The Appropriate Omalizumab Patient

Management of the uncontrolled asthma patient and case examples

Jill Karpel, MD, Donald A. Bukstein, MD,* Robert LoNigro, MD†

Beth Thalheim Asthma Center, North Shore University Hospital, Manhasset, N.Y.; *Family Medicine at University of Wisconsin–Madison; †Tufts Health Plan, Boston, Mass.

ABSTRACT

Allergy is a significant component in many asthma patients. Omalizumab is a monoclonal anti–immunoglobulin E antibody for the treatment of allergic asthma. Clinical trials have shown that omalizumab treatment is associated with improved symptom control and reduced inhaled corticosteroid doses, resulting in fewer exacerbations and reduced utilization of resources. Omalizumab therapy may benefit patients who remain uncontrolled or who cannot tolerate standard therapy.

Key words: adult, asthma, immunoglobulin E, monoclonal antibody, prior authorization

INTRODUCTION

An estimated 30.2 million people in the United States (about 10.5% of the population) are diagnosed with asthma at some point in their lives.[1] Currently 20.5 million people in the United States are diagnosed with asthma. In 2004, 11.7 million experienced an asthma episode or attack, resulting in 13.6 million outpatient visits, 1.8 million emergency room visits, 1.0 million hospital outpatient department visits, and 497,000 hospitalizations.[1] In 2003, 4,099 deaths from asthma were reported.[1]

Corresponding author:
Jill Karpel, MD
Phone: 516 465-5400
E-mail: jpkarpel@aol.com
Fax: 516 465-5454
Mailing Address:
410 Lakeville Road, Suite 107
New Hyde Park, N.Y. 11040

The costs associated with asthma are high. The direct costs, including hospitalization, emergency department (ED) visits, outpatient visits, physician services, and drugs, totaled $11.5 billion in 2004.[1] The indirect costs in the United States are also high, estimated at $4.6 billion annually resulting from lost work days, lost school days, and disease-associated mortality.[1] The total annual per-patient costs of asthma have been estimated at $4,912 ($3,180 in direct costs and $1,732 in indirect costs).[2] It is important to note that most of the costs of asthma are incurred by patients with more severe disease, with 80% of the total costs of asthma attributed to the 20% of patients with the most severe disease.[3]

The high cost of asthma treatment and the increased expense resulting from the advent of innovative biologic therapies have generated great interest in tools to help control the costs associated with managing this disease.[4] Health plans are faced with the dilemma of providing access to these novel treatments while minimizing increases in premiums.[4] Approaches to controlling costs have included reduced coverage, special copayments, drug rider policies, partnership with pharmacy services, and establishment of strict payment criteria (e.g., prior authorization) for the use of these therapies.[4]

Prior authorization (PA) requires the prescriber to obtain advance approval for a drug in order to have its use paid by the insurer. The use of PA to control treatment costs may be particularly effective in the case of agents with high potential for inappropriate use.[5] Proper use of PA procedures can help promote the use of rational drug therapy, improve utilization of health care resources, minimize overall medical costs, and enhance the access of health plan members to more affordable care.[5]

This article will review the clinical studies conducted for omalizumab with the goal of identifying patients that may benefit from omalizumab therapy.

SIGNIFICANT ROOM FOR IMPROVED ASTHMA CONTROL

Therapy for patients with asthma has several goals: (1) ensuring that the patient is free of symptoms and living an unrestricted life with normal physical activity; (2) maintaining lung function as close to normal as possible with a minimum of medications to minimize adverse effects; (3) minimizing exacerbations so as to have little to no need for ED visits and hospitalizations; and (4) providing care that meets patients' and families' expectations and satisfaction.[6] Current practices often fail to achieve these goals.

Asthma severity is usually categorized on the basis of a single assessment,[9] but it actually varies substantially over time. Even when they follow treatment guidelines, many

patients do not experience effective control of their asthma. Calhoun and colleagues found that patients initially diagnosed with moderate or severe persistent asthma and followed for 12 weeks demonstrated significant variability in disease severity during that period.[10] A similar analysis of pediatric patients with asthma yielded the same results.[11] These results indicate that the evaluation of asthma severity in many patients may underestimate disease severity and burden, resulting in inadequate therapy.[9]

Results from recent studies, including the Gaining Optimal Asthma Control (GOAL) study, indicate that aggressive management with currently available conventional therapies failed to achieve control, as defined by the National Asthma Education and Prevention Program and Global Initiatives for Asthma (GINA), over asthma in many patients. This 1-year study included 3,421 patients with uncontrolled asthma who were treated with fluticasone propionate or salmeterol/fluticasone. Dosages were increased incrementally until total control (as defined by achieving all specified criteria, including PEF, rescue medication use, symptoms, night-time awakening, exacerbations, ED visits, and adverse events) was achieved or until patients were receiving a maximum corticosteroid dose of 500 μg twice daily.

