Cost-Effectiveness Analysis of Omalizumab for the Treatment of Severe Asthma in Japan and the Value of Responder Prediction Methods Based on a Multinational Trial

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ABSTRACT

Objectives: Omalizumab improves health outcomes for patients with severe asthma. The purpose of this study was to conduct a cost-utility analysis of omalizumab from a societal perspective by using the results from a randomized controlled trial in Japan, and explore the efficient use of omalizumab. Methods: We developed a Markov model to compare omalizumab add-on therapy with standard therapy. Patients transitioned between symptom-free, day-to-day, and exacerbation states. Our model had a lifetime horizon in which 5-year omalizumab add-on therapy was followed by standard therapy. Preference-based utilities were extracted from another study. We estimated the expected value of perfect information for patients’ response to omalizumab.

Results: In the base case, incremental cost-effectiveness ratio (ICER) for omalizumab add-on therapy was US $755,200 (95% credible interval [CI] $614,200–$1,298,500) per quality-adjusted life-year gained, compared with standard therapy alone. One-way sensitivity analyses indicated that the results were sensitive to asthma-related mortality, exacerbation risk, and omalizumab cost. The ICER for a responder subgroup was 22% lower than that in the base case. Individual and population expected value of perfect informations for the response were $4100 (95% CI $2500–$6000) and $28 million (95% CI $17 million–$42 million) per year, respectively. Conclusions: With a willingness-to-pay of $45,000 per quality-adjusted life-year, omalizumab was not cost-effective in Japan. Confining omalizumab therapy to previously predicted responders, however, may be a reasonable strategy to reduce the ICER, as the cost-effectiveness was observed to improve for these patients. Further studies should be conducted to explore responder prediction methods. Decreasing the price of omalizumab would improve cost-effectiveness. Keywords: costs and benefits, decision making, economic evaluation, pharmacoeconomics, value of information.

Introduction

With an estimated 300 million patients worldwide, asthma is a common chronic disease that is recognized as a global public health problem [1]. Clinical features of asthma in most patients are well controlled with inhaled corticosteroids (ICS) via their anti-inflammatory effects, whereas persistent asthma in some patients is difficult to control with standard medications, including ICS, and is designated severe asthma [2]. Patients with severe asthma are obliged to decrease their health-related quality of life (HRQOL), visit emergency departments, and become hospitalized.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to IgE and inhibits its interaction with the IgE receptor. Many clinical trials have shown that omalizumab reduces exacerbation risk and improves HRQOL related to asthma [3–6]. Omalizumab, however, is an expensive medication (US $1874 per 4 weeks on average). Several economic evaluation studies have been published [7–11]. Some of the findings from these studies have been unfavorable for omalizumab, whereas others have indicated the cost-effectiveness of omalizumab in patients with a history of severe exacerbations and hospitalization. The National Institute for Health and Clinical Excellence has recommended omalizumab as an add-on therapy with optimized standard therapy only in adults and adolescents with severe asthma and recurrent severe exacerbations [12].

Omalizumab is making a growing contribution to the treatment of severe asthma worldwide as an increasingly used therapeutic modality [5,6]. What is needed to increase the cost-effectiveness of omalizumab? One measure may be to develop prediction methods for patients’ response to omalizumab ahead of omalizumab therapy. Omalizumab has been reported to provide different benefits for patients with severe asthma [3,4], although a prediction method for identifying responders has not been developed [5,6]. Predicting the response can contribute to minimizing unnecessary drug exposure and health care costs for nonresponders, who do not adequately respond to the therapy. Previous studies and National Institute for Health and Clinical Excellence recommendations have been based on clinical data from large studies performed in many countries, excluding Asian countries. The first randomized controlled trial (RCT) that

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enrolled Asian patients with severe asthma was performed in Japan [13,14]. Patients with severe asthma constitute a major burden on the Japanese health care system due to their high requirements for inpatient care [1]. Japan’s medical fees for health care services are relatively low among Organisation for Economic Co-operation and Development countries [15]. The price of omalizumab differs among different studies ($635 in our study, $489 [7], $522 [8], $562 [9], $568 [10], and $433 [11] per a 150-mg vial). These facts beg the question of whether omalizumab is cost-effective in the Japanese setting.

The aims of this study were to assess the cost-effectiveness of omalizumab in Japan by using clinical data from the RCT and cost data, and to explore the efficient use of omalizumab.

