ORIGINAL ARTICLE AIRWAY DISEASES

# The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective

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## Abstract

**Background:** Omalizumab, an anti-immunoglobulin E antibody, reduces exacerbations and symptoms in uncontrolled allergic asthma. The study objective was to estimate the costs and consequences of omalizumab compared to usual care from a US payer perspective.

**Methods:** We estimated payer costs, quality-adjusted survival (QALYs), and the incremental cost-effectiveness ratio (ICER) of omalizumab compared to usual care using a state-transition simulation model that included sensitivity analyses. Every 2 weeks, patients could transition between chronic asthma and exacerbation health states. The best available evidence informed the clinical and cost input estimates. Five years of omalizumab treatment followed by usual care was assumed to estimate a lifetime horizon. Omalizumab responders (60.5% of treated) were modeled as a separate scenario where nonresponders reverted back to usual care after 16 weeks of active treatment.

**Results:** The mean lifetime discounted costs and QALYs were $83 400 and 13.87 for usual care and $174 500 and 14.19 for omalizumab plus usual care resulting in $287 200/QALY (95% interval: $219 300, $557 900). The ICER was $172 300/QALY when comparing omalizumab to usual care in the responder scenario. One-way sensitivity analyses indicated that the results were sensitive to the difference in treatment-specific utilities for the chronic state, exacerbation-associated mortality, omalizumab price, exacerbation rates, and response definition.

**Conclusions:** The results suggest that adding omalizumab to usual care improves QALYs at an increase in direct medical costs. The cost-effectiveness of omalizumab is similar to other chronic disease biologics. The value increases when omalizumab response is used to guide long-term treatment.

Omalizumab is a humanized monoclonal antibody that binds to circulating IgE, thereby inhibiting its effect on the inflammatory process in allergic asthma. Published clinical trials have shown omalizumab, when added to inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), to be efficacious at reducing the rate of asthma exacerbations when compared to ICS with or without other controller therapies (1, 2). However, the cost of omalizumab has induced health care payers to restrict access using drug formulary placement and medical benefit policies in the United States.

Several cost-effectiveness analyses (CEA) have been conducted in an attempt to present the value of omalizumab from a health care payer point of view and inform coverage and reimbursement policies (3–6). The results of these analyses are mixed due, in part, to different methods and variation in the use of clinical and economic data. Concerns about certain input parameters and assumptions used in these models, and their potential influence on the results and conclusions, were presented in previous publications (7–9).

This article presents a report of a *de novo* economic evaluation of omalizumab from a US payer perspective. Our intention is to resolve some of the issues with the existing literature and to make the report relevant to US decision-makers. The analysis presented in this article is unique in the following ways: (i) use of actual payer reimbursement data which takes into account both a drug formulary and medical

benefit mix, (ii) use of meta-analysis patient level data of all available omalizumab clinical trials, and (iii) exploration of clinical response to omalizumab and the impact on US cost-effectiveness estimates. This adds critical data missing from the available literature.

## Methods

### Model overview and treatment alternatives

A Markov model programmed in Microsoft Excel® (Fig. 1) was used to simulate different treatment alternatives in adults with uncontrolled allergic asthma and to estimate incremental clinical and economic outcomes including asthma exacerbations, health care resource utilization, asthma-specific quality of life, quality-adjusted survival (QALYs), payer costs, and incremental cost-effectiveness ratios (ICER). The treatment alternatives were omalizumab therapy plus usual care versus usual care alone. Usual care was defined by the comparison arm of omalizumab trials used for the evidence generation of the model inputs. Generally, usual care was defined as ICS for long-term asthma control and the use of short-acting beta-agonist on an as-needed basis but additional therapies could include LABA and systemic corticosteroids (1, 2).

Five years of omalizumab treatment followed by usual care was assumed to estimate a lifetime horizon. The 5-year omalizumab treatment duration was a compromise between the observed treatment duration in trials and the increased assumptions and uncertainty associated with the costs and outcomes of lifelong treatment. All patients were assumed to adhere to therapy. All costs and outcomes were discounted at 3% per annum.

### Model structure

The model structure was based on three health states: chronic asthma, exacerbation, and death. Patients transitioned through these health states using 2-week transition probabilities. Two weeks was considered an appropriate length of time to capture the majority of morbidities associated with exacerbations and has been used in other asthma cost-effectiveness models. The model structure was similar to the Asthma Policy Model's structure that modeled asthma in three main states: chronic (chronic asthma state), acute (exacerbation states), and death (10). The model structure also mirrored previous omalizumab cost-effectiveness models in the Wu et al. application of the Asthma Policy Model (6), the Brown et al. Canadian perspective CEA (3), and the Dewilde et al. Swedish perspective CEA (4). Although the structure of this model was similar to past CEA publications, the underlying population, perspective, inputs, and assumptions remain unique and of particular importance to US payers.

