Incorporating Omalizumab into Asthma Treatment Guidelines: Consensus Panel Recommendations

Submitted on Behalf of the Consensus Panel by

Lanny J. Rosenwasser, MD, FAAAAI
National Jewish Medical and Research Center
Denver, Colorado

and

David B. Nash, MD, MBA, FACP
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Educational Objectives

- Describe the current NAEPP Guidelines for the diagnosis and treatment of asthma.
- Assess the NAEPP Guidelines in light of new and emerging therapies.
- Review the issues of suboptimally controlled asthma: diagnosis, management, patient outcome, economic impacts.
- Delineate treatment strategies for the management of mild intermittent, mild persistent, moderate persistent, and severe persistent asthma.

Abstract

Effective asthma management is hindered by several factors, such as (1) variability in clinical diagnosis and treatment patterns, (2) low adherence to therapy caused by improper use of medications, (3) poor technique in using therapeutic devices, (4) medication side effects, (5) inadequate responses to therapy, and (6) patients' acceptance of a poor quality of life. These barriers increase hospitalizations and emergency department visits, reduce productivity, and cause persistent morbidity and mortality.

New therapies target mechanisms that cause airway disease, reduce utilization of health care resources, and improve patient adherence. Omalizumab (Xolair™), an immunoglobulin E (IgE) blocker, reduces the clinical burden of asthma and the associated use of health care resources. This report

Disclosure

The Consensus Panel submitting this article was convened and funded by Genentech, Inc., and Novartis Pharmaceuticals. Panel participants are listed on page 402, and attention is directed to their disclosure of commercial relationships information (see below). This article discusses therapies (i.e., omalizumab) that have not been approved by the Food and Drug Administration (FDA) at the time of printing.

Panel Disclosure Information

Panel members D. Nash, D. Chiefari, M. Kaliner, and B. Seeger have no relationships to disclose relating to this topic.

The following panel members have disclosed relationships with Genentech and Novartis as consultants (CN), scientific advisors (SA), researcher/grant support (RE), Speakers Bureau (SP): L. DuBuske (RE and CN—Genentech, GlaxoSmithKline, Merck, Novartis, Schering; SA and SP—Merck, Schering); H. Kaiser (RE—3M, Altana, AstraZeneca, Aventis, Forrest, Genentech, GlaxoSmithKline, Invek, Merck, Schering; CN—Aventis, AstraZeneca, Genentech, Merck, SP—AstraZeneca, Aventis, GlaxoSmithKline, Schering); A. Luskin (CN—3M, AstraZeneca, Genentech, Merck; SA—Aventis); E. Meltzer (RE—Abbott, Alcon, AstraZeneca, Aventis, Baker Norton, Boehringer Ingelheim, Bristol-Myers Squibb, Dura, Ferraris, Flemington, Forrest, Genentech, GlaxoSmithKline, Hoffmann-LaRoche, Immunex, Inspire, Janssen, KOS, Mast, McNeil Consumer Products, Medeva, Merck, Millennium, Muro, Novartis, Pfizer, Sanofi Winthrop, Schering-Plough, Sepracor, Synergen, TAP, 3M, UCB, Wallace, Whitehall-Robins, Winston, Zambon; CN—Abbott, Aerogen, Agouron, Alcon, Almirall, Arris, AstraZeneca, Aventis, Asyx, Bausch and Lomb, Boehringer-Ingelheim, Dey, Entelos, Genentech, GlaxoSmithKline, Hoffmann-LaRoche, Immunologic, Inspire, Janssen, McNeil, Merck, Miles, Muro, Nastech, Novartis, Parke-Davis, Pfizer, Pharmacia-Upjohn, Riget, Sanofi/Synthelabo, Schering-Plough, Sepraacor, 3M, Wallace, Warner Lambert, Whitehall, Robins and Zambon; SP—Aventis, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Merck, Pfizer, Schering-Plough, UCB, and Wallace); T. Platts-Mills (SA—Aerocrine); S. Spector (various relationships with Abbott, Allen & Hansbury, Aventis, Boehringer Ingeheim, GlaxoSmithKline, Forrest, ICN, Key, Eli Lilly, 3M, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Sepraacor, Schering, Wallace, Whitby, AstraZeneca, Sepracor, Genentech); W. Storms (RE—3M, AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Byk Gulden, GlaxoSmithKline, Immunex, Inspire, Merck, Novartis, Genentech, Pfizer, Pilot Therapeutics, Schering, Sepraacor, CN—Adams Labs, Aegon, Atlan, Ascent Pediatrics, AstraZeneca, Aventis, GlaxoSmithKline, Inspire, Janssen, McNeil, Merck, Pilot, Therapeutics, Schering, Sepraacor, SP—AstraZeneca, Aventis, Merck, Novartis, Schering).
advances health care professionals on how to best incorporate IgE blocker therapy into current treatment guidelines.

Introduction
Asthma remains a daunting challenge for health care professionals. Management of this chronic condition is complicated by the dynamic nature of the disease, the presence of comorbid conditions, widespread variation in the implementation of treatment guidelines, the improper use of medications, the incorrect use of asthma devices, adverse drug events (ADEs), poor patient compliance, and acceptance by patients of a substandard quality of life. In response to these challenges, treatment guidelines have been published and new therapies have been developed to improve clinical outcomes and to reduce the use of health care resources. Despite these advances, however, the prevalence, morbidity, and mortality associated with asthma remain high.5 Successful management of asthmatic patients requires therapies that treat the underlying causes of the disease, reduce hospitalization and patients’ use of the emergency department, maximize patient adherence to therapy, and improve quality of life. Without these, optimal asthma management will remain elusive.