**Methods**

Our cost-utility analysis was performed from the societal perspective. The benefits of omalizumab, including effects on HRQOL, exacerbation risk, and mortality risk, were expressed as quality-adjusted life-years (QALYs) gained. The cost-effectiveness of omalizumab was expressed as an incremental cost-effectiveness ratio (ICER): omalizumab plus standard therapy (the omalizumab add-on group) versus placebo plus standard therapy (the standard therapy group). Standard therapy refers to treatments recommended prior to omalizumab therapy in the international clinical practice guidelines for the management of adult asthma [16]. Treatment was considered cost-effective if the ICER was below $45,000 ($5 million) per QALY gained [17]. Costs and benefits were discounted at 3% per annum. All costs were expressed as US dollars using the purchasing power parity rate for Japanese yen and European euro to US dollars in 2010 ($1 = ¥111 = $1, €0.805 = $1) from the Organisation for Economic Co-operation and Development National Accounts database. The models were developed by using TreeAge Pro 2009 Healthcare (TreeAge Software, Inc., Williamstown, MA).

**Model Development**

We developed a multistate transition model, or Markov model. The model structure was based on the following four states: symptom-free asthma, day-to-day asthma, asthma-related exacerbation, and death (Fig. 1). Symptom-free and day-to-day states were defined as no symptoms and relatively minor symptoms during the week, respectively. The exacerbation state was split into three mutually exclusive categories: mild exacerbation, severe exacerbation, and hospitalization. Mild exacerbation was defined as relatively major symptoms during the week. Severe exacerbation was defined as requiring treatment with systemic corticosteroids. We linked the hospitalization state with asthma-related death state. In previous economic evaluations of omalizumab [7–9], similar Markov models were used to evaluate the cost-effectiveness of omalizumab add-on therapy. We added the symptom-free state to the model used in previous studies so as to fit our model to end points that were assessed in the RCT in Japan.

The model cycle length was 1 week. The model had a lifetime horizon in which 5-year omalizumab add-on therapy was followed by standard therapy alone. The 5-year treatment duration was selected because of its use in previous studies [7–9], and represents a “compromise between the observed treatment duration in trials and the increased assumptions and uncertainty associated with the costs and outcomes of lifelong treatment” [9]. The study cohort matched the RCT population with an average age of 50 years and 50% men.

**Clinical Input**

We used clinical data from the intention-to-treat population of the RCT in Japan [13,14]. The RCT was a randomized, placebo-controlled, double-blinded, multicenter study. Omalizumab was evaluated for a 16-week treatment phase in 315 patients, aged 20 to 75 years, with moderate-to-severe persistent asthma despite high-dose ICS and other controller medications. The RCT assessed the number of symptom-free weeks, mild exacerbation weeks, severe exacerbation weeks, and hospitalizations for each patient. The RCT measured asthma symptom scores, which were a sum of exacerbation (range 3–9), wheezing (1), and cough (range 0.5–1) scores, with a score of 0 denoting no symptoms. Symptom-free weeks were defined as a total symptom score of 0 during the week. Mild exacerbation and severe exacerbation were defined as experiencing major symptoms to some degree and requiring systemic corticosteroids, respectively.

The number of exacerbation weeks experienced by patients was published for each treatment group. Rates were calculated as per person-week. Rate ratios were calculated as the ratio of the omalizumab add-on group compared with the standard therapy group. Transition probabilities were obtained with the following formula: $1 – \exp(-\text{rate})$.

The incidence of serious adverse effects, such as anaphylaxis, was rare and similar in patients treated with omalizumab and placebo [13,14]. The same was reported for a large multicountry study [3]. Therefore, we did not incorporate any adverse effect costs or utility decrements for either treatment group into our model.

**Response to Omalizumab**

Patients with severe asthma derive different benefits from omalizumab [3,4]. It is difficult to predict the extent of benefits derived by various patients based on pretreatment characteristics [5,6]. Responders are identified by physicians’ global evaluation of treatment effectiveness after 16-week omalizumab therapy [5,6]. Omalizumab add-on therapy is discontinued at 16 weeks in nonresponders [5,6,12]. In our model, nonresponders reverted to standard therapy alone after the termination of omalizumab add-on therapy at 16 weeks. Responders were not identified in the RCT in Japan. We incorporated a response rate of 60.5% into our model [3,4].

**Primary Utility Estimate**

Because of the lack of detailed HRQOL measures in the RCT, we derived preference-based utility values from one previous study...
value of omalizumab to nonselective patients leads to the treatment of unnecessary treatment of nonresponders.