After dose escalation, asthma was totally controlled in 31% of patients treated with salmeterol/fluticasone and 19% of those who received fluticasone alone. At the end of 1 year, 41% and 28% (salmeterol/fluticasone vs. fluticasone) experienced total control of asthma symptoms. In addition, 68% and 76% (salmeterol/fluticasone vs. fluticasone) of patients were receiving the highest doses of their respective medications at the end of treatment. These results confirm that more than half of all asthma patients do not experience total disease control with combination therapy and about 70% do not experience total disease control with an inhaled corticosteroid (ICS).[12] This may be partly due to substantial differences between patients in response to therapy.

Variability in responsiveness to treatment, even among patients with similar disease severity, underscores the importance of repeatedly assessing asthma control and adjusting treatment accordingly.[14] Patients should be monitored to determine whether the initial regimen is sufficient to achieve control or whether additional therapy is needed to reach this goal.[14]

Patient questionnaires such as the Asthma Control Test, the Asthma Therapy Assessment Questionnaire, and the Asthma Control Questionnaire focus on patient-oriented features of asthma, evaluating its effect on daily activities, sleep, and the need for rescue albuterol. These questionnaires are not dependent on the availability of a spirometer, can be used to assess disease in patients who use controller medications, and can provide information on asthma control over an extended period of time.[16-19]

Overall, a reading of these studies supports the conclusion that management of patients with asthma is rapidly evolving toward individualized care based on longitudinal assessment of symptom control.[14,20,21] Additionally, the new GINA guidelines[22] emphasize the importance of the partnership between the patient and the health care provider. The partnership is formed when the patient and health care professional review the patients' treatment and level of asthma control as assessed through the asthma action plan developed jointly by the patient and health care professional to manage the patient's disease.

Treatment is modified when the level of control (symptoms and/or peak expiratory flow) is not achieved.[22] This exemplifies individualized care based on presence or absence of symptoms.

The trend toward individualization of asthma therapy has been facilitated by the development of new treatments such as omalizumab that may be particularly suitable for subsets of patients whose asthma is inadequately controlled despite utilization of standard therapies.

EFFICACY OF OMALIZUMAB

Our understanding of the pathophysiology of asthma has changed dramatically in the past decade. Immunologically-mediated responses, particularly those involving immunoglobulin E (IgE)-dependent mechanisms, are now known to play a central role in the development and maintenance of airway inflammation in asthma.[23] IgE therapy, omalizumab, has been shown to be effective for the treatment of patients having a significant allergic component.[23-30]

The initial large-scale trial that demonstrated the efficacy of omalizumab included 317 adults and adolescents with moderate or severe persistent allergic asthma who experienced symptoms despite the use of ICS and β_2-agonist rescue medication. Patients received intravenous omalizumab (2.5 or 5.8 μg/kg) or placebo for 20 weeks, in addition to ongoing ICS therapy. At week 12 of treatment, there were significantly greater reductions in asthma symptom scores in the two omalizumab treatment groups than in the placebo group (P = .005 for low dose and P = .008 for high dose). Asthma symptom reduction was also significantly superior with high-dose omalizumab than placebo at 20 weeks (P = .048). In addition, more subjects in the two omalizumab groups were able to decrease or discontinue their use of ICS than in the placebo group.[29]

These results were confirmed in a 28-week trial that included a 16-week phase with stable ICS (daily symptom score range of ≥3 to <9), an 8-

week phase during which the steroid dose was decreased to the lowest level that maintained symptom control, and a 4-week phase during which the lowest steroid dose remained unchanged.

