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Guest editorial

Persistent severe asthma and aging: step-up therapy with omalizumab to improve control

As the number of deaths from asthma in the United States has declined from a peak of 5,627 in 1995 to 3,447 in 2007,¹ there is controversy about how to achieve and maintain effective control of this very complex disease.^{2–4} The management of some patients with asthma can require a high level of clinical acumen. Patients differ in their recognition of or lack of perception of underlying airway obstruction and dynamic hyperinflation. There are different phenotypes, changing levels of severity and extent of control across time, and variable responses to therapy.⁵ It is clear that many patients have not reached acceptable levels of control despite monotherapy with an inhaled corticosteroid or combination therapy with an inhaled corticosteroid/long-acting β_2 -adrenergic agonist with or without a leukotriene modifier.^{6,7} For the physician or health care professional managing a patient with persistent asthma, the most important goal is to prevent death, and next is to eliminate or reduce the number of severe exacerbations of asthma while recommending therapies that provide sufficient benefit and little or no harm to patients. The assessment of severity and control of asthma includes attention to current

impairment and risk.⁸ According to the National Asthma Education and Prevention Program Expert Panel Report 3,⁸ the dimension of risk includes (1) preventing or minimizing future exacerbations of asthma, emergency department visits, and hospitalizations; (2) preventing excessive loss of lung function, such as forced expiratory volume in 1 second or not achieving normal lung growth in children; and (3) trying to avoid adverse effects from medications.

In 2006 in the United States, there were approximately 444,000 hospitalizations for asthma (ICD code 493) or at least where asthma was listed first as a discharge diagnosis.⁹ The average length of hospital stay was 3.2 days for asthma, but this number increased with age, being 2.2 days in children 15 years or younger, 3.8 days in adults aged 45 to 64 years, and 4.5 days in adults 65 years and older.⁹ For comparison, the average length of stay for congestive heart failure was 5.1 days and for acute myocardial infarction was 6.1 days. Although the number of fatalities from asthma has declined, approximately 75% of the deceased were 45 years and older.^{1,9} Thus, prevention of severe exacerbations, hospitalizations, and deaths remains an important target for improved control of asthma.

In this issue of the *Annals*, in a 6-month observational study of adults with uncontrolled, persistent severe asthma, step-up therapy with omalizumab was evaluated with consideration of effectiveness (reduction in exacerbations), harm (adverse effects), and discontinuation of therapy to explore whether the benefit-harm relationship was favorable in patients 50 years and older.¹⁰ The data were generated from 2

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postmarketing surveillance studies with 220 physicians as investigators. The median dose of omalizumab was 300 mg per month. Approximately 50% of patients were receiving oral corticosteroids at the beginning of treatment in addition to at least the equivalent of 1,000 μ g of beclomethasone dipropionate and a long-acting β_2 -adrenergic agonist. Despite such pharmacotherapy, 95% of patients 50 years and older reported daily symptoms of asthma and 76% noted nocturnal awakenings, similar to findings in patients younger than 50 years. Absenteeism and asthma exacerbations were examples of inadequate control of asthma. After 4 months of omalizumab treatment, an assessment was made by investigators regarding effectiveness. Severe exacerbations of asthma decreased by approximately 65% in patients 50 years and older and by 72% in patients younger than 50 years.¹⁰ Similarly, daily symptoms, nocturnal awakenings, and absenteeism were reduced in both groups. Discontinuation of omalizumab treatment occurred in 20.9% of older and 11.1% of younger patients, thought primarily to be from lack of effectiveness rather than harm.

Once a new product is approved for use, such as after at least 2 prospective, randomized, blinded, controlled intervention studies that have demonstrated superiority over placebo or in other situations, noninferiority to an active agent comparator, it does not have to be proved repeatedly by using a placebo-treated group that there is efficacy. Indeed, it has been stated that one does not need to keep testing in studies “whether the parachute, to be an effective device, opens or not.” Strengths of the present observational study include the inclusion and clinical description of patients 50 years and older with persistent, ineffectively controlled, severe asthma, half of whom were receiving oral corticosteroids at the time of entry; the use of the same patients in a pretreatment and posttreatment design; the assessment of benefit/harm in both patient groups; and the recorded multicenter experiences of more than 200 physicians who selected the omalizumab dose (based on total IgE concentration and body weight) in a seemingly real-world study. Some weaknesses include the design, which may have introduced bias in data collection by relying on a questionnaire to record the asthma events in the previous 12 months and then by contrasting with prospective evaluation in the first 4 months before global assessment; the short-term period of evaluation, although this has been suggested as adequate in other studies to identify responders to treatment¹¹; and any “first impression” by physician-investigators that could have clouded the determination at 4 months. Not every patient received the preferred dosage of omalizumab, but the study investigators reported that there were few patients who were either underdosed or overdosed.¹⁰ The patients themselves had agreed to participate in the study, so the results may not be generalizable to patients with persistent severe asthma who refuse to participate in an office-based treatment study. This comment similarly applies to blinded, prospective studies. In observational studies such as this one, patients may have been more adherent to their proscribed pharmacotherapy than in the retrospective year, which is used