Recent advances in our understanding of the role of immunoglobulin E (IgE) in inflammatory processes have led to the development of new therapeutic agents that address many of the unmet needs in asthma care. Generally, however, a substantial “lag time” exists from approval of the agent by the Food and Drug Administration (FDA) until its inclusion in nationally recognized treatment guidelines. In this article, we review the epidemiology of asthma and the role of IgE in the pathogenesis of this disease, followed by an overview of the clinical response of patients with suboptimally treated asthma to IgE blocker therapy with omalizumab (Xolair®TM, Genentech/Novartis, www.xolair.com). (Tanox has partnered in the development, manufacturing, and marketing of Xolair®TM with Genentech and Novartis.) We then describe current treatment guidelines, issued by the National Asthma Education and Prevention Program (NAEPP), second Expert Panel Report, and discuss the possible clinical role of IgE blockers in the treatment of moderate-to-severe asthma.

Epidemiology and Economic Impact of Asthma
More than 31 million persons in the U.S., including nearly 9.2 million children, have been told by a health care professional that they have asthma.1 In 1998, the total cost of the disease was estimated to be in excess of $12 billion, with direct medical expenses (medications, hospitalizations, emergency-department visits, and physician services) accounting for nearly $7.4 billion and a reduced quality of life, loss of productivity at work or school, and other indirect costs accounting for the balance.5 The cost of asthma treatment is closely related to the severity of the illness,3,4 with a small cohort of patients consuming 80% of all asthma-related health care resources.3 High-cost patients require substantially more emergency visits and hospitalizations, and their condition is usually suboptimally controlled.3 Patients at greatest risk for asthma-related morbidity seem to be those with a history of the most frequent use of health care resources, including multiple prescriptions and hospitalizations as well as a history of intubation.6-8

Pathophysiology of Asthma: Current Knowledge
Airway inflammation is found in virtually all individuals with asthma symptoms.57 Susceptibility to asthma appears to be established during infancy; its course has been attributed to genetic features, such as atopy (the predisposition to form antibodies and to acquire allergies),9,10 and environmental factors, including viruses,11 allergens,12 and occupational exposures.13 Although a full description of the pathogenesis awaits elucidation, research on the factors that initiate, intensify, and modulate airway inflammation continues.14,15 Immune mechanisms appear to be causally related to the development of asthma in more than 90% of asthma patients younger than 16 years of age, in more than 70% of those between 17 and 30 years of age, and in more than 50% of patients over 31 years of age.16 In addition, patients with elevated serum IgE levels show a high incidence of self-reported asthma.16 Asthma prevalence has been shown to be associated with increased levels of total IgE, even in subjects who have tested negative for specific IgE to common allergens and in non-atopic (non-hypersensitive) individuals.16 Persistent wheezing, early sensitization, and bronchial hyperresponsiveness are associated with high serum IgE levels at all ages.17,18 It also has been reported that patients with non-atopic asthma produce IgE throughout the airways.19 IgE-dependent mechanisms are involved in many of the allergic responses at the level of the airway.15 After IgE antibodies are produced, mast cells and other airway cells are sensitized and become activated when specific antigens are encountered.

Following sensitization, a two-phase reaction occurs upon exposure to an allergen:

- The early-phase response peaks approximately 30 minutes after the allergen challenge and is mediated primarily by IgE-dependent processes. This response is initiated when IgE, bound to FcεRI receptors on the surface of effector cells, is subsequently cross-linked by an allergen. This interaction causes the release of stored inflammatory mediators from the effector cell. The early response is closely associated with the level of free IgE.20
• IgE is also postulated to be involved in the initiation of the late-phase response. Even though the role of IgE in the pathogenesis of the late response is not well defined, however, it appears as if this phase of the asthma response follows IgE-dependent activation of the allergic reaction. Non-IgE processes might also be involved.

IgE also plays a central role in the pathogenesis of other atopic diseases, including seasonal allergic rhinitis, atopic dermatitis, latex allergies, various food allergies, anaphylaxis, and urticaria. Many of these conditions frequently present together with asthma, and the combination can lead to an increased use of the emergency department and hospital services and can exert a negative effect on daily functioning and
quality of life. Early diagnosis and aggressive management of these disorders seem to offer the possibility of successfully altering their natural history.

Unmet Needs: Barriers to Improved Outcomes

Patients with the greatest unmet needs are those with moderate-to-severe asthma that is suboptimally controlled. These patients remain symptomatic despite the use of multiple medications. The hallmark feature of these patients is frequent, severe exacerbations that often require costly emergency treatment, hospitalization, or both. This observation supports the theory that current therapies are underused, are used inappropriately, or are not consistently effective.

The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimen (TENOR) Study was initiated to describe the natural history of asthma patients, to elucidate the relationship between IgE and disease, and to examine the relationship between severity of asthma, its treatment, and clinical outcomes.

Early TENOR results identified a discrepancy between a physician assessment of asthma severity and the assessment of asthma severity based on the second NAEPP Expert Panel Report guidelines. Severity was deemed much greater when the physician assessment took into account the patient’s overall health status and the volume of asthma care resources utilized in addition to the frequency of symptoms and spirometry findings.