This study enrolled 546 patients with allergic asthma who continued to experience symptoms despite ICS therapy and who received placebo or omalizumab every 2 or 4 weeks (with the omalizumab dose adjusted on the basis of body weight and serum IgE). Study results indicated that the omalizumab group had 58% fewer exacerbations per patient than the placebo group during stable steroid dosing ($P < .001$) and 52% fewer exacerbations ($P < .001$) when the steroid dose was reduced.[30]

A second study with a similar design provided comparable results. This trial included 525 patients with severe allergic asthma who were randomized to 28 weeks of treatment with placebo or omalizumab (as described immediately above). Omalizumab treatment was associated with significantly fewer asthma exacerbations per subject (0.28 versus 0.54, $P = .006$) and with fewer subjects experiencing an exacerbation (14.6% versus 23.3%, $P = .009$) compared with placebo during stable ICS treatment.

During the steroid-reduction phase, omalizumab treatment was associated with significantly fewer asthma exacerbations per subject and with fewer patients experiencing an exacerbation compared with placebo (0.39 versus 0.66, $P = .003$; and 21.3% versus 32.3%, $P = .004$).[23] Long-term (24-week) extensions of these two trials indicated that continued omalizumab treatment was associated with significantly fewer exacerbations and a decreased need for ICS.[28, 31]

Results from other recent clinical trials have demonstrated further that omalizumab is effective in patients with poorly controlled moderate-to-severe allergic asthma. A 12-month, randomized, open-label study of 312 patients with poorly controlled (≥1 ED visit or hospitalization or ≥1 course of oral corticosteroids over the prior year) moderate-to-severe allergic asthma were randomized to receive best standard care alone or with omalizumab. Patients receiving omalizumab experienced 49.6% fewer asthma deterioration-related incidences (ADRI) per patient-year (i.e., asthma exacerbations requiring ≥2 days of systemic corticosteroids or a supplemental burst course of systemic steroids, ≥2 days of antibiotic therapy, or ≥2 lost work/school days, unscheduled physician visits, an ED visit, or hospitalization) versus those who received the best standard care (95% CI, 27.8–64.8%).

Patients receiving omalizumab experienced a longer length of time to ADRI (Figure 1, page 46). Furthermore, omalizumab-treated patients required less rescue medication ($P < .001$), had fewer clinically significant exacerbations ($P < .001$), had better morning forced expiratory volume in 1 second (FEV_1) values ($P < .05$) and asthma symptoms scores ($P < .001$), and had a greater reduction in the mean daily ICS dose ($P < .001$) than patients who received standard care.[24]

Results from the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) study showed further that addition of omalizumab to ongoing asthma therapy significantly reduced exacerbations (Figure 2, page 47) and visits to EDs for patients with severe persistent asthma that was not controlled by the best currently available therapy. This 28-week trial included 419 patients with inadequately controlled asthma despite therapy with high-dose ICS and long-acting β_2-agonist, with either omalizumab or placebo added to treatment.

The addition of omalizumab was associated with significant reductions in the rates of ED visits (0.24 versus 0.43, $P = .038$) and severe asthma exacerbations (0.24 versus 0.48, $P = .002$).[32]

A meta-analysis carried out by Holgate and colleagues that included 1,412 patients with moderate or severe asthma indicated that the addition of omalizumab to therapy was associated with significant reductions in the frequency of significant asthma exacerbation episodes (episodes that required a doubling of baseline ICS dose [two studies] or use of systemic steroids [all three studies]).

Patients treated with omalizumab also showed significantly greater im-

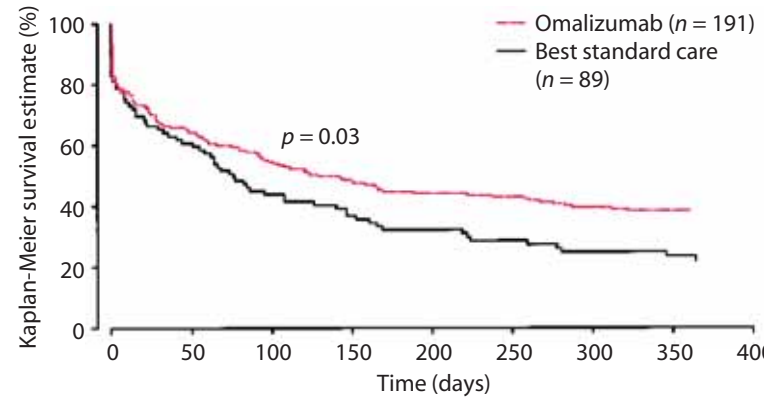

FIGURE 1 Kaplan-Meier survival curves of time to first asthma deterioration-related incident in patients with poorly controlled (moderate to severe) allergic asthma treated with best standard care, alone or in combination with omalizumab.[24]