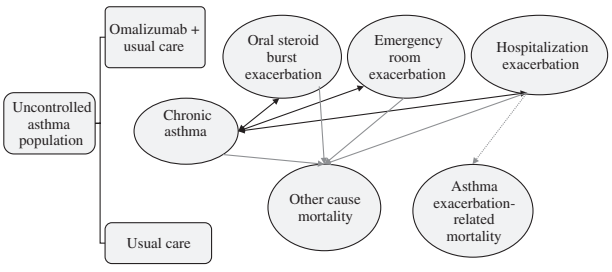


**Figure 1** Cohort Model Structure for Omalizumab plus Usual Care versus Usual Care Alone. Usual Care: inhaled corticosteroids (ICS) for long-term asthma control and the use of short-acting beta-agonist on an as-needed basis.

### Model population

The model's patient population reflects that of the US omalizumab label indication, namely patients with moderate-to-severe persistent asthma, a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and symptoms inadequately controlled with ICS (11). The model cohort matches the omalizumab trial population with an average age of 40 and 60% women (1).

### Clinical inputs

The best available evidence was used to estimate the clinical and cost inputs (Table 1). Where possible, we used evidence from a meta-analysis of omalizumab trials over evidence from any single omalizumab trial. A patient-level meta-analysis of omalizumab trials informed health care utilization and transition probabilities between the chronic asthma and exacerbation states (1). We viewed the strength of the evidence from the patient-level meta-analysis (1), in synthesizing data from all participants in each trial and all time-points simultaneously, to be superior to the study level meta-analysis (2). The asthma-specific quality-of-life, health-related quality-of-life utilities, and responder scenario details needed for the model were not available by meta-analysis, so we relied on previously reported patient-level data. The double-blind, controlled INNOVATE trial was determined to be the best source for the utilities and responder data (12) over the open label Ayres et al. (13) omalizumab trial.

*Risk of death given hospitalization for severe exacerbations*

There is a small but significant relationship between severe exacerbations (i.e., asthma hospitalizations) and death (14). We uniformly modeled this link between asthma hospitalizations and death across treatment alternatives as well as an all-other-cause mortality rate based on the US age and gender-specific population (15).

*Exacerbations*

Asthma exacerbations were split into three mutually exclusive categories in order of increasing severity: a worsening of asthma symptoms that required (i) an oral corticosteroid burst or, (ii) an emergency room visit, or (iii) a hospital stay.

**Table 1** Model inputs by treatment alternatives

| Model input | Usual care | Omalizumab + usual care | Omalizumab responders + usual care | Source |
|---|---|---|---|---|
| Oral corticosteroid burst rate per person-year | 1.346 | RR 0.634 (95% CI 0.552, 0.729) | RR 0.360 (95% CI 0.204, 0.507) | Bousquet et al. (1), Humbert et al. (12) |
| Asthma emergency room visit rate per person-year | 0.066 | RR 0.397 (95% CI 0.192, 0.820) | RR 0.360 (95% CI 0.204, 0.507) | Bousquet et al. (1), Humbert et al. (12) |
| Asthma hospitalization rate per person-year | 0.062 | RR 0.489 (95% CI 0.246, 0.972) | RR 0.360 (95% CI 0.204, 0.507) | Bousquet et al. (1), Humbert et al. (12) |
| Chronic asthma utility | 0.669 (SE 0.15) | 0.732 (SE 0.15) | 0.779 (SE 0.14) | Humbert et al. (12), Tsuchiya et al. (17) |
| Oral corticosteroid burst utility | | 0.572 (SE 0.36) | | Price et al. (19) |
| Emergency room visit utility | | 0.449 (SE 0.37) | | Price et al. (19) and assumption |
| Hospitalization utility | | 0.326 (SE 0.39) | | Price et al. (19) |
| Risk of death given a hospitalization | | 0.011 (SE 0.004) | | Sullivan et al. (14) |
| Usual care pharmacotherapy per year | $2410 | $2410 | $2410 | Ayres et al. (13), Sullivan et al. (33) |
| Omalizumab 150-mg vials per year | 0 ($0) | 35.94 ($561.96/vial*) | 35.94 ($561.96/vial*) | Bousquet et al. (1) |
| Omalizumab administrations per year | 0 ($0) | 18.4 ($36/administration†) | 18.4 ($36/administration†) | Bousquet et al. (1) |
| Mild exacerbation unit cost | | $120 (SE $12) | | MarketScan (20) |
| Emergency room unit cost | | $548 (SE $55) | | MarketScan (20) |
| Hospitalization stay unit cost | | $9132 (SE $913) | | MarketScan (20) |

RR = rate ratio, SE = standard error of the mean.