The TENOR Study also confirmed that patients with moderate-to-severe, suboptimally controlled asthma had the highest rates of health care utilization and a high frequency of hospitalization and intubation, despite prescribed regimens of multiple “standard-of-care” asthma therapies. The study confirmed the need to effectively target the underlying pathological processes, to control symptoms, to reduce exacerbations and hospitalizations, to enhance patient quality of life, and to maximize patient adherence to therapy.

Therapies for Asthma

Current Therapies

Over the last 20 years, pharmacotherapeutic management of asthma has progressed, but it remains imperfect. Patients with suboptimally controlled asthma remain symptomatic and experience serious exacerbations despite regular treatment with multiple standard-of-care anti-inflammatory agents and quick-relief medications, suggesting persistent inflammation in the airways. Current pharmacotherapeutic interventions (e.g., anti-inflammatory agents and smooth-muscle relaxants) generally alleviate asthma symptoms but do not address the underlying mechanisms of the disease process.

During the selection of a regimen for asthma, the effect of a therapy on hospitalization rates, emergency-department use, and quality of life should also be considered. The limitations of existing asthma treatment support the need for continued research into novel therapeutic options, particularly those that modify the disease process.

Emerging Asthma Therapies

Most patients with asthma are atopic (allergy-prone) and possess specific IgE antibodies to allergens responsible for driving airway inflammation. Although allergen avoidance is always recommended, this strategy is rarely completely effective. Because of the central role of IgE in atopic diseases, the inhibition of IgE-mediated events with IgE blockers represents a novel approach to reducing the severity of asthma.

Omalizumab, a humanized murine monoclonal antibody, inhibits the binding of IgE to mast cells by forming complexes with circulating free IgE (Figure 1). This agent binds to the Cε3 domain of the IgE, the region where IgE binds to the mast cell FceRI receptor (Figure 2). Omalizumab forms complexes only with free IgE and cannot displace or cross-link mast cell–bound IgE. Therefore, this agent is free from the undesirable side effects associated with receptor cross-linking, mast cell and basophil degranulation, and subsequent release of inflammatory mediators (Figure 3). Further, by removing free IgE from the circulation, omalizumab indirectly down-regulates FcεRI
expression. This is an important feature because down-regulation of IgE receptors further reduces the potential for basophil/mast cell activation by IgE molecules.28

Treatment of allergic individuals with omalizumab prevents IgE from triggering the release of inflammatory mediators in response to an allergen. Blocking IgE has a clear advantage over current anti-inflammatory therapies: instead of attempting to suppress inflammation once it has occurred, inflammation is inhibited at its source. Early trials demonstrated the ability of intravenously administered omalizumab to impede allergen-induced airway responses.29,30

Randomized, double-blind, placebo-controlled, multicenter phase III trials have included symptomatic adolescent and adult patients (aged 12–75 years) with moderate-to-severe allergic asthma.31,32 All enrolled patients were given standard inhaled corticosteroid (ICS) and beta-agonist therapy, as recommended by the NAEPP guidelines.32 The studies consisted of a run-in phase, a steroid-stable phase, a steroid-withdrawal phase, and a double-blind extension phase. During the run-in phase and before randomization, patients were switched to beclomethasone dipropionate (BDP) and were stabilized on this therapy. Omalizumab was administered once or twice monthly via subcutaneous injection, with doses adjusted to body weight and total serum IgE.31,32

The primary endpoint of the pivotal phase III omalizumab clinical trials was the number of asthma exacerbations experienced per patient during the steroid-stable and steroid-withdrawal phases.31,32 An exacerbation was defined as an episode severe enough to require either a doubling of the baseline BDP dose or administration of a course of systemic corticosteroids. Exacerbation frequency was selected as the primary efficacy indicator because, unlike FEV1 (forced expiratory volume in one second) or other surrogates of clinical efficacy, exacerbations are a direct marker of disease control and are strongly related to morbidity and mortality, quality of life, and total cost of illness.3 The number of exacerbations also reflects the degree of control of airway inflammation. Secondary outcomes included corticosteroid requirements, the number and frequency of symptoms, the use of rescue medications, lung function, and quality of life.

Results
Omalizumab therapy reduced asthma exacerbations even with the use of a significantly lower dose of BDP. The reduction in the BDP dose was achieved without precipitating asthma exacerbations, worsening symptoms, decreasing lung function, or increasing the use of rescue medications. In addition, more subjects treated with omalizumab were able to achieve complete discontinuation of corticosteroid therapy.31,32

In the omalizumab group, symptom control was enhanced during the steroid-stable phase as well as during the steroid-withdrawal phase. Notably, symptom control was maintained with lower doses of steroids and with less frequent use of rescue medications.

Peak expiratory flow (PEF) rates improved significantly for patients who received omalizumab, and smaller but significant improvements in FEV1 were also observed. Improved pulmonary values were maintained throughout the steroid-withdrawal phase, suggesting that omalizumab might improve lung function on its own without concomitant use of steroids and rescue medications.31,32

With omalizumab treatment, quality of life also improved significantly over baseline values, including a reduction in asthma exacerbations, a lessening of the need for steroids and rescue medications, and better lung function and symptom scores.31
### Table 1: Disease Severity Classification Scheme Recommended in Current Guidelines

