) were found to be more effective than leukotriene receptor antagonists in the treatment of adults. There was insufficient evidence to conclude about the efficacy of these agents in children.

For patients already taking inhaled corticosteroids, one systematic review concluded that "the addition of anti-leukotrienes brings modest improvement in asthma control, but it remains unclear whether (anti-leukotrienes) are as effective as increasing the dose of inhaled steroids." However, one randomized controlled trial of patients taking a stable dose of budesonide found that adding montelukast increased asthma-free days and decreased nocturnal waking as compared with placebo at 16 weeks.
The NAEPP expert panel concluded that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults as well as, by extrapolation (until data become available), children. Leukotriene modifiers may be added to the treatment regimen of patients with moderate persistent asthma whose symptoms are not controlled with inhaled corticosteroids. However, it should be noted that leukotriene modifiers are not as effective as long-acting beta2-agonists as add-on therapy; one systematic review found that in patients who experience asthma symptoms despite taking inhaled corticosteroids, the addition of a long-acting beta2-agonist “provides significantly greater protection against exacerbations, greater improvement in lung function, and modest additional improvement in symptoms, use of rescue medication, quality of life and satisfaction as compared to the [addition] of antileukotrienes.”

Some patients may prefer the convenience of taking a tablet rather than using an inhaled corticosteroid, which may in turn improve adherence and control. However, as leukotriene modifiers are not as effective as inhaled corticosteroids, patients may be at an increased risk of asthma exacerbations.

**Omalizumab**

Omalizumab is a humanized recombinant monoclonal anti-immunoglobulin E (IgE) antibody that selectively binds to human IgE. It is indicated in patients with moderate-to-severe asthma who exhibit an allergen-induced component to their asthma exacerbations. Omalizumab inhibits the binding of IgE to mast cell and basophil receptor sites by selectively binding free IgE, consequently inhibiting the IgE inflammatory cascade. Omalizumab has not demonstrated long-term efficacy exceeding that of current optimized asthma therapies. It may help patients decrease the amount of inhaled or oral corticosteroids utilized. It may also decrease asthma exacerbations or visits to the emergency department and unscheduled visits to the primary care provider’s office. However, given its high cost and the need for monthly, sometimes bimonthly, treatment, omalizumab should be reserved for patients who would most benefit from it. Figure 2 describes the criteria for using omalizumab.

**Managing Asthma During Pregnancy**

There has been particular interest in asthma management during pregnancy, as asthma is considered the “most common potentially serious medical problem to complicate pregnancy.” Studies have shown that pregnant women with asthma have an increased risk of adverse perinatal outcomes, whereas controlled asthma has been associated with reduced risks. A recent practice guideline indicates that “[f]or pregnant women with asthma, the use of inhaled cromolyn or inhaled budesonide should be considered as first-line agents. Short-acting beta-agonists can be used as needed in all asthma categories.” This statement is consistent with a recent NAEPP expert panel update on the management of asthma during pregnancy. The update also indicates that there are minimal data on the use of leukotriene modifiers during pregnancy. The report concludes that “[i]t is safer for pregnant women with asthma to be treated with asthma medications than for them to have asthma symptoms and exacerbations [and that] inadequate control of asthma is a greater risk to the fetus than asthma medications are.”
The fiscal effect of omalizumab use can be substantial, since omalizumab is dosed based on the patient’s weight and immunoglobulin E (IgE) levels. With the average wholesale price (AWP) of $521.25 per 150-mg vial, the annual drug costs are high. If a patient weighing 70 kg received 300 mg every 4 weeks, the cost (AWP) would be about $13,552 per year. If a 70-kg patient received the maximal dose of 375 mg every other week, the cost (AWP) could be as much as $41,000 per year.

