

Omalizumab for severe allergic asthma: Dollars and sense

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The US National Heart, Lung, and Blood Institute–sponsored National Asthma Education Prevention Program released its third iteration of the national asthma guidelines (Expert Panel Report 3 [EPR-3]), which appeared in a recent issue of the Journal.¹ As in previous reports, the EPR-3 recommends increasingly intensive therapy for patients with more severe disease (so-called stepped therapy), beginning with as-needed short-acting bronchodilators in patients with intermittent asthma (step 1) and inhaled corticosteroids (ICSs) with or without additional controller medications in patients with persistent asthma (steps 2 through 6). For the first time, national asthma guidelines include recommendations about when clinicians should consider the use of omalizumab therapy, the first biologic agent approved by the US Food and Drug Administration (FDA; in 2003) for the treatment of allergic asthma (ie, patients in whom step 4 or 5 therapy fails).² Omalizumab (Xolair; Genentech, Novartis, South San Francisco, Calif), administered by means of subcutaneous injection once or twice per month, is a humanized mAb that binds to free circulating IgE, reducing the potential for mast cell and basophil activation and the release of histamine, leukotrienes, and other mediators of allergen-induced airway inflammation and bronchospasm.

Should omalizumab be initiated in all patients with allergic asthma in whom EPR-3 step 4 or 5 therapy fails? The answer to this question depends on the answer to 4 additional questions.

First, how effective is omalizumab? A meta-analysis of 14 randomized controlled clinical trials in more than 3000 study participants with allergic asthma found that treatment with omalizumab, compared with placebo, significantly reduced the need for ICSs and the risk of exacerbations.³ However, the reduction in ICS dose was modest, raising questions about the clinical relevance of this finding. Moreover, the beneficial effect of

Abbreviations used

EPR-3: Expert Panel Report 3
FDA: US Food and Drug Administration
ICS: Inhaled corticosteroid
QALY: Quality-adjusted life year

omalizumab on exacerbations was not equally effective in all patients. Patients taking oral corticosteroid therapy (a marker for more severe asthma) did not experience a significant reduction in the oral corticosteroid dose or risk of exacerbations.³

Second, how safe is omalizumab? Severe injection-site reactions are more common after omalizumab compared with placebo (12% vs 9%).⁴ Also, postmarketing reports suggest that the risk of anaphylaxis might be 0.2% and that it is difficult to predict which patients are at risk.⁵ Anaphylaxis has occurred as early as after the first dose but also after regular use for more than 1 year. There are also reports of anaphylaxis occurring several days after omalizumab administration. These issues prompted the FDA to issue an Alert in February 2007, updated in July 2007, about a new Black Box warning for omalizumab and a new Medication Guide that is to be distributed to patients with each dose of omalizumab.⁶

Third, how convenient is the use of omalizumab? Because of the risk of adverse events, the FDA recommends that omalizumab be administered in a health care setting in which there are trained staff prepared to manage life-threatening events and that patients be closely monitored for an “appropriate” (but unspecified) time period after administration (about half [59%] of the cases of anaphylaxis reported to the FDA have occurred within 1 to 2 hours of administration).⁵ Although practice patterns can vary, we suspect that omalizumab administration once or twice per month is likely to be followed by an additional 1 or 2 hours of in-office observation. Patients also need to be prepared to use intramuscular epinephrine (and obtain more help) in case symptoms of anaphylaxis develop after the office visit; individual patients will need to decide whether this is convenient. In addition, omalizumab needs to be prepared each time before administration by swirling (not shaking) the drug in sterile water for 15 to 20 minutes (sometimes longer). Clearly, trained staff with the appropriate combination of space, equipment, and time are needed to administer omalizumab and discuss and manage the risks of this therapy; as with patients, each health care practice will need to decide whether this is convenient.

