

Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma

Yuji Oba, MD, and Gary A. Salzman, MD *Kansas City, Mo*

Background: Omalizumab can reduce hospitalization and emergency department visits and improve quality of life in patients with moderate-to-severe, suboptimally controlled allergic asthma. Given the high cost and modest efficacy of this agent, it is not clear that it is cost-effective if given to a broad population with asthma.

Objective: The purpose of this study was to evaluate the cost-effectiveness of omalizumab in adults and adolescents with moderate-to-severe allergic asthma.

Methods: A retrospective economic analysis was performed to determine the cost-effectiveness of omalizumab using 52-week data from 2 randomized controlled clinical trials in adults and adolescents with moderate-to-severe allergic asthma. The analysis was conducted from a third-party payer's perspective, and only direct costs were considered.

Results: The incremental cost-effectiveness ratios showed that the cost to achieve an additional successfully controlled day was \$523, and the daily cost to achieve at least a 0.5-point increase in Asthma Quality of Life Questionnaire score was \$378 in 2003 dollars.

Conclusion: From a pharmacoeconomic standpoint, omalizumab would be better used in allergic asthmatic patients with poorly controlled symptoms despite maximal therapy, given the high cost and modest efficacy of this agent. It could be cost saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy. (*J Allergy Clin Immunol* 2004;114:265-9.)

Key words: Adult, atopic asthma, cost, omalizumab, pharmacoeconomics

Asthma continues to impose a significant clinical and economic burden on society.

In 2001, 31.3 million persons (114/1000 persons) in the United States had ever been given a diagnosis of asthma during their lifetimes.¹ In 1998, it was estimated that the total annual cost of asthma care was in excess of \$12 billion. Direct expenditures accounted for nearly \$7.4

Abbreviations used

AQLQ: Asthma Quality of Life Questionnaire
BDP: Beclomethasone dipropionate
CEA: Cost-effective analysis
FSS: Federal Supply Schedule
ICS: Inhaled corticosteroid
QALY: Quality-adjusted life-year
SCD: Successfully controlled day
WAC: Wholesale acquisition cost

billion, with medications emerging as the single largest cost component.² There are many patients whose symptoms are suboptimally controlled despite the use of multiple medications, including inhaled corticosteroids (ICSs), and the prevalence, morbidity, and mortality associated with asthma remain high.³

A novel therapeutic approach with omalizumab, a recombinant humanized monoclonal anti-IgE antibody can reduce hospitalization and emergency department visits⁴ and improve quality of life in patients with moderate-to-severe, suboptimally controlled allergic asthma. But the magnitude of treatment effects does not seem to be as impressive as the remarkable reduction in circulating free IgE levels.⁴

The wholesale acquisition cost (WAC) of omalizumab is \$433 for one 150-mg vial.⁵ The estimated annual cost is approximately \$10,000 to \$12,000, which is far more expensive than other asthma medications. Given the high cost and modest efficacy of this agent, it is not clear that it will prove to be cost-effective if given to a broad population with asthma. To our knowledge, there have been no cost-effectiveness analyses to support use of this agent. The purpose of this study was to evaluate the cost-effectiveness of omalizumab in adults and adolescents with moderate-to-severe allergic asthma.

METHODS

Study selection

We performed a pooled analysis from the 2 pivotal trials (studies 008 and 009)^{6,7} after searching Medline and EMBASE for potentially relevant studies. Two studies used an identical protocol and are multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trials conducted in adolescents (age ≥ 12 years) and adults that enrolled 1071 patients. Patients had to be symptomatic despite treatment with inhaled ICSs and had to have positive immediate skin

From the Division of Respiratory and Critical Care Medicine, University of Missouri-Kansas City School of Medicine.

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Reprint requests: Yuji Oba, MD, School of Medicine, Blue 5 unit, University of Missouri-Kansas City, 2411 Holmes, Kansas City, MO 64108-2792.
E-mail: obay@umkc.edu.

