Omalizumab and Other New Drug Therapies Occupy a Small Space in Asthma Disease Management

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Asthma disease management can be a frustrating experience for clinician and patient, and it seems what we don’t know about the subject is about as much as what we do know. Asthma is a stubborn disease to manage due to variability in patient response to treatment and difficulty in identifying (targeting) the patients at risk of exacerbation sufficient to precipitate urgent care in the form of hospitalization or emergency room visits. Nonetheless, despite the increasing prevalence of asthma in the United States, hospital discharge rates for asthma decreased 16.2% between 2003 and 2005.1

The patient variability in response to pharmacotherapy suggests that there may be a strong pharmacogenetic influence. For example, the long-acting beta-2 agonists (LABAs) have a black-box warning of increased risk of exacerbation of asthma and death, but the results of the Salmeterol Multicenter Asthma Research Trial (SMART) suggest that the risk associated with LABAs seems significant primarily in certain subgroups of patients.4 For example, retrospective analysis of data from 6 randomized controlled trials (RCTs) showed that persons homozygous or heterozygous for the arginine (Arg)-16 Gly polymorphism may have worse outcomes on LABAs, regardless of use of inhaled corticosteroids.5 Hall noted that 15% of the white population has this genetic characteristic, but there are not yet sufficient data to ascertain the role of Arg-16 in the variable response to the bronchodilator effects of LABAs.6

We have also recently learned more about how the effectiveness of asthma disease management is influenced by psychological factors. Negative child affect, measured by the Children’s Depression Inventory and the Revised Children’s Manifest Anxiety Scale, and negative parent affect, measured by the Center for Epidemiologic Studies Depression Scale, have been found to predict higher asthma symptom scores (a composite of self-reported wheezing, tightness of chest, shortness of breath, coughing from exercise, coughing from other causes, and nighttime symptoms).7 This new research has implications for both clinical trials and clinical practice; i.e., clinicians need to consider the emotional state of the asthma patient and of the parent of an adolescent or child patient.

Aside from the role of psychological and genetic factors in asthma disease management, from a population perspective there are 3 risk factors that appear to help explain the rising prevalence of asthma and disease severity: (a) control of infectious diseases and reduced exposure to endotoxins in the food and water supply that interfere with development of childhood antibody responses to allergens; (b) prolonged indoor exposure to allergens, particularly house mites and cockroaches; and (c) a sedentary lifestyle since there appears to be a direct relationship between physical activity and anti-inflammatory response.8 The relationship between upper airway disease and allergies has intrigued clinicians and researchers for decades, and recent research points to possible localized sensitization to immunoglobulin E (IgE).9 This evolution in research in the etiology of airway disease is logical because allergic rhinitis can occur without systemic evidence of IgE sensitization (i.e., negative skin allergy test and no specific serum IgE).

What About Omalizumab?

In this issue of JMCP, Pesko suggests that injectable omalizumab (Xolair), approved by the U.S. Food and Drug Administration (FDA) 6 years ago in June 2003, represents a promising therapeutic option for asthma disease management, citing the product labeling that includes the following indication, “For adults and adolescents 12 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.”10 Notably, the primary off-label use of omalizumab appears to be seasonal allergic rhinitis,11 despite the absence of evidence of safety or efficacy in allergic conditions other than asthma.

An underlying theme in Pesko’s suggestions that the market space for omalizumab might be larger than previously thought has to do with the number of patients who are inadequately controlled with other first-line and second-line drugs. For example, some of the results of the Gaining Optimal Asthma control (GOAL) trial might be cited as evidence that even with intervention in a clinical trial to control asthma with escalation of the dose of inhaled corticosteroid (ICS), a large proportion of patients remain uncontrolled.12 In fact, it is impressive that 59% of patients in the GOAL study with previously uncontrolled asthma were well controlled at 1 year with higher doses of fluticasone alone, and 71% of patients were well-controlled with higher doses of fluticasone plus LABA.13 However, the persistence of
symptoms in some patients with severe asthma despite treatment invites continued research on the pathophysiology of asthma.

The raison d’être for Pesko’s commentary is that the National Asthma Education and Prevention Program (NAEPP) guideline update (2007)\(^\text{14}\) should precipitate some action by health plans to reassess prior authorization (PA) criteria and utilization management of omalizumab. Two points are important with respect to this assertion. First, omalizumab was not available for consideration when the 2002 NAEPP update was written because omalizumab did not receive FDA approval until June 2003.\(^\text{13}\) Second, there was no sudden realization in the 2007 NAEPP update that omalizumab had an important place in therapy.