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Fourth, does treatment with omalizumab represent a good value for the health care dollar? This is a particularly important question because omalizumab is more expensive than any other FDA-approved medication for asthma. The wholesale price for omalizumab alone exceeds \$1000 per patient-month! In this issue of the Journal, Wu et al⁶ report findings from a rigorously performed cost-effectiveness analysis that suggest that in patients with severe allergic asthma, omalizumab costs more than \$800,000 per quality-adjusted life year (QALY) gained. This value greatly exceeds the World Health Organization's definition of a cost-effective intervention, which is 3 times the per capita gross domestic product (approximately \$45,000 in the United States).⁷ With this in mind, how do we evaluate the validity of the analysis and interpret the findings reported by Wu et al?⁶

One characteristic of a properly executed cost-effectiveness analysis is the transparency of its assumptions. In this analysis Wu et al⁶ used data from a pivotal clinical trial and a Cochrane systematic review to justify assumptions about the beneficial effect of omalizumab on acute exacerbations (46% lower), the duration or intensity of asthma-related hospitalizations (63% shorter or less intense), and improvements in FEV₁ (2.9%). These estimates were combined with estimates of costs and improvements in health-related quality of life in a model that simulated asthma care over a time horizon of 10 years. Parenthetically, the authors probably biased the analysis in favor of omalizumab treatment by using a very conservative estimate for its cost. For other model parameters, it seems clear that they used the best available evidence to inform the analysis.

Another important feature of a credible cost-effectiveness analysis is the presence of a sensitivity analysis, in which the assumptions of the model are varied to determine whether the results are robust. In this analysis the results were relatively insensitive to varying assumptions about improvements in quality of life and exacerbation rates. Omalizumab was found to cost \$100,000 per QALY gained (which some consider to be an upper bound for cost-effectiveness) only when the acquisition cost of the drug was reduced from the base case assumption of \$1300 to \$200. Because the findings of the 1-way sensitivity analyses showed that the results were quite robust, it seems unlikely that a probabilistic sensitivity analysis (in which all model parameters are varied simultaneously) would have produced a different conclusion.

Finally, cost-effectiveness analyses should specify the "perspective" of the analysis. The authors of this analysis adopted the societal perspective, which means that all costs were included regardless of who bore them. Thus one must consider whether society is willing and able to pay \$800,000 per QALY gained when there are other pressing needs for limited health care resources. The study by Wu et al⁶ suggests that lower drug acquisition costs would substantially improve the cost-effectiveness of omalizumab; other studies suggest that limiting omalizumab to those patients who respond to therapy (variably measured) could also improve the cost-effectiveness of omalizumab.⁸⁻¹⁰

In many other Western countries, coverage and reimbursement decisions are informed by considerations of value (ie, cost-effectiveness), but this is not the case in the United States, where coverage and reimbursement are determined solely on the basis of effectiveness. Hence in the United States it is up to either the individual provider or groups of providers to make decisions about whether an intervention represents a good value for the health care dollar. This often puts the provider in an uncomfortable position. Advocating for patients while ignoring costs will accelerate health care spending, increase insurance premiums, and increase the numbers of uninsured. However, if we limit access to care that is effective but not cost-effective, we risk alienating patients and further eroding the doctor-patient relationship. Some have argued that clinicians must honor their fiduciary duty to patients by not limiting access to interventions for which there is any evidence of effectiveness.¹¹ Others respond that containing costs is an important social goal and that bedside rationing by clinicians is already pervasive and typically applies to interventions that provide marginal benefits.¹²

Do the dollars make sense? The findings from Wu et al⁶ indicate that treatment of severe asthma with omalizumab does not appear to be cost-effective. As highlighted by the EPR-3, all patients with allergic asthma in whom step 4 therapy fails should be evaluated carefully (preferably by an asthma specialist) before initiating omalizumab. This evaluation should (1) confirm the diagnosis of asthma, (2) identify and treat comorbid conditions associated with poor asthma control, (3) evaluate the possibility of incomplete adherence with current therapy,¹³ and (4) engage patients in a partnership for care in which they are adequately trained to use appropriate medications and environmental control strategies. Given the high cost of omalizumab, clinicians and patients should develop (and update when necessary) a mutually agreeable approach to monitoring response to therapy (eg, symptom frequency, ability to work or attend school, and number of exacerbations requiring systemic corticosteroids). Omalizumab should only be continued if there is clear improvement in these measures of asthma-related health status. Unfortunately, in the absence of additional research, more specific recommendations about monitoring response to omalizumab therapy cannot be made. Nevertheless, we believe that such an approach appropriately balances the interests of individual patients and society at large.

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