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prick test responses to more than 1 common allergen (mites, cockroach, dog, and cat), total serum IgE levels of greater than 30 to less than 700 IU/mL, and FEV₁ values of greater than 40% to less than 80% of predicted values. Patients taking other asthma controller drugs and current smokers were excluded. Omalizumab was administered subcutaneously every 2 or 4 weeks according to body weight and baseline IgE levels (≥ 0.016 mg/kg IgE [IU/mL] every 4 weeks) in both studies. Other available studies were excluded for various reasons, such as pediatric population, intravenous administration of omalizumab, and insufficient data.⁸⁻¹⁰

Outcome measures

Effectiveness measurements in this analysis included an increase of 0.5 points or greater in the Juniper Asthma Quality of Life Questionnaire (AQLQ) score from baseline values^{11,12} and successfully controlled days (SCDs). The AQLQ is grouped into 4 domains: activity limitations (11 items), emotions (5 items), symptoms (12 items), and exposure to environmental stimuli (4 items). Each question is answered by patients on a 7-point scale according to the level of impairment. A lower score reflects greater impairment. Previous analyses of the AQLQ have determined that an increase in domain or total score of greater than 0.5 points is clinically meaningful from the patient's perspective,¹³ and therefore it was considered a treatment success in this analysis. The proportion of patients meeting the desired end point at the end of the steroid-stable phase was calculated, and all patients who achieved treatment success were included in the denominator of the cost-efficacy equation. Proportions of asthma-free days in studies 008 and 009 were found on the Food and Drug Administration Web site.¹⁴ An *asthma-free day* was defined by the manufacturer as a day on which all of the following were met: morning peak expiratory flow rate of 90% or greater of baseline value (mean of the 14 days before randomization), daytime asthma score of 1 or less (on a scale of 0-4), nighttime asthma score of 0 (on a scale of 0-4), and rescue medication use of 2 puffs or fewer.¹⁴ We decided to refer to this measurement as SCD rather than asthma-free day because the definition of this end point allowed for some daytime symptoms and the daily use of 2 puffs of albuterol rescue medication. SCDs were estimated by using the median percentage of each proportion category.

All costs are reported in 2003 dollars (adjusted when necessary) by using the medical care component of the Consumer Price Index.¹⁵ The results of these analyses are reported in terms of daily cost per unit of efficacy.

Unit costs

The cost-effective analysis (CEA) was conducted from a third-party payer's perspective, and hence only direct costs were included in this analysis. Costs incorporated in the CEA included costs of omalizumab, rescue medication (albuterol), treatment costs for drug-related adverse events, unscheduled physician visits, emergency department visits, and hospitalizations. The WAC was used for omalizumab, and the average wholesale price¹⁶ was used for other medications. The WAC of omalizumab is \$433 for one 150-mg vial (personal communication, Angela G. Pikus, Novartis). The daily cost of omalizumab was estimated on the basis of the weight ranges¹⁴ and mean IgE levels (198 IU/mL) of the study population. We assumed 25% of the study population randomized to the omalizumab group received 225 mg twice monthly, which requires four 150-mg vials per month because of 75-mg doses (remaining products discarded), and 75% received 300 mg monthly, which requires two 150-mg vials per month. The average costs of rescue albuterol and maintenance beclomethasone dipropionate (BDP) use were calculated to be 14 cents and 11 cents per inhalation, respectively. The cost of oral steroids was not included because of the very low cost of oral prednisone. The average costs for an emergency department visit and

an asthma hospitalization were calculated to be \$280 and \$3690, respectively, in 2003 dollars on the basis of the study by Stanford et al.¹⁷ The cost of a physician visit was based on average reimbursement of the Current Procedural Terminology 4 code (99214) for a visit made by an established patient to a general practitioner.¹⁸ The average Current Procedural Terminology 4 cost was estimated to be \$70.