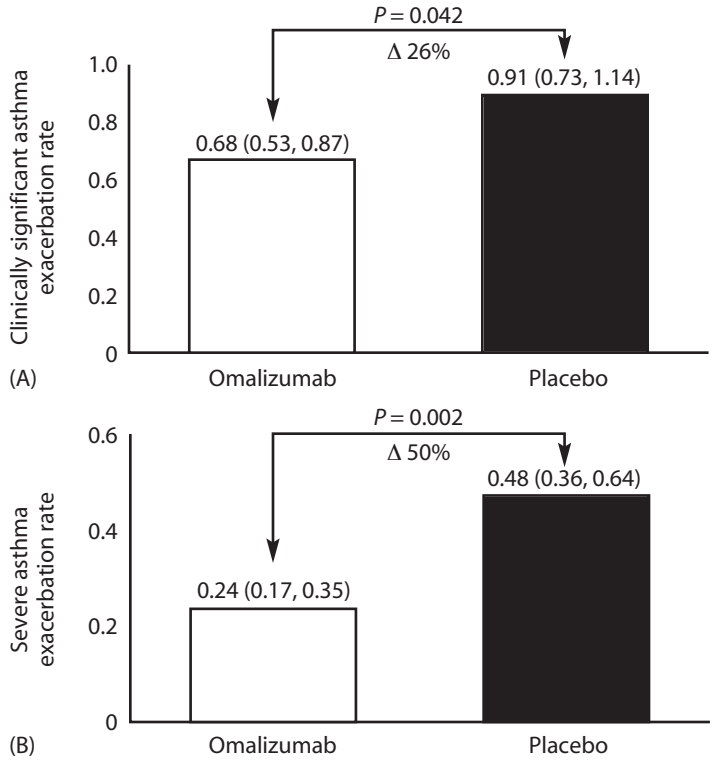

FIGURE 2 Effect of omalizumab on the rate of clinically significant (A) and severe (B) asthma exacerbations over 28 weeks of treatment.[32]

provements from baseline in overall asthma-related quality of life (P = .042) and mean nocturnal (P = .007) and mean total (P = .011) asthma symptom scores versus placebo.[27] Another pooled analysis of results from 767 adult and adolescent patients with allergic asthma enrolled in three randomized, double-blind, placebo-controlled studies indicated that omalizumab use was associated with a significant reduction in the rate of serious asthma exacerbations versus placebo, documented as an unscheduled outpatient visit, ED visit, or hospitalization.

Furthermore, the rate of unscheduled asthma-related outpatient visits was lower for the omalizumab-treated patients than for those who received placebo, as were asthma-related ED visits and hospitalizations (Figure 3, page 48).[26] These results were confirmed in a larger pooled analysis that included results from 4,308 patients (93% with severe persistent disease, 2,511 treated with omalizumab) in seven clinical trials. This assessment showed that omalizumab treatment was associated with a 38% reduction in exacerbations and a 47% reduction in the rate of ED visits (both $P < .0001$ versus control).[33]

In addition, results from 3 studies demonstrated significant improvements in Asthma Quality of Life Questionnaire scores among adult patients treated with omalizumab (Figure 4, page 49).[21,32,34]

APPROPRIATE USE

The United States Food and Drug Administration (FDA) has approved omalizumab for use in patients who meet all of the following criteria: moderate-to-severe persistent asthma, age >12 years, symptomatic despite ICS therapy, and a positive skin test or in vitro reactivity to a perennial aeroallergen.[35] At present, IgE-blocker therapy should target patients who have asthma with a documented allergic component and who have frequent exacerbations, high health care resource utilization, and a poor record of adherence to therapy, and in whom disease may be complicated by IgE-mediated comorbidities (Table below).[36,37]

As with any therapy, the risks and benefits associated with the therapy

TABLE Consensus panel guidelines for the use of IgE-blocker therapy in patients with asthma.[37]

- Patient at least age 12
- Evidence of reversible disease (such as 12% or greater improvement in FEV_1 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 β_2 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

