

## Using Consensus Panel Recommendations for Incorporating Omalizumab into Clinical Guidelines for Asthma

a report by

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Approximately 15 million Americans live with asthma, and this places an enormous burden on the US healthcare system.<sup>1</sup> In 2000, asthma patients made over nine million physician office visits and had more than 900,000 hospitalizations. In addition, over 5,000 deaths occur each year because of the disease.<sup>1</sup> In 1998, the total cost of the disease was estimated to be US\$12.7 billion.<sup>1</sup> Direct expenditures accounted for almost US\$7.4 billion, with 42 cents of every dollar being spent on medications, 29 cents on in-patient hospitalizations, 11 cents on physician services, 10 cents on out-patient services, and eight cents on emergency department (ED) visits.<sup>1,2</sup> This illustrates that medications are the largest cost component of asthma care, which underscores the importance of incorporating effective medical management into clinical guidelines for asthma.<sup>1,2</sup>

### Incorporating New Technologies into Established Guidelines

Despite internationally recognized, evidence-based guidelines for managing asthma,<sup>3-6</sup> the disease remains inadequately controlled in a significant number of patients.<sup>7</sup> Factors may include access to care, comorbid conditions, and issues involving patient and physician adherence. Other possibilities are that better treatment regimens have yet to be fully elucidated, or that national standards have yet to

reflect updated knowledge of recently approved treatment modalities.

One such novel therapeutic approach is a recombinant deoxyribonucleic (DNA)-derived, humanized monoclonal anti-immunoglobulin E (IgE) antibody that inhibits the binding of IgE to the surface of mast cells and basophils. This inhibition limits the release of inflammatory mediators (i.e. histamine, prostaglandins, and leukotrienes), which themselves initiate an allergic response that includes mucosal edema and smooth muscle contraction. In multiple studies, omalizumab has proven to be an effective treatment for moderate-persistent to severe-persistent asthma, improving symptoms while reducing exacerbations and healthcare utilization.

At the completion of phase III trials for omalizumab, its developers (Genentech, Inc. and Novartis Pharmaceuticals) and the Department of Health Policy at Jefferson Medical College convened a panel of asthma experts to revisit the 1997 National Asthma Education and Prevention Program (NAEPP) guidelines, and to review the potential role of IgE blocker therapy within these current asthma guidelines. The expert panel consisted of leaders in the fields of allergy and immunology, pulmonology, pediatrics, and pharmacology, as well as medical executives who represented major managed care



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organizations.<sup>8</sup> The panel endorsed the 1997 NAEPP recommendations for mild-intermittent and mild-persistent asthma,<sup>3</sup> but recommended several additions to the remainder of the guidelines in light of the new technology (see *Table 1*).

First, the panel acknowledged that patient non-adherence probably contributes to the lack of control in the moderate- and severe-persistent asthma categories. Because of this, the panel recommended that guidelines include an aggressive and comprehensive patient education and evaluation program for these patients, especially those unable to achieve optimal control. This program would include instruction on the use of devices, environmental control and avoidance measures, rescue action plans, and techniques for self-management and adherence.

receptor agonists (see *Table 1*).

Approximately six months following the US Food and Drug Administration (FDA) approval of omalizumab (January 2004), a second consensus panel was convened. This was intended to evaluate the first six months of real-world experience with the drug, to revisit the panel's previous recommendations, and to address unanswered questions regarding management of allergic asthma and the barriers to acceptance and implementation of the updated guidelines.

The panel endorsed the previously released asthma guideline recommendations (i.e. including criteria for considering IgE blocker therapy and a comprehensive education and evaluation program). The panel also acknowledged several challenges and barriers to the

*In multiple studies, omalizumab has proven to be an effective treatment for moderate-persistent to severe-persistent asthma*

Second, the panel questioned the value of distinguishing between moderate- and severe-persistent asthma. The panel of experts agreed that making a distinction between these two groups is difficult in clinical practice, and even if possible, the panel felt that differences in the associated treatment regimens were so unnecessarily confusing that they would probably lead to patient non-adherence anyway. Because of these issues, the panel recommended eliminating the distinction between moderate- and severe-persistent asthma groups, opting instead for standardization of therapy among patients with sub-optimally controlled asthma.