A sensitivity analysis for successful treatment was performed by calculating the costs to achieve a 1.5-point increase, as well as a 0.5-point increase in the AQLQ score. These numbers were also calculated in the different phases of the trials. For both effectiveness parameters, sensitivity analysis was also performed by using best- and worst-case scenarios. We found that the average hospitalization cost ranged from \$2,613 to \$18,012 in 2003 dollars, depending on the severity of illness.¹⁷ The lowest acquisition of omalizumab, the lowest hospitalization cost for the omalizumab group, and the highest hospitalization cost for the placebo group were used for the best-case scenario. The highest acquisition cost of omalizumab was used for the worst-case scenario. The dosage of omalizumab depends on the patient's weight and IgE level, and therefore the lowest and highest acquisition costs of omalizumab were calculated on the basis of various IgE levels and body weights. The Federal Supply Schedule (FSS) cost of omalizumab (\$323.29 for one 150-mg vial)¹⁹ was also used for sensitivity analyses. The FSS is administered by the Department of Veterans Affairs and defines the quantities and prices paid by federal agencies for medical goods.

RESULTS

Demographics

A total of 1071 patients were included in this analysis. A summary of demographic characteristics is reported in Table I. Forty-five percent of the patients were male, 90% were white, and the average age was 39.4 years. Patients taking asthma controller drugs other than ICSs and current smokers were excluded in the original studies. The patients' usual ICSs were switched to an equivalent dose of BDP. These trials were divided into 3 phases, a stable-steroid phase (weeks 0-16), a steroid-reduction phase (weeks 16-28), and an extension phase (weeks 28-52). During the stable-steroid phase, the baseline BDP dose was maintained. During the steroid-reduction phase, the dose of BDP was reduced by 25% every 2 weeks for 8 weeks until discontinuation or worsening of asthma symptoms. For the last 4 weeks, the lowest effective dose of BDP that did not result in worsening of symptoms was maintained.

Cost analysis

Mean asthma treatment costs for patients treated with omalizumab were \$39.85 per patient per day compared with \$2.08 per patient per day for those treated with placebo (Table II). The total cost of asthma treatment was much higher for the omalizumab group, mainly because of the acquisition costs of omalizumab. Overall, the cost of other health care resources, including hospitalizations, emergency department visits, and unscheduled office visits was \$0.09 per patient per day for the omalizumab group compared with \$0.37 for the placebo group.

The overall incidence rate of asthma-related hospitalization was 0.39 per 100 patient-years for omalizumab

TABLE I. Summary of demographic characteristics

	Omalizumab (n = 542)	Placebo (n = 529)
Age (y), mean (range)	39.7 (12-76)	39.0 (12-74)
Sex (M/F)	245/297	238/291
Race (white/other)	494/48	471/58
Smoking status (%)		
Never smoked	417 (77%)	388 (73%)
Ex-smoker	125 (23%)	141 (27%)
Daily BDP dose (μg), mean (range)	670 (420-1600)	673 (200-2000)
Serum total IgE (IU/mL), mean (range)	198 (20-860)	196 (21-814)
FEV ₁ (% predicted)	69.0%	68.8%
Severe asthma		
Severe persistent* (study 008)	99.3%	99.6%
Severe† (study 009)	21.9%	21.7%

*Based on National Heart, Lung, and Blood Institute guidelines.

†Baseline FEV₁ of less than 65% of predicted value and mean total symptom score of greater than 4.

treatment compared with 2.77 per 100 patient-years for placebo. Two asthma-related hospitalizations occurred during 516.2 patient-years of follow-up during omalizumab treatment compared with 13 hospitalizations during 469.5 patient-years of follow-up with placebo. The average length of hospitalization was not available from the included studies. We assumed that the average cost of an asthma-related hospital stay was \$3690 in 2003 dollars, with the average length of stay being 3.8 days on the basis of the previous study,¹⁷ as mentioned above. The incidence rate of emergency department visits for asthma exacerbation was lower for the omalizumab group (omalizumab, 1.16 per 100 patient-years; placebo, 2.98 per 100 patient-years), 6 asthma-related emergency department visits being reported during 516.2 patient-years of follow-up for those receiving omalizumab treatment compared with 14 visits during 469.5 patient-years of follow-up for those receiving placebo.