*The price per vial was based on the 2009 wholesale acquisition cost. In the model, the WAC cost was reduced by the average patient out of pocket contribution to approximate the payer perspective.

†The omalizumab administration unit cost includes 2008 CPT code 99211 (follow-up office visit for routine administration, $17.60) and CPT code 90772 (therapeutic injection, $18.25) both for nonfacility payments (21).

*Quality of life*

Asthma-specific quality of life was estimated using the Asthma Quality of Life Questionnaire (AQLQ) (16). We estimated the health-related quality-of-life utilities for each health state. Within the chronic asthma state, heterogeneity between treatment alternatives was estimated using a mapping function (17) between the AQLQ and EuroQol Group's EQ-5D instrument (18) and then transforming the EQ-5D scores into utilities. INNOVATE patients without exacerbations were used to estimate the treatment alternative-specific utilities for the chronic asthma state. Utility estimates for the exacerbation health states came from a study conducted in the UK at four specialty asthma centers (19) among moderate-to-severe asthma patients because the INNOVATE trial was not designed to capture utility decrements during an exacerbation.

### Cost inputs

Payer perspective cost estimates were a function of unit costs and health care resource utilization rates. Even though some omalizumab trials report a reduction in ICS use for the active arm, we conservatively assumed that all non-omalizumab pharmacotherapy not related to an asthma exacerbation was equal between the treatment alternatives using usual care treatments in an open label trial (13). Omalizumab utilization was estimated based on the meta-analysis of omalizumab trials (1) with an average of 18.4 administrations of omalizumab and 35.9 150-mg vials per year (including vial wastage). Resource utilization rates that were captured as asthma exacerbations included asthma hospitalizations, asthma emergency room visits, and oral corticosteroid bursts. For the oral corticosteroid burst exacerbation, resource use of one general practice physician's visit was assumed because a prescription is required for oral corticosteroids.

Unit costs for physician visits, emergency room visits, and hospital stays were based on the average paid amounts for asthma diagnosed (ICD-9 493.xx) services from 2005 MarketScan data, a large medical and pharmacy claims database (20). Omalizumab 150-mg vial cost was estimated from the 2008 Wholesale Acquisition Cost (WAC) of $561.96. The omalizumab administration unit cost includes 2008 Current Procedural Terminology (CPT) code 99211 (follow-up office visit for routine administration, $17.60) and CPT code 90772 (therapeutic injection, $18.25) both for nonfacility payments (21). To estimate the true payer perspective, we adjusted the cost of omalizumab to the payer by subtracting the average patient out of pocket contributions, as has been recommended by the International Society for Pharmacoeconomics and Outcomes Research panel on standards for estimating drug cost (22). Under a pharmacy benefit structure (47.5% of omalizumab usage in US), the average patient co-pay per omalizumab administration was $60.26(23). Under a medical benefit (52.5% of omalizumab usage in US), we used the average patient co-insurance rate of 19.2% of the WAC up to a $1000 annual maximum (23). All costs were reported in 2008 US dollars using the medical care component of the Consumer Price Index to inflate costs prior to 2008(24).

### Scenario and sensitivity analyses

The 1-year asthma exacerbation rates from the model were estimated and calibrated to that of the Bousquet et al. meta-analysis findings (1). Other clinical and cost estimates were produced at 1 year to provide face validity, transparency, and to compare and contrast the short-run versus long-run incremental costs and QALYs. The lifetime horizon where patients were treated for 5 years of omalizumab followed by usual care was the base-case scenario.

Clinical response to treatment enhances the value of the intervention (25). Omalizumab responders (60.5% of treated) were modeled as a separate scenario where nonresponders remained in the omalizumab arm, but reverted back to usual care after 16 weeks of active treatment. The definition of response was based on the physician global evaluation of treatment effectiveness (GETE) (26) for omalizumab patients described in the Humbert et al. INNOVATE trial (12) that achieved either complete control (19.5%) or marked improvement of their asthma control (41%). The responder scenario is a subgroup analysis and the GETE is not uniformly used to evaluate omalizumab responders in practice. Therefore, one may place more uncertainty on the responder scenario findings but also may discover these results useful in approximating the value of identifying responders to omalizumab.