Finally, the panel noted that IgE blocking therapy presents an alternative treatment option when current established therapies are unsuccessful. For example, the panel recommended that IgE blockers be used as an alternative treatment in patients with inadequately controlled asthma who are on high-dose inhaled corticosteroids or in patients who require frequent courses of systemic corticosteroids. The panel suggested that IgE blockers could also be considered in patients who are inadequately controlled, despite a three-month trial of medium-dose inhaled corticosteroids and long-acting beta agonists, or leukotriene

appropriate diffusion of updated guidelines (e.g. patient adherence and confusion about definitions of 'optimal control' and 'allergic asthma'). Specific unanswered questions concerning IgE blocker therapy included duration and characteristics of an optimal drug trial, defining appropriate end-points of therapy, and appropriate payment mechanisms for the drug.

### Summary

The growing awareness of the limitations of standard therapy is one of the most compelling reasons to develop new modalities to treat asthma. For instance, a plateau effect has been observed in the dose-response curve of inhaled corticosteroids, whereby increasing the dose increases only the systemic effects and not the physiologic improvement. With the FDA approval of omalizumab, a panel of experts proposed additions to the NAEPP clinical guidelines, advising, for example, that specific patient education be added for all severity levels and that IgE blockers be used as an alternative treatment in patients with moderate- to severe-persistent asthma whose disease is sub-optimally controlled on high-dose inhaled corticosteroids or in patients who require courses of systemic

**Table 1: Consensus Panel Approach to Effective Asthma Management**

<b>Disease State</b>	<b>Daily Medication</b>	<b>Considerations For Anti-IgE Therapy</b>
Severe–Persistent Asthma	Preferred Treatment: High-dose inhaled corticosteroids AND Long-acting inhaled $\beta_2$ agonists, AND, if needed, Corticosteroid tablets or syrup long-term (2mg/kg/day, generally not exceeding 60mg/kg/day). Repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.	Patient at least 12 years of age  Historic evidence of reversible disease (such as $\geq 12\%$ improvement in FEV with at least a 200ml increase or $\geq 20\%$ improvement in PEF)  IgE level $>30$ IU/ml  Historic evidence of specific allergic sensitivity (i.e. positive skin test or blood test for specific IgE)
Moderate–Persistent Asthma	Preferred Treatment: Low-to-medium dose inhaled corticosteroids and long-acting $\beta_2$ -agonists Alternative Treatment (alpha-listed): Increase inhaled corticosteroids within medium-dose range, OR low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline	Inadequately controlled despite medium dose of inhaled corticosteroids for at least 3 months in combination with a trial of long-acting inhaled $\beta_2$ -agonists or leukotriene modifier (or medication intolerance)  Systemic corticosteroids or high-dose inhaled corticosteroids required to maintain adequate control  May consider as directly observable therapy in patients who are not adherent with prescribed therapy
Mild–Persistent Asthma	Preferred Treatment: Low-dose inhaled corticosteroids Alternative treatment (alpha-list): Cromolyn, leukotriene modifier, nedocromil, or sustained release theophylline to serum concentrations of 5-15 mcg/ml.	None
Mild–Intermittent Asthma	No daily medication needed. Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. Course of systemic corticosteroids is recommended.	None

Examples of Inadequate Control: Utilization of ED, hospitalization and/or urgent care visits; excessive use of short-acting  $\beta_2$ -agonist and/or use of oral steroids; and/or impairment in activities of daily living, such as work, school, exercise, and sleep.

corticosteroids. IgE blockers can also be considered in patients who are inadequately controlled despite a three-month trial of medium-dose inhaled corticosteroids and long-acting beta agonists or leukotriene receptor agonists.

While a cure for asthma does not exist, new technologies and treatments, such as IgE blockers, offer opportunities for improved control in many patients. ■

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