In fact, the NAEPP update in 2007 recommended use of omalizumab in a more narrow corridor than stated in the omalizumab product label approved 4 years earlier by the FDA (i.e., appropriate for use only in patients with “severe persistent asthma” versus the FDA-approved labeling that includes patients with “moderate-to-severe persistent asthma”). In the justification for this recommendation and in Figure 3-22 (long-term control medications), the NAEPP Full Report includes the warning that “Adverse effects reported from omalizumab in the trials have also included injection-site pain and bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5%) as did those receiving placebo (5 of 2,236, or 0.2%), but there were no trends for a specific tumor type.”\(^\text{14}\)

In essence, Pesko suggests in his commentary that we should ignore the wisdom of the experts, as reflected in the NAEPP 2007 update and the guidance (TA133) from the National Institute for Health and Clinical Evidence (NICE) released in November 2007 (Appendix),\(^\text{16}\) and instead rely on a product label that was developed based on data evaluated by the FDA prior to approval of the omalizumab. Pesko also fails to inform readers adequately about some important points raised by the authors of the NICE guidance. Ignored completely in this commentary are the 25 malignancies cited in the NICE guidance among 5,015 patients treated with omalizumab (0.50%) in 35 clinical trials, compared with 5 of 2,854 patients (0.18%) treated with standard therapy. Also skirted is the thrust of the summary of the NICE guidance: “The Committee concluded that it would only be clinically appropriate to consider the use of omalizumab add-on therapy once standard therapy has been optimized and that for the purposed of this guidance, optimized standard therapy is defined as a full trial of, and documented compliance with, inhaled high-dose corticosteroids and LABAs in addition to leukotriene receptor antagonists, theophyllines, oral corticosteroids and beta-2 agonist tablets and smoking cessation where clinically appropriate.”\(^\text{16}\)

Unfortunately, omalizumab falls short of being a “magic bullet” for allergic asthma. Among the outcomes that under-perform the expectations for this drug, the NAEPP 2007 update referred to the steroid-sparing effect of omalizumab as “modest” (median 25% reduction),\(^\text{14}\) and the NICE guidance noted the evidence that “asthmatic patients who are known to be refractory to high-dose oral corticosteroids may be less likely to respond to omalizumab treatment, whereas omalizumab may provide steroid-sparing benefits on lower doses of oral steroids.”\(^\text{16}\)

Omalizumab is administered by subcutaneous injection, and it is expensive. It should be dosed by body weight and baseline serum IgE level, and the drug cost alone is $4,000 to $30,000 per year of therapy, with an average drug cost of about $1,000 per month.\(^\text{17,18}\) Actual claims analysis for calendar year 2008 in 1 employer health plan showed that omalizumab had an average cost of about $20 per day of therapy at its lowest dose (150 mg every 4 weeks).\(^\text{19}\) The key to cost-effective use of omalizumab depends on selectivity and specificity in the asthma population,\(^\text{20}\) but the clinical characteristics that predict individual patient response to therapy are unreliable.\(^\text{21}\)

There is also a sizable safety risk associated with the use of omalizumab beyond the aforementioned increased risk of malignancies. Four years after approval of omalizumab by the FDA on June 20, 2003, a black-box warning was added in July 2007.\(^\text{22,23}\) The black-box warning followed an FDA alert released 5 months earlier, in February 2007, regarding possible anaphylaxis after any dose of omalizumab, up to 24 hours after the dose is administered, and even if there was no reaction to the first dose.\(^\text{24}\)

**Narrowing the Target Space for Omalizumab**

The size of the space that omalizumab might occupy in asthma management is small, but the precise size is unknown. We know that severe persistent asthma accounts for less than 20% of the asthma population. For example, of the adults in Michigan who took asthma medication in the past 30 days, 16.1% were categorized as severe persistent, and about 1 in 5 of all adult asthma patients report daily symptoms.\(^\text{25}\)

In an attempt to precisely identify the target population of asthma patients most likely to benefit from omalizumab, it is helpful to recall that the clinical trials of omalizumab enrolled patients who had demonstrated sensitivity by positive skin test to specific perennial aeroallergens (specifically, dust mites, cockroaches, dog or cat dander) and baseline serum IgE levels in the range of 30 to 700 international units (IU) per milliliter for patients 12 to 75 years of age.\(^\text{17}\) Bousquet et al. (2004) found that 3 factors predicted response to omalizumab, although the absolute differences compared with placebo are small and statistically insignificant for forced expiratory volume: high dose of the ICS beclomethasone (800 mcg or more per day; 65% for omalizumab vs. 40% for placebo, \(P = 0.037\)), a history of emergency treatment for asthma in the past year (67% for omalizumab vs. 40% for placebo, \(P = 0.015\)), and poor lung function (forced expiratory volume in 1 second [FEV\(_1\)] ≤ 65% predicted; 67% for omalizumab
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vs. 53% for placebo, \( P = 0.072 \)). These results were derived from pooled analysis of 2 placebo-controlled clinical trials involving 1,070 allergic asthma patients (n = 542 assigned to omalizumab) who remained symptomatic despite moderate-to-high doses (mean 725 mcg per day) of inhaled beclomethasone.