To ensure that omalizumab is used in a cost-effective manner, a patient selection criteria should be utilized. Patients could be considered for omalizumab therapy if they meet the following sample criteria:

1. The patient has moderate-to-severe persistent asthma >1 year and is followed by a pulmonologist or allergist.
   • The patient has a baseline forced expiratory volume within the first second (FEV$_1$) <80% of predicted value; or
   • If the patient has >80% of predicted value the patient has responded to oral steroids.
   [AU: please clarify this point; a word may be missing: “and”?]
2. The patient has reversible asthma; and
   • An FEV$_1$ of 12% or greater within 30 minutes after administration of a short-acting beta2-agonist; or
   • At least 20% reversibility in peak flow.
3. The patient is at least 12 years old.
4. The patient has allergic asthma determined by specific allergy sensitivity testing, skin test, or RadioAllergoSorbent Test (RAST; with in vitro antigen defined).
5. The patient has a baseline total serum IgE level ≤30 IU/mL.
6. The patient weighs less than 150 kg, or has a total IgE level <700 IU/mL, as there is presently no recommended dose for such patients.
7. The patient is compliant and does not respond to maximal tolerated inhaled steroid dose in combination with a long-acting beta-agonist and leukotriene modifiers for 3 months.
8. Within the year of requesting omalizumab, the patient had:
   A. At least one acute asthma-related emergency department visit.
   B. One acute inpatient discharge visit with asthma as the principle diagnosis.
   C. Four unscheduled outpatient visits for asthma, or the patient initiated therapy with steroids for the treatment of acute asthma exacerbations.
   D. Impairment in activities of daily living, such as work, school attendance, exercise, and sleep.

If omalizumab use is agreed upon, the approval would be for 16 weeks with re-evaluation of the patient. If the patient continues to be stable (e.g., the patient has fewer emergency department visits or less than four unscheduled outpatients visits for asthma, no oral prednisone use, and no increase in inhaled steroid dose; and improvement in activities of daily living), the approval would be for 24 weeks.
IV. Summary

The medical management of asthma changes continually. New pharmacologic agents are introduced into the market along with newer delivery systems. Currently available delivery systems include metered-dose inhalers, breath-actuated inhalers, nebulizers, and dry-powder inhalers. With the move away from CFC-containing inhalers, more medications will be provided using dry-powder technology. Regardless of the severity of disease, all patients should receive a short-acting beta$_2$-agonist for rescue therapy. Albuterol is the most cost-effective short-acting beta$_2$-agonist.

The NAEPP expert panel utilized the systematic reviews on key asthma topics published by the National Heart, Lung, and Blood Institute to update their recommendations for clinical practice. The documents may be obtained at the following websites: http://www.nhlbi.nih.gov/guidelines/asthma/asthafullrpt.pdf http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

Understanding asthma as a chronic inflammatory disorder of the airways allows for selection of the most effective therapeutic modalities. Inhaled corticosteroids should be provided for all patients, except those with mild intermittent asthma, as these agents are the most effective therapy for reducing exacerbations. There are no data to suggest that one inhaled corticosteroid is superior in efficacy or has decreased adverse effects when compared with the others. Rather, inhaled corticosteroids tend to be clinically equivalent when administered in equipotent doses. Of note, adherence to inhaled corticosteroids may be improved by dosing twice daily. If patients are using more than one albuterol canister a month or have worsening symptoms, their medical regimen should be adjusted.

Adjustment of the medical regimen could be accomplished by increasing the dose of inhaled corticosteroid or by adding a long-acting inhaled beta$_2$-agonist. In patients who are already receiving medium doses of inhaled corticosteroids, further dose increases are unlikely to provide additional benefit, and therefore the addition of a long-acting inhaled beta$_2$-agonist is recommended.
In patients with moderate or severe persistent asthma who are taking appropriate doses of inhaled corticosteroids and long-acting beta₂-agonists, the addition of a leukotriene modifier may decrease exacerbations. Leukotriene modifiers should not be used in place of an inhaled corticosteroid in patients with mild persistent asthma.

Omalizumab may be effective in decreasing the number of exacerbations in patients with moderate-to-severe persistent asthma who have frequent exacerbations despite optimized medical regimens. Omalizumab has not been shown to improve lung function in these patients. However, the high cost and monthly (or twice monthly) injections limit its clinical use.
Endnotes