*Examples of inadequate control: (1) utilization of emergency department, hospitalization, or urgent-care visits; (2) excessive use of a short-acting β agonist or oral steroids; and (3) impairment in activities of daily living, such as work, school attendance, exercise, and sleep.

must be considered. An analysis of 12 studies by Deniz and Gupta[38] determined that omalizumab had a safety profile similar to standard therapy. Malignant neoplasms have been reported in 0.5% of omalizumab-treated patients versus 0.2% of control patients in clinical studies of asthma and other allergic disorders.[35] Low titers of antibodies to omalizumab have been detected in <0.1% of patients treated with omalizumab. Since results for this type of testing are easily influenced by various factors, it is difficult to determine whether this incidence is different from the incidence seen with other products.[35] The presence of omalizumab in human breast milk has not been studied; thus the potential for absorption or harm to the infant are unknown and caution should be exercised when nursing women use the therapy.[35]

Since omalizumab is administered via subcutaneous injection in a clinician's office every 2–4 weeks and requires an observation period after the injection, it is important to employ the therapy in patients who are most likely to benefit from it.

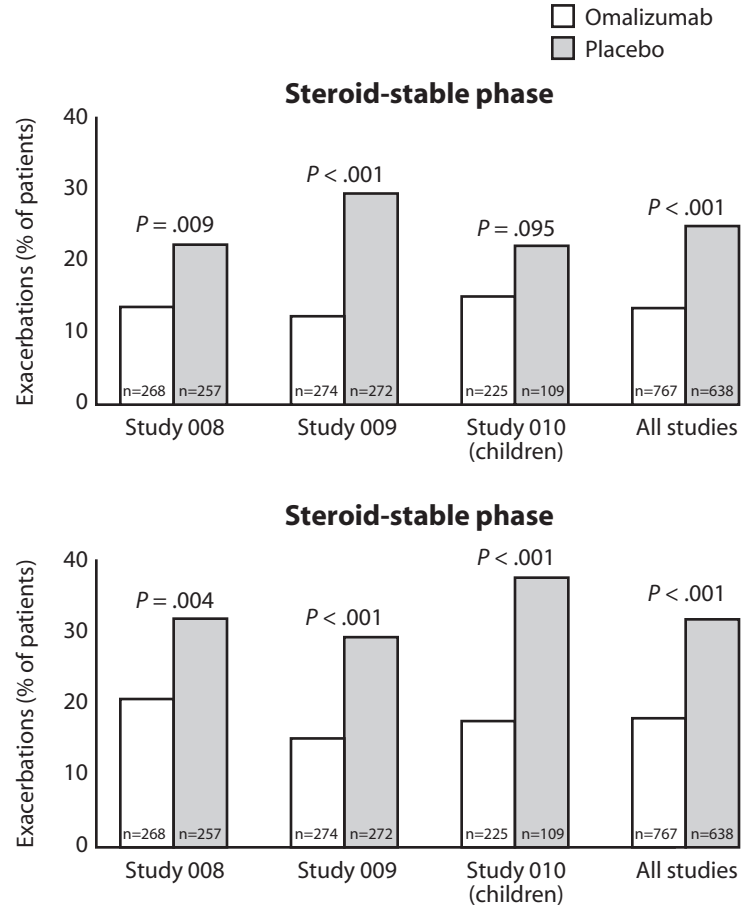

FIGURE 3 Proportion of patients experiencing asthma exacerbations during 28-week studies of omalizumab in adults, adolescents, and children.[26]

ENSURING ACCESS TO MEDICATIONS

Currently, payment by most health plans in the Northeast (the first author's practice area) for prescribed omalizumab requires PA and may involve recertification for prescription refills after a defined period of time. PA is a tool for promoting the use of rational drug therapy, improving utilization of health care resources, minimizing overall medical costs, and enhancing health plan member access to affordable care.[5] Such authorization certainly seems appropriate; however, patients who have not experienced an adequate response to traditional therapy or who are unable to tolerate such therapies need to have access to omalizumab. Therapies outlined in nationally accepted treatment guidelines, such as GINA, should be readily available to patients. PA should not be a tool that promotes suboptimal outcomes, decreased patient satisfaction, or increases costs.[39,40] The process could potentially be streamlined with automation to increase medication access for patients, which has been described in a program by Culley for leukotriene antagonists.[41]