Some health plans in the United States have adopted PA criteria for coverage of omalizumab that incorporate a high level of detail derived from these clinical trials including restriction of coverage to nonsmokers and patients with severe persistent asthma defined as: symptoms throughout the day, nighttime awakenings often (7 times per week), use of short-acting beta agonists (SABAs) for symptom control several times per day, extreme interference with normal activity, and compromised lung function measured as FEV\(_1\) less than 60% of predicted and a ratio of FEV\(_1\) to forced vital capacity (FVC) reduced by more than 5%. Strunk and Bloomberg also propose that the clinical trial data predict poor response to omalizumab in patients who require daily oral corticosteroids to control their asthma.

New Therapies Fall Short for the Difficult-to-Treat Asthma Patient

Currie et al. (2009) reviewed the characteristics of the difficult-to-treat adult asthma patient. This category of patient represents about 5%-10% of adults with asthma but accounts for disproportionately high morbidity, medical costs, and fatal and near-fatal exacerbations. There are few new approaches to better manage this difficult population, and the clinical results are not encouraging. The tumor necrosis factor (TNF) antagonist etanercept showed initial promise, but a double-blind RCT over 12 weeks found no significant improvement in patients with steroid-dependent asthma. And, a 24-week trial with the human anti-TNF monoclonal antibody golimumab showed not only no improvement in efficacy but significantly increased risk of infections and malignancies. A number of older drugs such as cyclosporine, methotrexate, gold, and subcutaneous terbutaline have been tried with apparent efficacy in difficult-to-treat adult asthma, but these drugs have been used by specialists rather than mainstream primary care practitioners.

The outlook for possible biologic interventions seemed to brighten, at least for small subsets of asthma patients, with the publication of 2 studies in March 2009 of the interleukin-5 monoclonal antibody mepolizumab in a total of 38 patients with eosinophilic asthma. In 1 of the 2 studies, Halder et al. found that monthly injections of mepolizumab 750 mg for 12 months in 29 patients with refractory eosinophilic asthma and a history of recurrent severe exacerbations was associated with improvement in the primary end point (exacerbations per subject at 50 weeks) and improvement in the Asthma Quality of Life Questionnaire (AQLQ) score but no improvement in other outcomes including asthma symptoms, FEV\(_1\) after bronchodilator use, or airway hyperresponsiveness; there were 3 cases (10%) of hospitalization for asthma in the mepolizumab group versus 11 (34%) in the placebo group, and 1 of the 29 patients was withdrawn from the study due to an adverse drug reaction (a transient maculopapular rash that developed 24 hours after the first infusion of mepolizumab). Mepolizumab was associated with mean exacerbations of 2.0 per patient versus 3.4 for placebo over 50 weeks of treatment (relative risk = 0.57, 95% CI = 0.32-0.92, \( P = 0.02 \)).

In the second study, Nair et al. found 1 asthma exacerbation in 9 prednisone-dependent patients with persistent sputum eosinophilia treated with 5 monthly injections of mepolizumab 750 mg compared with 12 asthma exacerbations in 10 patients who received placebo (\( P = 0.002 \)). The dose of prednisone was reduced by a mean 83.8% (SD = 33.4%) of the maximum dose in the mepolizumab patients versus 47.7% (SD = 40.5%) in the placebo group (\( P = 0.04 \)). The collective data from these 2 studies of mepolizumab and what was already known about eosinophilic asthma tell us that (a) eosinophils may not be the major cell involved in the genesis of asthma, even in patients with severe asthma; (b) except for the measure of exacerbations, mepolizumab had no effect on other physiological and clinical factors; (c) the subjects recruited in the 2 recent studies were extraordinary asthma patients (e.g., Nair et al. screened hundreds of severe asthma patients to obtain the 20 patients in their study); and (d) the eosinophilic form of asthma accounts for about 5% of the total number of cases of adult-onset asthma, the more likely target group compared with childhood-onset asthma. Therefore, the newest light on biologic factors in asthma appears to illuminate better the path to further research rather than provide solutions to the challenge of improving outcomes in patients with difficult-to-treat asthma.