<table>
<thead>
<tr>
<th>Step</th>
<th>Symptoms</th>
<th>Nighttime Symptoms</th>
<th>Lung Function</th>
<th>Long-Term-Control Medications</th>
<th>Quick-Relief Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 4 Severe persistent</td>
<td>• Continual • Limited physical activity • Frequent exacerbations</td>
<td>Frequent</td>
<td>• FEV₁₀ ≤ 60% predicted • PEF ≤ 40% predicted • PEF variability &gt; 30%</td>
<td>Preferred treatment: • High-dose inhaled corticosteroids and • Long-acting inhaled beta₂ agonists and (if needed) • Corticosteroid tablets or syrup long-term</td>
<td>• Short-acting beta₂ agonist (two to four puffs as needed) • Intensity of treatment depends on severity • Use of quick-relief more than two times per week might indicate need to step up long-term-control therapy</td>
</tr>
<tr>
<td>Step 3 Moderate persistent</td>
<td>• Daily • Daily use of inhaled short-acting beta₂ agonists • Exacerbations affect activity levels • Exacerbations occur one or more times a week; can last several days</td>
<td>&gt; One time per week</td>
<td>• FEV₁₀ &gt; 60%–&lt;80% predicted • PEF variability &gt; 30%</td>
<td>Preferred treatment: • Low-to-medium dose inhaled corticosteroids and • Long-acting, inhaled beta₂ agonists Alternative treatment: • Increase inhaled corticosteroids to a medium dose and add long-acting inhaled beta₂ agonists or • Low- to medium-dose inhaled corticosteroids and either a leukotriene modifier or theophylline</td>
<td>• Short-acting beta₂ agonist (two to four puffs as needed) • Intensity of treatment depends on severity • Use of quick-relief more than two times per week might indicate need to step up long-term-control therapy</td>
</tr>
<tr>
<td>Step 2 Mild persistent</td>
<td>• Occurring more than two times a week but less than once a day • Exacerbations can affect activity levels</td>
<td>More than two times per month</td>
<td>• FEV₁₀ or PEF &gt; 80% predicted • PEF variability 20%–30%</td>
<td>Preferred treatment: • Low-dose inhaled corticosteroids Alternative treatment: • Cromolyn sodium • Leukotriene modifiers • Nedocromil or • Sustained-release theophylline to serum concentration of 5–15 mcg/ml</td>
<td>• Short-acting beta₂ agonist (two to four puffs as needed) • Intensity of treatment depends on severity • Use of quick-relief more than two times per week might indicate need to step up long-term-control therapy</td>
</tr>
<tr>
<td>Step 1 Mild intermittent</td>
<td>• Occurring two or fewer times per week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (few hours for a few days); intensity varies</td>
<td>Two or fewer times per month</td>
<td>• FEV₁₀ or PEF &gt; 80% predicted • PEF variability &lt; 20%</td>
<td>Preferred treatment: • No daily medication needed • Systemic corticosteroids may be required in event of severe exacerbation</td>
<td>• Short-acting beta₂ agonist (two to four puffs as needed) • Intensity of treatment depends on severity • Use of quick-relief more than two times per week might indicate need to step up long-term-control therapy</td>
</tr>
</tbody>
</table>

The need for unscheduled outpatient visits, emergency-room treatments, and hospitalizations was also reduced.36 The number of hospitalizations in the omalizumab-treated group decreased by up to 92%, and the average duration of a hospital stay was up to 63% shorter than that in patients taking placebo. These decreases in hospital use have significant implications for both quality of life and the economic impact of the disease.36

Omalizumab therapy was well tolerated, and no complications associated with reduced circulating IgE or antibodies against omalizumab were observed. The incidence of ADEs was similar between treatment groups, and no drug-related serious adverse effects were reported.31,32 As with any protein, local or systemic reactions, including anaphylaxis and anaphylactoid reactions, have the potential to occur. Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur. Parasitic infections may result in elevated serum IgE concentrations. The effects of omalizumab have not been examined in the presence of any known concurrent parasitic infections. In addition, current long-term clinical data do not indicate that treatment with omalizumab is associated with malignancies.

These results confirm that omalizumab can be an effective therapy for patients with symptomatic, moderate-to-severe allergic asthma that is poorly controlled with inhaled corticosteroids. Omalizumab therapy reduced the frequency and severity of exacerbations and improved symptom control despite the reduction in the use of inhaled corticosteroids and rescue medications. Twice-monthly or monthly administration of omalizumab also reduced the use of unscheduled medical services, improved quality of life for patients, and was safe and well tolerated.

Treatment Guidelines

The first Expert Panel Report on the Management of Asthma, published in 1991, provided clinicians with an evidence-based set of recommendations for the diagnosis and treatment of asthma. This report recognized the role of airway inflammation in the pathogenesis of asthma and recommended that anti-inflammatory agents form the foundation of asthma therapy. Subsequent editions of the Expert Panel Report were published in 199737 and 2002.33 Although the NAEPP has striving to keep clinical practice guidelines up to date, the continual emergence of new data makes this task challenging.

The 1997 Expert Panel Report recommends that the primary goals of asthma therapy are to control symptoms, to reduce exacerbations, and to minimize the amount of time lost to asthma-related inactivity. A stepwise approach to asthma therapy is encouraged when the number and frequency of medications are increased as asthma severity increases and are decreased as asthma symptoms come under control.33

According to the guidelines, asthma is classified as (1) mild intermittent, (2) mild persistent, (3) moderate persistent, or (4) severe persistent, and patients are treated accordingly (Table 1). Patients are assigned to the grade of asthma that is consistent with their most severe symptoms. Because the natural course of asthma is highly variable, there are overlaps between classifications, and classifications are likely to vary with time. Patients at any level of severity can have mild, moderate, or severe exacerbations.