CASE STUDIES

The patient dependent on oral corticosteroids

A 40-year-old woman with childhood asthma who worked as a nurse's aide at a community hospital presented with daily wheezing and shortness of breath with even minimal exertion. She received long-term disability benefits from her employer because of these symptoms, experienced monthly exacerbations that prompted ED visits, and was hospitalized three to four times per year for her symptoms. At presentation, the patient's spirometry was as follows: forced vital capacity (FVC) was 1.35 L (48% predicted), FEV_1 was 0.80 (33% predicted), and FEV_1/FVC was 59%. A 20% improvement in FEV-1 was demonstrated immediately after bronchodilator treatment. The patient also had multiple positive radioallergosorbent tests that were positive for perennial antigens (IgE level was 646 IU/mL). Current and past medications included fluticasone/sal-

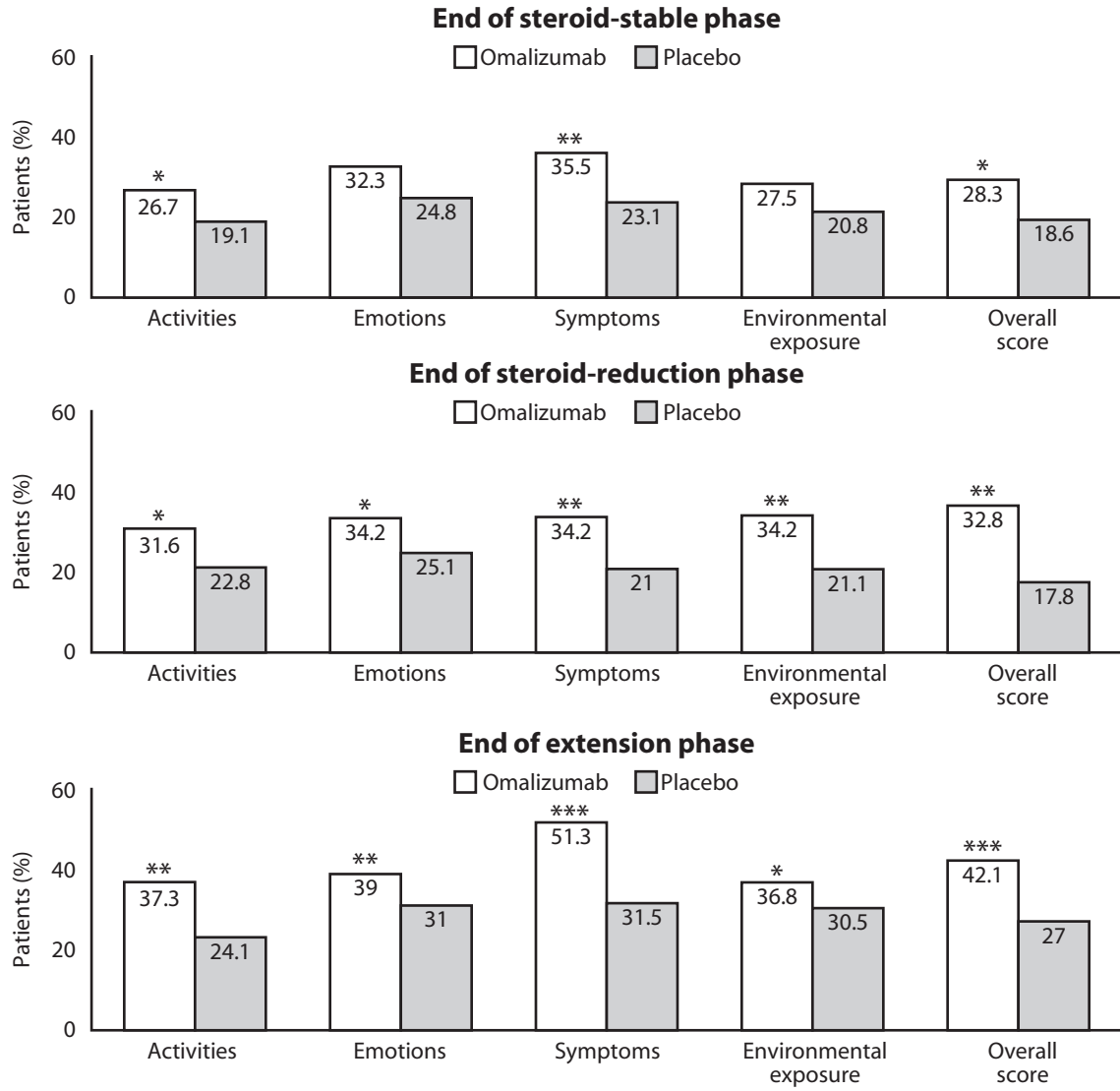

Figure 4 Proportion of patients achieving a large improvement in quality-of-life scores (defined as an increase in score of ≥1.5 points from baseline) during treatment with omalizumab or placebo in patients with severe allergic asthma. *$P < .05$, **$P < .01$, and ***$P < .001$ versus placebo.[34]