We undertook a one-way and probabilistic sensitivity analysis (PSA) to estimate the influence that the range of input values had on the incremental cost per QALY. The one-way sensitivity analysis varied one input parameter at a time using the lower and upper 95% interval bounds and recorded the change in the incremental cost per QALY. Standard errors in Table 1 and distributional assumptions of the inputs were used to generate the 95% bounds. The unit price of omalizumab was reduced by 20% from the WAC price as a separate one-way scenario to estimate the effect of omalizumab price on the ICER. Distributional assumptions of the input parameters were made to perform a PSA. Utilities were varied jointly to maintain the ordered nature of the health states in the PSA. Through 5000 random draws of the input parameter distributions, the PSA informed 95% intervals for outputs of the model.

## Results

### Calibration and first-year results

The first-year per patient rates for each arm were estimated for model calibration and were found to be similar to those reported by Bousquet et al. The rates for the omalizumab plus usual care arm were 0.029 hospitalizations, 0.025 ER visits, and 0.829 corticosteroid bursts compared to 0.030, 0.026, and 0.854, respectively, from Bousquet et al. The rates for the usual care arm were 0.060 hospitalizations, 0.064 ER visits, and 1.306 corticosteroid bursts compared to 0.062, 0.066, and 1.346, respectively, from Bousquet et al.

First-year results were presented as per patient averages (Table 2). The estimated cost of the omalizumab intervention

**Table 2** Average first-year per patient costs and outcomes

| | Omalizumab mean (95% interval) | Usual care mean (95% interval) | Difference* mean (95% interval) |
|---|---|---|---|
| Outcomes | | | |
| Hospitalizations | 0.03 (0.02 to 0.04) | 0.06 (0.04 to 0.09) | −0.03 (−0.06 to −0.01) |
| ER visits | 0.03 (0.02 to 0.03) | 0.06 (0.05 to 0.08) | −0.03 (−0.05 to −0.03) |
| Corticosteroid bursts | 0.83 (0.59 to 1.10) | 1.30 (0.98 to 1.65) | −0.48 (−0.68 to −0.31) |
| Quality-adjusted survival (QALY) | 0.72 (0.38 to 0.95) | 0.66 (0.33 to 0.91) | 0.06 (0.03 to 0.08) |
| Costs | | | |
| Hospitalization costs | $260 ($160 to $400) | $550 ($360 to $780) | −$290 (−$510 to −$95) |
| ER visit costs | $14 ($6 to $12) | $35 ($26 to $46) | −$21 (−$35 to −$19) |
| Corticosteroid burst costs† | $99 ($44 to $82) | $156 ($120 to $199) | −$57 (−$123 to −$71) |
| Intervention Costs | $19 800 ($19 600 to $19 900) | – | $19 800 ($19 600 to $19 900) |
| Other drug costs | $2400 ($1900 to $2900) | $2400 ($1900 to $2900) | – |
| Quarterly GP visit costs‡ | $480 ($390 to $570) | $480 ($390 to $570) | – |
| Total costs | $23 000 ($22 500 to $23 500) | $3600 ($3100 to $4200) | $19 400 ($19 100 to $19 600) |
| ICER | | | |
| Cost/QALY | | | $306 200 ($237 500 to $636 900) |

*Rows may not add up because of differences in rounding.
†Assumed to require a GP visit for the prescription of a corticosteroid burst treatment.
‡Quarterly GP visits are for routine asthma management.
Deterministic means and probabilistic 95% confidence intervals.

was $19 800 after 1 year of treatment. This cost was offset by lower hospitalizations, ER visits, and oral corticosteroid-related costs in the omalizumab arm, with differences of $290, $21, and $57, respectively. The total annual cost of omalizumab plus usual care was $23 000 compared to $3 600 for usual care alone. The 1-year improvement in QALYs with the addition of omalizumab was 0.063, resulting in an incremental cost-effectiveness ratio of $306 200/QALY.

### Lifetime results

Lifetime results were presented as per patient averages in Table 3. Patients in the omalizumab arm experienced 0.15 fewer hospitalizations, 0.19 fewer ER visits, and 2.37 fewer oral corticosteroid bursts. Treatment with omalizumab resulted in extended life years (LYs) and improved QALYs. Discounted LYs were 22.97 for the omalizumab arm and 22.94 for the usual care arm; undiscounted LYs were 39.85 and 39.79, respectively. Discounted QALYs were 14.19 for the omalizumab arm and 13.87 for the usual care arm; undiscounted QALYs were 22.87 and 22.51, respectively.