Treatment decisions are based on matching therapy to the intensity of symptoms. Hence, planning effective and safe strategies for managing asthma depends on the correct diagnosis of disease severity.

Current Guidelines: Consensus Panel Review

Despite the existence of guidelines that provide evidence-based asthma-treatment strategies, asthma remains sub-optimally controlled in a significant number of patients.25 Several factors might account for this difficulty in asthma control, such as:

- the dynamic nature of the disease.
- poor patient adherence to therapy.
- ignorance of the effect of comorbid conditions on treatment outcomes.
- a focus on increasing FEV1 and other surrogate markers as indicators of clinical effectiveness.
- poor access to care and the cost of health care (critical factors).

Genentech, Inc., and Novartis Pharmaceuticals recently convened a panel of experts to review the current asthma-treatment guidelines and to evaluate IgE blocker therapy and its place in the guidelines. The goal of this meeting was to create a practical treatment guide that specifically addressed gaps in the current recommendations, particularly for patients with moderate-to-severe asthma who have a history of frequent, severe exacerbations and poor asthma control (Table 2). The primary proposals set forth by the Panel included (1) the implementation of comprehensive asthma evaluation and patient-education programs and (2) recommendations on the use of IgE blocker therapy to treat moderate-to-severe asthma.

Many features of the Panel’s treatment recommendations are consistent with the current NAEPP guidelines. Both sets of proposals encourage the use of a modified stepwise approach to asthma therapy, with the initial treatment matched to asthma severity. After symptoms are controlled, the drug dose is titrated to a level that most effectively minimizes their occurrence and lessens the chance of exacerbations.

Mild Intermittent Asthma

The Panel recommends that patients with mild intermittent asthma continue to adhere to the current NAEPP guidelines. Accordingly, no daily anti-inflammatory medication is necessary, because these patients exhibit daytime and nocturnal symptoms less than twice a week and they experience infrequent exacerbations.33 The use of a short-acting beta2 agonist is recommended, as needed, for acute symptom relief.

It is important to note that frequent or sustained use of a relief medication can indicate worsening asthma. A course of systemic corticosteroids might be required to regain control in cases of severe exacerbation.33 An education program emphasizing the basic facts of the disease, proper environ-
### Table 2 Approach for the Management of Asthma

<table>
<thead>
<tr>
<th>Severe persistent</th>
<th>Daily Medication</th>
<th>Considerations for IgE Blocker Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred treatment:</td>
<td>• Patient at least 12 years of age</td>
</tr>
<tr>
<td></td>
<td>• High-dose inhaled corticosteroids</td>
<td>• Evidence of reversible disease (such as 12% or greater improvement in FEV₁, with at least a 200-ml increase or 20% or greater improvement in PEF)</td>
</tr>
<tr>
<td></td>
<td>and</td>
<td>• IgE level ≥ 30 IU/ml</td>
</tr>
<tr>
<td></td>
<td>• Long-acting inhaled beta₂ agonists</td>
<td>• Evidence of specific allergic sensitivity (i.e., positive skin test or blood test for IgE)</td>
</tr>
<tr>
<td></td>
<td>and (if needed)</td>
<td>• Inadequately controlled despite medium dose of inhaled corticosteroids for at least three months in combination with a trial of long-acting inhaled beta₂ agonists or a leukotriene modifier</td>
</tr>
<tr>
<td></td>
<td>• Corticosteroid tablets or syrup long-term (2 mg/kg/day, generally do not exceed 60 mg/day). (Make repeated attempts to reduce systemic corticosteroid therapy and maintain control with high-dose inhaled corticosteroids.)</td>
<td>• Systemic corticosteroids or high-dose inhaled corticosteroids required to maintain adequate control</td>
</tr>
<tr>
<td></td>
<td>Preferred treatment:</td>
<td>• As directly observable therapy in patients who are not adherent to prescribed therapy</td>
</tr>
<tr>
<td></td>
<td>• Low-to-medium dose inhaled corticosteroids and long-acting beta₂ agonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alternative treatment (listed alphabetically):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase inhaled corticosteroids within medium-dose range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low-to-medium dose of inhaled corticosteroids and either leukotriene modifiers or theophylline</td>
<td></td>
</tr>
</tbody>
</table>

#### Considerations for IgE Blocker Therapy

- Patient at least 12 years of age
- Evidence of reversible disease (such as 12% or greater improvement in FEV₁, with at least a 200-ml increase or 20% or greater improvement in PEF)
- IgE level ≥ 30 IU/ml
- Evidence of specific allergic sensitivity (i.e., positive skin test or blood test for IgE)
- Inadequately controlled despite medium dose of inhaled corticosteroids for at least three months in combination with a trial of long-acting inhaled beta₂ agonists or a leukotriene modifier
- Systemic corticosteroids or high-dose inhaled corticosteroids required to maintain adequate control
- As directly observable therapy in patients who are not adherent to prescribed therapy

#### Patient evaluation and education

All patients with persistent asthma require further evaluation and education, including identification of allergic triggers and comorbidities, as well as detailed advice regarding management.

Types of education:

- Disease state
- Environmental controls
- Inhaler technique
- Pharmacotherapy
- Immunotherapy
- Action plan

#### Mild persistent

Preferred treatment:

- Low-dose inhaled corticosteroids

Alternative treatment (listed alphabetically):

- Cromolyn sodium, leukotriene modifiers, nedocromil
- Sustained-release theophylline to serum concentrations of 5–15 mcg/ml

Treatment:

- No daily medication needed

Possible occurrence of severe exacerbations, separated by long periods of normal lung function and no symptoms

A course of systemic corticosteroids is recommended.