for comparison. If that were the case, the benefit attributed to omalizumab would be overstated. However, the benefit from omalizumab therapy, such as office visits every month with interaction with nurses and physicians for contemporaneous concerns about asthma control, may have provided a framework for the reductions in exacerbations and improvement in overall control of asthma. From that perspective, the demonstrated benefits of omalizumab (or other step-up therapy) in a randomized controlled trial could be understated because the placebo-treated patients may have improved their own adherence to pharmacotherapy during the study and minimized the differences in outcomes compared with in the real world.

What are the characteristics of good responders to omalizumab? In 2004, Bousquet et al¹² reported that a history of an emergency department visit, hospitalization, or unscheduled office visit for asthma in the past year; beclomethasone dipropionate dosages of 800 μ g or greater; and forced expiratory volume in 1 second of 65% or less were some variables that identified better responders to omalizumab therapy compared with placebo-treated patients. Furthermore, some responders to omalizumab therapy already were improving in 4 weeks, whereas others required 12 weeks to improve. This information suggests that omalizumab treatment should continue for at least 12 weeks.¹² Subsequently, it has been suggested that the physician’s global assessment of response at 16 weeks was a useful tool for identifying responders.¹¹ The present study provides evidence for omalizumab treatment of patients with persistent severe asthma 50 years and older.¹⁰

There are various biological effects of using an anti-IgE antibody.^{13–15} For example, there are reductions in the early and late responses during allergen bronchoprovocation¹⁶ and in nasal¹⁷ and skin¹⁸ challenges. Methacholine reactivity decreases.¹⁹ The free IgE concentration declines by up to 99% within days.¹⁴ In bronchial biopsy samples obtained after 16 weeks of omalizumab treatment, the number of IgE⁺ cells and Fc ϵ RI⁺ cells decrease in epithelium and submucosa, and tissue eosinophils and interleukin 4⁺ cells also declined.¹⁹ Fc ϵ RI numbers are reduced on basophils²⁰ and dendritic cells.²¹ When omalizumab is added to allergen immunotherapy, the binding of allergen-IgE complexes by B cells, serving in their antigen presentation mode, is reduced.²² All of these actions contribute to our understanding of how the only monoclonal antibody approved for use in asthma may act. As the study in this issue points out, patients with persistent severe asthma, half of whom were corticosteroid dependent, still had ineffective control despite currently recommended pharmacotherapy. As step-up therapy, omalizumab was beneficial and had a favorable safety profile. But, we need additional meaningful improvements in our treatment armamentarium. Those of us who investigate or care for patients with asthma need to continue to teach other physicians, health care professionals, policy makers, and the public about what it means to achieve effective control of asthma and what it will take to make progress toward this

ambitious goal not only in children and young adults but also in the aging population.

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Guest editorial

The impact of food allergy and bullying

Food allergy is a common childhood illness, affecting approximately 3.9% of the US population.¹ To add to the psychological stress of the potential morbidity² and even mortality associated with this illness, in this issue of the *Annals*, Lieberman et al³ highlight the fact that 24% of children who participated in a questionnaire survey reported having been teased, harassed, or bullied as a result of their food allergy. Furthermore, 57% of those who reported harassment described acts of physical provocation, such as being touched by the food allergen or having it waved at them or put into their food. Even more disconcerting

was the fact that teachers or school staff were reported as the perpetrators of the harassment in 21% of cases.

This article is informative and thought provoking to the allergist caring for food-allergic children. Furthermore, it should prompt new research that extends beyond the limitations of this sentinel work. These limitations include the fact that the surveys were completed by a subset of food-allergic families attending a Food Allergy & Anaphylaxis Network meeting and may not be representative of the larger population of food-allergic children. Most questionnaires were completed not by the allergy sufferers but by parents or caregivers of the food-allergic children. New research should encompass a more diverse patient population and include reports from parents, children, and, perhaps, other observers to confirm or correct the startling statistics presented in this article.

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