The mean costs of inhaled BDP were calculated on the basis of study 009 only because the mean BDP doses at the end of the extension phase were not available in study 008. The major safety concerns for the use of omalizumab include anaphylactic reactions and the development of a new or recurrent cancer. However, the costs of possible adverse events were not included in this analysis because the reported incidence of severe anaphylactic reactions is rare (<0.1%), the incidence of adverse events was not statistically significant in both clinical studies analyzed, and there is a lack of clear-cut evidence that omalizumab could increase the incidence of malignancies.

Cost-efficacy and sensitivity analysis

A 0.5-point increase in the AQLQ score with the WAC cost of omalizumab at the end of the steroid-stable phase was used in the base case as a criterion to define successful treatment. The cost-efficacy ratio reported as the mean daily cost of treatment for each patient achieving at least a 0.5-point increase in the AQLQ score was \$378 (WAC).

TABLE II. Mean daily treatment costs (per person; 2003 dollars)

	Cost per day	
	Omalizumab	Placebo
Hospitalization	0.04	0.28
ED visits	0.01	0.02
Physician office visits	0.03	0.06
Rescue albuterol	0.42	0.52
Inhaled BDP*	0.69	1.19
Omalizumab	38.66	—
Total daily costs	39.85	2.07

ED, Emergency department.

*Based on study 009 only.

TABLE III. Sensitivity analyses

Parameter	Cost-efficacy ratio (per patient per day)
Change in AQLQ score	WAC/FSS (best-worst)
Steroid-stable phase	
≥0.5-point change	\$378 (\$146-\$919)/\$280 (\$107-\$684)
≥1.5-point change	\$517 (\$200-\$1259)/\$383 (\$146-\$937)
Steroid-reduction phase	
≥0.5-point change	\$334 (\$129-\$813)/\$248 (\$94-\$605)
≥1.5-point change	\$286 (\$110-\$696)/\$212 (\$81-\$518)
Extension phase	
≥0.5-point change	\$1079 (\$417-\$2626)/\$800 (\$305-\$1954)
≥1.5-point change	\$343 (\$133-\$836)/\$254 (\$97-\$622)
SCDs	WAC/FSS
Base case	\$523/\$388
Best case	\$202/\$148
Worst case	\$1273/\$947

All costs are reported in 2003 dollars.

Using SCD as an effectiveness parameter yielded a mean daily cost-efficacy ratio of \$523 (WAC), indicating that it costs, on average, an extra \$523 per day for an additional SCD with omalizumab. Results of the sensitivity analysis are reported in Table III. The daily costs to achieve meaningful improvement in the AQLQ score ranged from \$81 to \$2626, and the daily costs to achieve an additional SCD ranged from \$148 to \$1273.

DISCUSSION

This study showed that the incremental cost associated with the use of omalizumab in the population studied to gain one SCD was \$523 in 2003 dollars. This number is far greater than those associated with other controller medications. For example, the incremental costs per symptom-free day gained were \$3.35 to \$7.5 with ICSs,²⁰⁻²⁴ \$5.71 to \$12.08 with zafirlukast,²¹⁻²³ and \$3.79 to \$9.06

with the salmeterol–fluticasone propionate combination.²⁴ Rutten–van Molken et al²⁵ evaluated the cost-effectiveness of ICS therapy and considered an incremental cost of \$5 per day (1989 value) as an acceptable benchmark amount to pay for each symptom-free day gained. Even after adjusting for inflation, the incremental cost associated with omalizumab seems considerably high when this is used as a benchmark for an acceptable incremental cost per symptom-free day. The cost per symptom-free day associated with omalizumab is probably even higher given the fact that the definition of SCDs allowed for some daytime symptoms and the daily use of 2 puffs of albuterol rescue medication in the original studies.