Confining the Space for Omalizumab

In the category of drugs to suppress IgE, the biological omalizumab should be effective, but (a) Currie et al. remind us that the Scottish Medicines Consortium advises the use of omalizumab only in patients who require maintenance oral steroids when all other treatments have failed, and (b) NICE advises its use only in patients with severe unstable allergic asthma who have had at least 2 severe exacerbations requiring hospital admission within the previous year. The important takeaway message from the collective evidence is that the therapeutic space for omalizumab is a small. NAEPP 2007 makes this very clear: omalizumab is considered add-on treatment at the end steps of management of persistent asthma in patients who have allergies and continue to have symptoms uncontrolled with high-dose ICS and LABA (step 5) and with oral corticosteroid (step 6), and administered by clinicians who are “prepared and
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equipped to identify and treat anaphylaxis that may occur.¹⁴

NICE is somewhat less nice to omalizumab, restricting its recommended use to add-on therapy in patients with:
• confirmation by clinical history and skin test of IgE-mediated allergy to a perennial allergen;
• evidence of severe exacerbations of asthma in the last year, defined as (a) at least 2 exacerbations that required hospital admission, or (b) 3 or more exacerbations that included at least 1 hospital admission and 2 emergency room visits;
• discontinuation of omalizumab at 16 weeks in the absence of response to therapy (Appendix).

Despite ostensible promise in patients with allergic asthma, omalizumab is appropriate in only a small proportion of asthma patients.

APPENDIX NAEPP 2007 and NICE Recommendations (2007) for Appropriate Use of Omalizumab

NAEPP 2007 Guidelines
• “The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B).”

NICE Technology Appraisal Guidance 133 – Omalizumab for Severe Persistent Allergic Asthma

1.1 Omalizumab is recommended, within its licensed indication, as an option for the treatment of severe persistent allergic (IgE mediated) asthma as add-on therapy to optimized standard therapy, only in adults and adolescents (12 years and older) who have been identified as having severe unstable disease.

1.2 For the purposes of this guidance, optimized standard therapy is defined as a full trial of, and documented compliance with, inhaled high-dose corticosteroids and long-acting beta-2 agonists in addition to leukotriene receptor antagonists, theophyllines, oral corticosteroids and beta-2 agonist tablets and smoking cessation where clinically appropriate.

1.3 Omalizumab add-on therapy should only be initiated if the patient fulfills the following criteria of severe unstable allergic asthma: (a) confirmation of IgE mediated allergy to a perennial allergen by clinical history and allergy skin testing, and (b) either 2 or more severe exacerbations of asthma requiring hospital admission within the previous year, or 3 or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient’s usual regimen, in an accident and emergency unit.

1.4 Omalizumab add-on therapy should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist centre.

1.5 Omalizumab add-on therapy should be discontinued at 16 weeks in patients who have not shown an adequate response to therapy. Response to treatment should be defined on the basis of a full clinical assessment comprising: degree of asthma control, quality of life, control of exacerbations, avoidance of unscheduled healthcare utilization; spirometry and peak expiratory flow measures and a global evaluation of treatment effectiveness, as assessed by the physician.”

The NICE TA133 Guidance includes some particularly succinct points regarding cost-effectiveness:
“Overall, therefore, the Committee concluded that there were a number of considerations which meant the ICER was higher than acceptable for patients with severe persistent allergic asthma. However, the Committee was persuaded that for a narrowly defined severely affected group of asthma patients, at an elevated risk of asthma-related mortality, cost-effective treatment with omalizumab was possible, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimized to reduce costs. The Committee concluded that omalizumab add-on therapy is recommended as an option for the treatment of asthma in patients with severe unstable disease (that is, those who have had either two or more severe exacerbations of asthma requiring hospital admission within the previous year, or three or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient’s usual regimen, in an accident and emergency unit), who have clinical confirmation of IgE mediation of asthma exacerbations and have had a full trial of, and documented compliance with all standard asthma medication (see 4.4). It also concluded that omalizumab treatment should only be initiated and monitored by physicians experienced in both allergy and chest medicine in a specialist centre.”

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DISCLOSURES

The author reports no conflicts of interest related to the subjects or products discussed in this article.

Page 225 of the National Asthma Education and Prevention Program 2007 Full Report.¹⁴

¹⁴National Institute for Health and Clinical Excellence. Omalizumab for severe persistent allergic asthma. NICE technology appraisal guidance TA133, November 2007.¹⁶
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