Hospitalization, ER visits, and oral corticosteroid burst costs were lower in the omalizumab arm, by a difference of $1 300, $100, and $260, respectively. Treatment cost with omalizumab was $92 700 that included both the drug and its administration. The total cost for those taking omalizumab in addition to usual care was $174 500 compared to $83 400 for those on usual care alone.

With a total cost difference of $91 200 and QALY difference of 0.36 the incremental cost-effectiveness ratio for omalizumab plus usual care compared to usual care alone was $287 200/QALY with a 95% interval ranging from $219 300/QALY to $557 900/QALY.

### Responder results

A lifetime analysis of the responder scenario resulted in lower costs for the omalizumab intervention arm (no effect on the usual care arm). Lifetime costs of the intervention were $59 200, and the total cost of the omalizumab arm was $140 700. Discounted LYs and QALYs for the omalizumab arm were 22.96 and 14.21, respectively. The ICER equaled $172 300/QALY (95% interval: $121 800, $511 300).

### Sensitivity analysis

The one-way sensitivity analysis indicated that the chronic health state utility values were influential. In the base case, the omalizumab arm had a chronic state utility 0.06 higher than the usual care arm. When varied based on its 95% bounds (0.02, 0.07), the ICER ranged from $690 800 to $245 200, respectively. Results were also sensitive to the probability of dying from a severe exacerbation (from $261 600 to $301 000), the cost of omalizumab (from $257 500 to $287 200), and the proportion of severe exacerbations (from $273 800 to $299 600) (Fig. 2).

**Table 3** Average lifetime per patient costs and outcomes

| | Omalizumab mean (95% interval) | Usual care mean (95% interval) | Difference* mean (95% interval) |
|---|---|---|---|
| Outcomes | | | |
| Life years (undiscounted) | 39.85 (38.82–40.21) | 39.79 (38.99–40.22) | 0.07 (0.01–0.19) |
| Quality-adjusted survival (QALY) (undiscounted) | 22.87 (11.78–31.26) | 22.51 (11.50–31.04) | 0.36 (0.19–0.47) |
| Life years | 22.97 (22.60–23.14) | 22.94 (22.50–23.13) | 0.04 (0.01–0.11) |
| QALY | 14.19 (7.32–19.41) | 13.87 (7.06–19.25) | 0.32 (0.16–0.42) |
| Costs | | | |
| Total costs | $174 500 ($162 200–$185 800) | $83 400 ($71 200–$95 200) | $91 200 ($89 700–$92 100) |
| ICER | | | |
| Cost/QALY | | | $287 200 ($219 300–$557 900) |

Deterministic means and probabilistic 95% confidence intervals.
*Rows may not add up because of differences in rounding.

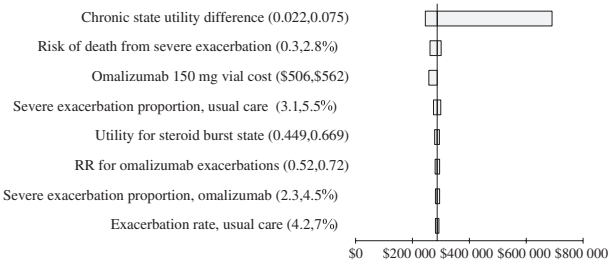


**Figure 2** Tornado Diagram of One-way Sensitivity Analysis on US Cost per quality-adjusted survival Outcome. (Parameters that had less than a US $10 000 difference in the ICER were not displayed).

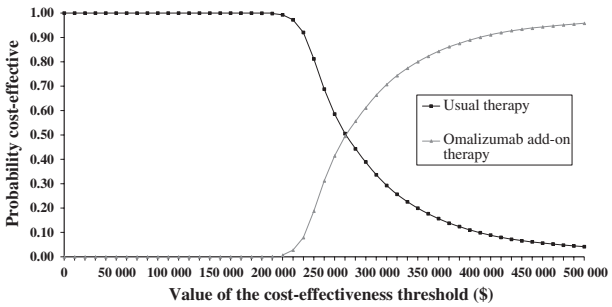


**Figure 3** Cost-Effectiveness Acceptability Curve. (Displays the probability of an intervention strategy being cost-effective over a range of willingness-to-pay thresholds for an additional quality-adjusted life year).