meterol (500 μg/50 μg), montelukast (10 mg), theophylline (300 mg BID), prednisone (never <10 mg/d, with bursts almost monthly), nebulizers with ipratropium and levalbuterol, and albuterol as needed.

The patient was diagnosed with severe persistent asthma and was dependent on prednisone. Treatment with omalizumab (375 mg every 2 weeks) was initiated 2 weeks after an intensive care unit admission requiring intubation and mechanical ventilation. After omalizumab therapy was initiated, the patient experienced decreased exacerbations and symptomatic and functional improvement. Her prednisone dose was decreased to 7.5 mg/d. The patient had no further hospitalizations or ED visits during the 1-year follow-up period. Spirometry results after 1 month of treatment with omalizumab were as follows: FVC was 1.76 L (71%), FEV_1 was 1.06 L (52%), FEV_1/FVC was 60%, and peak expiratory flow rate was 200 L/min.

This patient's outcome is consistent with the results of controlled clinical studies of omalizumab in patients with moderate-to-severe asthma, which reported reductions in exacerbations, unscheduled asthma-related outpatient visits, ED visits, and hospitalizations due to asthma in patients with asthma who

were symptomatic despite treatment with ICS.[26,30,32] In addition, a significant reduction in her oral dose of corticosteroids was achieved.

Thus, administration of omalizumab to a patient with severe asthma who was dependent on oral steroids and who had multiple emergency-department visits and hospitalizations resulted in significant symptomatic improvement, a decreased requirement for steroids, improved quality of life, and the ability to return to work.

The hidden patient: improved quality of life

A 46-year-old railroad conductor with asthma since childhood told his physician that he wanted better control over his asthma. The patient complained that he could not exercise or play with his children, that his lifestyle was limited by his condition, and that he feared asthma attacks. He noted occasional-to-frequent nighttime awakenings associated with dyspnea. He had never been hospitalized nor required emergency-department visits for asthma and had no history of prednisone use. The patient's current medication was albuterol three to four times per day and albuterol with exercise and fluticasone/salmeterol 250 μg/50 μg two times per day. The patient's FEV_1 was 2.08 L (60%).

The patient was referred to a pulmonary consultant who prescribed an increase in his fluticasone/salmeterol dose to 500 μg/50 μg two times per day, initiated a peak expiratory flow rate and symptom diary, and obtained IgE levels and RAST testing. Test results indicated an IgE of 289 IU/mL and sensitivity to dog and other perennial allergens. The patient improved marginally on this regimen.

This patient was subsequently treated with an omalizumab dose of 225 mg every month. With this regimen, the patient's work performance and quality of life improved. The patient is now able to play with his children, has substantially increased his daily activities and exercise capacity, and is asymptomatic at work. He has decreased his albuterol use to twice per week and no longer has nocturnal awakenings. His dose of fluticasone propionate/salmeterol was reduced, back to 250μg/50 μg twice per day.

This patient's outcome is consistent with those reported in clinical studies of omalizumab evaluating quality of life in patients with asthma with an allergic component.[21,32,34] In summary, this patient with uncontrolled symptoms despite ICS was able to achieve an improved quality of life after beginning omalizumab therapy.

CONCLUSIONS

Asthma is a very common disease that imposes a significant burden on patients and society, as reflected by high treatment costs, lost productivity, school absences, and reduced quality of life. Although, for many patients, asthma can be controlled with conventional therapies, others do not realize complete symptom relief with these medications. Omalizumab has met the standard criteria of providing improvement in many patients with allergic asthma. Improvements have been noted in outcomes that are important to patients, payers, and employers, including decreased hospitalization and emergency-department visits, decreased use of rescue and controller medications, improved quality of life, and decreased days off from work or school.

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