Interpreting the AQLQ score end point is a little more difficult because there are few published data on the economic value of an improvement in the AQLQ score. However, it takes approximately \$140,000 to maintain clinically significant improvement (0.5 points or greater) of AQLQ score for an entire year with the use of omalizumab in the group studied. Considering an acceptable cost per quality-adjusted life-year (QALY) is \$50,000,^{26,27} and willingness to pay per QALY gained in asthma patients was estimated to be \$7000 to \$46,000,²⁸ this number also seems excessive both from a third-payer perspective and a patient's perspective.

Because of the relatively low outcome event rate in the population studied, it was believed that cost-effectiveness analyses were much more sensitive to the variation in the acquisition cost of omalizumab rather than to variations in clinical efficacy, hospitalization rates, length of stay, and emergency department visits (Table II). We could not get the average sales price or average manufacturer's price of omalizumab, which is more reflective of the actual average acquisition cost. However, we used both WAC and FSS. The WAC is the manufacturer's charge to the wholesaler to purchase the drug and does not reflect any rebates or discounts. The FSS is the price paid to manufacturers by the Department of Veterans Affairs and other federal agencies. Generally, the FSS price might not be higher than the lowest contractual price charged by the manufacturer to any nonfederal purchaser. The average drug acquisition cost probably falls somewhere between the WAC and FSS. The best cost-effective ratio was found in a low-to-average weight (30–90 kg) patient with a relatively low IgE level (30–100 IU/mL), in which it requires the lowest dose of omalizumab (150 mg every 4 weeks) by using the FSS cost. The lowest cost to achieve an additional SCD was \$148, and the lowest daily cost to achieve clinically significant improvement in AQLQ score was \$81 at the end of the steroid-stable phase in this group of patients. These numbers are still greater compared with those for other controller medications.

Although the incremental cost associated with omalizumab seems considerably high compared with those of other asthma controller medications, it could be cost saving if it is used in a highly restricted population. Omalizumab has been shown to prevent 86% of hospitalizations in adolescent and adult asthmatic patients.⁴ Considering hospitalization accounts for a large part of

the expense of asthma care, and the average cost of asthma hospitalization is \$3690 in 2003 dollars, including the associated emergency department visit, omalizumab could be cost saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy. In terms of emergency department visits, omalizumab could be cost saving if given to patients who require emergency department visits 7 or more times per month, given that omalizumab reduces emergency department visits by 61% in adolescent and adult asthmatic patients. Omalizumab would not be cost saving from the office visit standpoint unless a patient requires an unscheduled office visit every day. Apparently, the symptoms of the subject populations studied were able to be managed with modest amounts of treatment and did not include subjects with refractory asthma.¹⁴ It is very unlikely that this agent will prove to be cost-effective, as suggested in this analysis, if given to a broad population, such as in that in studies 008 and 009.

This analysis has several limitations. One of the included studies was primarily performed outside the United States.⁷ There might be differences that affect the results, including the accessibility to medical care, the need for medical treatment, and the mode of asthma treatment. However, we believe that the effect of the possible differences is probably minimal because the 2 studies used an identical protocol, and event rates were comparable between the 2 studies.

The information available in the data set posed other problems. For example, we could not calculate the cost per QALY gained, as is currently recommended for all economic evaluations,²⁹ because the AQLQ score cannot be transformed to the 0 to 1 scale necessary to construct QALYs,³⁰ and the information on quality weights was not available from the included studies. A prospective study is necessary to estimate the cost per QALY gained. However, it should probably be done in patients requiring frequent asthma hospitalizations for the reason mentioned above.

Omalizumab is a new medication, and we have little information on its chronic side effects. The major safety concerns for the use of omalizumab include anaphylactic reactions and the development of a new or recurrent cancer. Those possible side effects might add more to the incremental cost of omalizumab once an increased incidence of those side effects is clearly observed.

In conclusion, this is the first CEA of omalizumab in asthma. The study showed that omalizumab is clearly more expensive than other controller medications in patients with moderate allergic asthma. However, it could be cost saving if it is used in a very restricted group of patients with severe asthma.

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