The cost-effectiveness acceptability curve illustrates the probability that each intervention has the best net health benefit at different willingness-to-pay thresholds. At a $272 000/QALY threshold, omalizumab had the best net health benefit in 51% of the simulations (Fig. 3).

## Discussion

The objective of this article was to estimate both the short- and long-run costs and consequences of omalizumab plus usual care compared to usual care alone from a US payer perspective. We calibrated our model to ensure that the short-run clinical results at 1 year mirrored the findings from the patient-level meta-analysis of omalizumab trial (1). We used the US Panel on cost-effectiveness recommended outcome of quality-adjusted life years (27) so that the US payer could compare the value of omalizumab to other interventions. We found the incremental value of adding omalizumab to usual care was similar across various time horizons with the 1-year analysis yielding $306 200/QALY and the lifetime analysis including 5 years of omalizumab treatment yielding $287 200/QALY. The value of implementing a definition of clinical response, a 16-week trial of omalizumab, was approximated at $172 300/QALY.

The outcome was most sensitive to differences in utility values. Based on a mapping algorithm from the AQLQ (17), the utility difference for the chronic asthma health state was empirically estimated from the double-blind INNOVATE trial (12).

Wu et al. published the only other US-based omalizumab cost-effectiveness analysis reporting cost per QALY (6). With their estimate of $821 000/QALY, they concluded that omalizumab was not cost-effective for most patients with severe asthma. Wu and colleagues also found that quality of life was an extremely important input for their results with their one-way sensitivity analysis on quality of life yielding ICERs ranging from about $200 000/QALY to $1 400 000/QALY. The present research differs from the Wu et al. analysis in that they used the changes in $FEV_1$ percent predicted to estimate changes in utility values. Unlike ICS or LABAs for long-term control of asthma, omalizumab has not shown dramatic improvements in lung function. Rather, omalizumab reduces exacerbations, improves asthma symptoms, and asthma-specific quality of life. Further, studies have shown that the correlations

between $FEV_1$ and symptoms, hospitalizations, and asthma-specific quality of life are weak, at best (28, 29). Therefore, we argue that using utility values that hinge on changes in asthma-specific quality of life (AQLQ) from a double-blinded, randomized, controlled omalizumab trial produces better unbiased estimates than that from changes in $FEV_1$ percentage predicted.

The National Asthma Education and Prevention Program recommends considering omalizumab as adjunctive therapy in those patients in step 5 or 6 with moderate-to-severe, persistent allergic asthma not controlled with ICS and LABA (30). Additionally, US reimbursement policies of targeted biologics in other therapeutic areas may provide reference points regarding willingness to pay. In a recent article, Sullivan et al., suggests that cost-effectiveness estimates for the treatment of rheumatoid arthritis, Crohn's disease, and multiple sclerosis vary from less than $100 000/QALY to more than $1 000 000/QALY (9).

There are limitations to this study. The findings were based on a simulation model. Although models are not as internally valid as a randomized, controlled trial, there are no trials that could provide the data needed to estimate the long-run costs and consequences of omalizumab. The best available evidence was used for the inputs to the model. The model structure was similar to that of other peer-reviewed asthma cost-effectiveness models. One-year clinical findings were calibrated to that of the meta-analysis inputs. The findings from the lifetime results were not very different from the 1-year results and demonstrated only a small difference of 15 days in the lifetime survival across the treatment alternatives. Uncontrolled asthma is a chronic disease with a limited number of asthma-related deaths, but a great deal of asthma-related morbidity (31). This observation supports the long-run model assumptions and findings.

Another limitation was the inability to use the patient-level meta-analysis for the purposes of estimating the health-related quality-of-life utilities. Given that the treatment-specific chronic asthma utility estimate is a main contributor to the uncertainty in the ICER result, it is recommended that further research be conducted on this input parameter. The costs and outcomes related to anaphylaxis were not included in the model for any treatment strategy. In premarketing clinical trials, the frequency of anaphylaxis attributed to omalizumab use was estimated to be 0.1% (11). The policy-relevant interpretation of the findings is not expected to change based on this assumption because of the rarity of the incremental risk and the relatively low cost to treat an average anaphylaxis event (32).

The findings suggest that adding omalizumab to usual care improves QALYs at an increase in direct medical costs. The cost-effectiveness of omalizumab from the US payer perspective may be similar to other biologics. The findings also suggest that the cost-effectiveness improves when a 16-week assessment to determine response is used to guide decisions regarding long-term treatment.

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