#### Mild intermittent

None

---

*Examples of inadequate control: (1) utilization of emergency department, hospitalization, or urgent-care visits; (2) excessive use of a short-acting beta agonist or oral steroids; and (3) impairment in activities of daily living, such as work, school attendance, exercise, and sleep. IgE = immunoglobulin E; IU = International Units; FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow. Adapted from the 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, 1997.³⁵*
Mild Persistent Asthma

The Panel recommendations are aligned with the NAEPP guidelines for the treatment of mild persistent asthma. Asthma control in these patients can be maintained with daily use of low-dose inhaled corticosteroids or with the use of cromolyn sodium (e.g., Cromolyn Sodium Inhalation Solution, Dey, or Intal®, Aventis/King), leukotriene modifiers, nedocromil (Tilade®, Aventis/King), or theophylline to serum concentrations of 5 to 15 mcg/ml. Acute asthma symptom relief is provided by the use of a short-acting beta, agonist. Pharmacological management should be combined with an asthma-education program to increase the likelihood of success.33

Obtaining an accurate diagnosis is a challenge, because clinicians tend to underestimate the severity of asthma. According to one study, asthma specialists correctly classified the severity only 63% of the time.

Moderate-to-Severe Persistent Asthma

Many patients with moderate-to-severe persistent asthma remain symptomatic despite the use of multiple daily medications and the occasional to frequent use of systemic corticosteroids. Unscheduled visits to medical facilities are quite common. Features of suboptimal or inadequately controlled asthma include high rates of hospitalization and use of the emergency department, excessive use of rescue medications and/or oral steroids, and an impaired ability to work, attend school, exercise, or sleep. Some patients also exhibit a history of non-adherence with medication regimens. Consequently, the Panel recommends incorporating an aggressive, comprehensive, and ongoing evaluation and education program for all patients in these situations.

The Panel also recommends the use of therapies proven to reduce the quantity of health care resources utilized by these patients. As presented in Table 2, the Panel recommends that patients with moderate-to-severe asthma be enrolled in an ongoing, intensive educational program along with their primary caregivers. Patients should receive instruction on the use of devices, environmental control and avoidance measures, rescue action plans, and self-management and adherence techniques through discussions with health care professionals, from brochures and videos, and from information acquired via the Internet or support groups. Educating patients is a cost-effective way to minimize exacerbations and to reduce mortality for both children and adults, particularly among high-risk patients.38 Patients who are knowledgeable about their disease and the therapies being used to manage it are also more motivated to adhere to their treatment plans.39

Incorporating New Therapies into the Guidelines

The 1997 NAEPP guidelines suggest that patients with moderate and severe persistent asthma be segregated into two groups and treated with increasingly aggressive therapy:

- **Moderate persistent asthma.** The preferred treatment includes daily use of a combination of low-dose inhaled corticosteroids and long-acting beta agonists (LABAs). Alternative therapies include inhaled corticosteroids at a medium dose or a combination of low-dose to medium-dose inhaled corticosteroids and either a leukotriene receptor agonist or theophylline.

- **Severe persistent asthma.** The currently recommended treatment is combination therapy with high-dose inhaled corticosteroids and long-acting beta agonists. If needed, corticosteroid tablets or syrup (2 mg/kg/day, not to exceed 60 mg/day) can be added to maintain control; however, all attempts should be made to reduce the use of systemic corticosteroids and to maintain control with high doses of inhaled corticosteroids.33

Dividing patients with suboptimally controlled asthma into two distinct groups increases the complexity of disease management, because it requires an accurate diagnosis of asthma severity and patient adherence to a medication regimen that fluctuates with symptoms. Obtaining an accurate diagnosis is a challenge, because clinicians tend to underestimate the severity of asthma. According to one study, asthma specialists correctly classified the severity only 63% of the time.40

Adherence to therapy can also be negatively affected because therapeutic regimens—to be successful—must be simple and convenient and should not cause side effects or additional deterioration in quality of life. Patient adherence to treatment plans is extremely low when therapies are time-consuming, difficult to use, or expensive; that are perceived not to offer any benefit; or that necessitate fluctuations in dosages. Even patients with moderate-to-severe asthma and a history of frequent use of emergency-department services, hospitalizations, oral corticosteroid use, and nocturnal symptoms have poor adherence in these cases.41

The combination of improper diagnosis and poor adherence to therapy can contribute to suboptimal asthma control. To address this issue, the Panel has recommended that (1) the distinction between the moderate and severe categories of asthma be eliminated and (2) treatment strategies for both patient groups be standardized. The recommended goal of therapy is the true reduction of overall asthma burden, as indicated by actual markers of patients’ daily functioning and control of their asthma. The Panel encourages the use of a wider range of strategies for management, including control of infections, avoidance of allergens, and the use of IgE blockers to achieve this goal.31,32,37

Trial data indicate that IgE blockers present an attractive
alternative in patients with moderate-to-severe, suboptimally controlled asthma after unsuccessful attempts with current standard measures to produce adequate control.31,32 This new intervention appears to reduce asthma exacerbations in patients who:

- are at least 12 years of age,
- have evidence of reversible airway disease (e.g., a greater than 12% improvement in FEV1 with at least a 200-ml increase or at least a 20% or greater improvement in PEF),
- have an IgE level of 30 IU/ml or more,
- show evidence of specific allergic sensitivity by positive skin or blood tests for a specific IgE.

IgE blockers can be used as an alternative in patients with inadequately controlled asthma despite a combination of medium-dose inhaled corticosteroids and long-acting beta agonists or leukotriene receptor agonists, administered for three months. In addition, patients who are taking a course of systemic corticosteroids or who require high-dose inhaled corticosteroids for daily asthma control are also appropriate patients for IgE blockers. As a result of infrequent dosing requirements, IgE blockers are also effective for patients who do not adhere to prescribed therapy with multiple dosing requirements.

Current NAEPP guidelines do not consider the impact of comorbidities on the treatment of asthma.33,37 The presence of coexisting conditions often warrants multiple medications and further hinders adherence and achievement of treatment goals. Asthma, particularly allergic asthma, rarely presents in isolation from other IgE-mediated diseases, such as seasonal allergic rhinitis and atopic dermatitis. IgE blockers have the potential to address both asthma and the comorbid conditions.

Summary

Asthma continues to impose a significant clinical and economic burden on society. Patients with suboptimally controlled, moderate-to-severe asthma pose a considerable challenge to physicians and are among the most frequent users of health care resources. Current treatment strategies recommend the use of multiple medications to control symptoms and to preserve surrogate markers of clinical efficacy, such as FEV1. The complexity of these regimens contributes to patient nonadherence.

Successful asthma management is also hindered because of the cost of asthma care and limited access to health care resources. Novel treatments, such as IgE blockers, have demonstrated a direct impact on disease indicators by minimizing exacerbations, reducing hospitalization and emergency-department visits, and improving quality of life in patients with moderate-to-severe, suboptimally controlled asthma. Proposed treatment guidelines encourage the use of IgE blockers in these patients. The use of such therapies has proved beneficial in reducing the clinical and economic burden of asthma and therefore has important implications for patients, health care providers, and third-party payers.

As additional clinical experience is gained, the ultimate role of IgE blockers will be further defined. Issues such as cost, long-term acceptability, and safety remain to be addressed.

References

Multiple Choice
Select the one correct answer.

1. Which of the following is the mechanism by which omalizumab inhibits IgE from triggering the release of inflammatory mediators?
   a. forming complexes with the mast cell receptors
   b. forming complexes with circulating free IgE
   c. forming complexes with mast cell–bound IgE
   d. none of the above

2. In phase III clinical trials, omalizumab reduced asthma exacerbations:
   a. but required doubling the corticosteroid dose.
   b. but required doubling the beclomethasone dipropionate (BDP) dose.
   c. despite the use of a higher dose of omalizumab.
   d. despite the use of a lower dose of BDP.

3. According to the article, treatment decisions should be based on matching therapy to the intensity of symptoms.
   a. True
   b. False

4. Which of the following statements is incorrect?
   a. Airway inflammation is found in virtually all individuals with asthma symptoms.
   b. The occurrence of asthma symptoms is correlated with elevated serum IgE levels.
   c. Asthma prevalence has been shown to be associated with decreased levels of total IgE.
   d. The occurrence of asthma symptoms is correlated with airway hyperresponsiveness.

5. According to this article, patients with the greatest unmet needs are those:
   a. with moderate asthma that is suboptimally controlled.
   b. with severe asthma that is suboptimally controlled.
   c. with mild asthma that is suboptimally controlled.
   d. both a and b.

6. According to the early results of TENOR, patients with moderate-to-severe, suboptimally controlled asthma have the highest rate of health care utilization and a high frequency of hospitalization.
   a. True
   b. False

7. According to the Consensus Panel Recommendations, which of the following considerations may support the use of IgE blockers in the treatment of patients with severe and moderate persistent asthma?
   a. patients who are at least 12 years old
   b. evidence of specific allergic sensitivity by a positive skin test or blood test for specific IgE
   c. an IgE level of 30 IU/ml or greater
   d. all of the above

8. Which of the following was not listed as a feature of suboptimally or inadequately controlled asthma?
   a. frequent usage of the emergency department
   b. impaired ability to work, attend school, exercise, or sleep
   c. excessive use of rescue medications and/or oral steroids
   d. low rates of hospitalization

9. Which of the following was not mentioned in the article as a characteristic of therapy that is associated with low adherence?
   a. regimens that are time-consuming
   b. regimens that are easy to use
   c. regimens that are expensive
   d. regimens that fluctuate in dosing

10. According to the guidelines in Table 2, all patients with persistent asthma require further evaluation and education as well as detailed advice regarding the management of:
    a. disease.
    b. inhaler technique.
    c. pharmacotherapy.
    d. all of the above.
Continuing Education for Pharmacists
Examination Answer Sheet

TOPIC: Incorporating Omalizumab into Asthma Treatment Guidelines: Consensus Panel Recommendations

Program #079-999-03-018-H01
Expiration Date: June 30, 2004

Complete this answer sheet (including the questions and information requested below), detach, and mail to:

Office of Health Policy and Clinical Outcomes
Thomas Jefferson University Hospital
attn: Continuing Pharmacy Education
1015 Walnut St., Suite 115
Philadelphia, PA 19107

Directions
Select the one best answer to each question and darken the appropriate circle.

1. (a) b c d
2. (a) b c d
3. (a) b c d
4. (a) b c d
5. (a) b c d
6. (a) b c d
7. (a) b c d
8. (a) b c d
9. (a) b c d
10. (a) b c d

Program Evaluation
(Circle the appropriate response):

ExcellentoPoor

General quality of article 1 2 3 4 5
Applicability to practice 1 2 3 4 5
Objectives met 1 2 3 4 5
Ease of comprehension 1 2 3 4 5

Time (in hours) to read the article and complete the exam:
____________________________________________

Suggested topics for future consideration:
____________________________________________
____________________________________________
____________________________________________

I certify that I have completed this course independently:
____________________________________________
(Signature)

Date Completed ______________________________

This article is approved for continuing pharmacy education only.

Name (print) ________________________________
Degree:  □ PharmD
          □ RPh
          □ Other______________________________
Social Security Number ________________________
Address ________________________________
City ____________________Zip ________________
Phone ______________________________
Email ________________________________

Note: Payment of $10.00 per exam is required for processing and maintenance of records.
Make check payable to P&T®.
This processing fee is non-refundable.
Continuing Medical Education for Physicians

**TOPIC:** Incorporating Omalizumab into Asthma Treatment Guidelines: Consensus Panel Recommendations

**Accreditation**
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Jefferson Medical College and MediMedia USA, Inc.

Jefferson Medical College of Thomas Jefferson University, as a member of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. All faculty/authors participating in continuing medical education activities sponsored by Jefferson Medical College are expected to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of their article(s). Full disclosure of these relationships appears on the last page of the article.

**Continuing Medical Education Credit**
This CME activity is designed to assist physicians and other health care professionals who are P&T committee members in making formulary decisions. Its goal is to increase participants’ ability to recognize and treat important medical problems.

Jefferson Medical College designates this continuing medical education activity for a maximum of one hour of Category 1 credit toward the Physician’s Recognition Award (PRA) of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This credit is available for the period of one year from the date of publication.

Although forms will be processed when received, certificates for CME credits will be issued every six months, in February and August. Interim requests for certificates can be made by contacting the Jefferson Office of Continuing Medical Education at (215) 955-6992.

**How to Apply for CME Credit**
1. Each CME article is prefaced by learning objectives for participants to use to determine whether the article relates to their individual learning needs.

2. Read the article carefully, paying particular attention to the tables and other illustrative materials.

3. Complete the CME Registration and Evaluation Form. Type or print your full name and address in the space provided, and evaluate the activity as requested. In order for the form to be processed, all information must be complete and legible.

4. Send the completed form, with $20 payment to:
   Office of Continuing Medical Education/P&T
   Martin Building, Room 309
   201 South 11th Street
   Philadelphia, PA 19107

5. Be sure to mail the Registration and Evaluation Form within one year of the date of publication. After that date, this article will no longer be designated for credit and forms cannot be processed.
CME Registration and Evaluation Form

Date of publication: June 2003

Title: Incorporating Omalizumab into Asthma Treatment Guidelines: Consensus Panel Recommendations

Authors: Lanny J. Rosenwasser, MD, FAAAAI, and David B. Nash, MD, MBA, FACP

Submission deadline: June 30, 2004

Registration

Name: ____________________________________________________________ Degree: ____________________________________

Street address: _________________________________________________ Institutional affiliation: ____________________________

Zip: _____________ City: ___________________ State: ______ Telephone: ____________________________

Specialty: _______________________________________ Years in practice: _____ Subscriber number: ______________________

Time needed to complete this CME activity: ☐ < 1 hr ☐ 1 hr

Certification: I attest to having completed this CME activity. ________________________________________________________

Signature (required) __________________________________________________________

Date

Evaluation

1. Rate the overall effectiveness of this CME activity. 5 4 3 2 1
   (very effective) (not at all effective)

2. Circle Yes or No
   A. The learning objectives were useful to me in determining whether performing this CME activity would be a worthwhile educational experience. Yes No
   B. The objectives accurately described the content and potential learning value of this article. Yes No
   C. This activity will influence how I practice medicine. Yes No
   D. The activity was free from commercial bias. Yes No
   E. I learned something new that was important from the article. Yes No

3. Which of the following best describes a change you might consider making in your practice as a result of something you learned from this activity? (Please circle only one response.)
   A. Slightly modify what I currently do.
   B. Make a major change in what I currently do.
   C. Follow a procedure, use a technique/technology that is completely new to me.
   D. Follow a procedure, use a technique/technology that I currently use but for a different purpose.
   E. None of the above, but some change.
   F. Not considering any changes.

4. Please describe any change(s) you plan to make in your practice as a result of this activity: ______________________________
   __________________________________________________________________________________________________________
   __________________________________________________________________________________________________________

5. How committed are you to making these changes? 5 4 3 2 1
   (very committed) (not at all committed)

6. Other comments: __________________________________________________________________________________________
   __________________________________________________________________________________________________________
   __________________________________________________________________________________________________________

Payment

Please check one of the following payment options.
☐ I am enclosing a check (payable to JMC/CME).
☐ Please charge my MasterCard or Visa (circle type of card),

Account Number: __ __ __ __ -__ __ __ __- __ __ __ __- __ __ __ __- __ __ __ __
Expiration Date: __ __/ __

Signature (required) __________________________________________________________

Send the completed form to:
Office of Continuing Medical Education/P&T, Martin Building, Room 319, 201 South 11th Street., Philadelphia, PA 19107.

414 P&T • June 2003 • Vol. 28 No. 6