The ICER of omalizumab add-on therapy in the responder subgroup relative to the standard therapy group was calculated by subgroup analysis. The responder subgroup was entirely composed of responders receiving 5-year omalizumab therapy. Clinical outcomes for the responders were further improved when compared with the total number of patients treated with omalizumab [3,4]. The clinical parameters of responders from the large multicountry study were incorporated into our model [5,25,26].

We estimated the individual EVPI for the omalizumab response from the difference in net monetary benefits between the omalizumab add-on group (i.e., the total number of patients treated with omalizumab) and the responder subgroup. We then calculated the population EVPI per year for the total number of expected patients in Japan by multiplying the individual EVPI (minus screening costs for each patient) by the incidence of eligible patients, which was estimated from the incidence of adult asthma (3.6/1000 and 4.6/1000 person-year in men and women, respectively) [27] and the proportion of severe asthma (1.6%) [28]. We assumed that the screening test for each patient cost $180, which is similar to the cost of gene mutation testing in Japan.

**Cost Input**

Direct health care costs of omalizumab, standard therapy, and health care resource use for exacerbation and direct non–health care costs of transportation were included in our model. These unit costs were obtained from Japan’s official databases [21,22]. Age-specific risk of death from other causes was based on Japan’s vital statistics [22].

**Mortality**

No fatalities were recorded in the RCT [13,14]. Our model, however, included asthma-related death and death from other causes because the Asthma Policy Model included both types of death [20]. We calculated asthma-related mortality risk among hospitalized asthmatic patients by using Japan’s official databases [21,22]. Age-specific risk of death from other causes was based on Japan’s vital statistics [22].

**The Value of Information Analysis**

The expected value of perfect information (EVPI) is the price that the health care system would be willing to pay to conduct further research and gain access to perfect information because perfect information can eliminate the possibility of making a wrong decision based on existing (prior) information [24]. Administering omalizumab to nonselective patients leads to the treatment of nonresponders, which results in wasteful health care expenditure. Prediction methods for the identification of responders ahead of omalizumab treatment would help physicians avoid the unnecessary treatment of nonresponders.

We performed probabilistic sensitivity analysis with 5000 Monte Carlo simulations to obtain 95% credible intervals (CIs) for outputs of the model. We also performed one-way sensitivity analyses to estimate the impact of the range (95% confidence interval) of rate ratios (but not going above or below 1), utility values, omalizumab cost, and our assumptions on the results. To estimate the impact of utility values, we ran utilities over an arbitrary range from 10% above to 10% below each value (but not going above 1) by using the primary utility set. We also evaluated the following scenarios: different asthma-related mortality, different standard therapy cost, different unit cost of emergency department visit, different unit cost of hospitalization, different transportation cost, and different discount rate. We conducted a threshold analysis to provide the break-even price of omalizumab for the base case. In addition, we performed a subgroup analysis in which the target population was assumed to suffer from particularly severe asthma, with exacerbations rate double that of the base case and a symptom-free rate half that of the base case.

**Alternative Utility Estimate**

To examine the impact of utility estimates on the results, we conducted additional analyses by using another set of utility values reported by another previous study [19], which examined utilities associated with asthma exacerbations by using a visual analogue scale. We regarded day-to-day and mild exacerbation states as “current asthma state” and “mild exacerbation,” respectively, and severe exacerbation and hospitalization states as “severe exacerbation.” This previous study did not examine values for the symptom-free state. We made an arbitrary and extreme assumption that the utility value for patients in the symptom-free state was 1. This assumption created a bias in favor of omalizumab because patients in the omalizumab add-on group were more likely to be in the symptom-free state than in the standard therapy group.

**Sensitivity Analysis**

We performed probabilistic sensitivity analysis with 5000 Monte Carlo simulations to obtain 95% credible intervals (CIs) for outputs of the model. We also performed one-way sensitivity analyses to estimate the impact of the range (95% confidence interval) of rate ratios (but not going above or below 1), utility values, omalizumab cost, and our assumptions on the results. To estimate the impact of utility values, we ran utilities over an arbitrary range from 10% above to 10% below each value (but not going above 1) by using the primary utility set. We also evaluated the following scenarios: different asthma-related mortality, different standard therapy cost, different unit cost of emergency department visit, different unit cost of hospitalization, different transportation cost, and different discount rate. We conducted a threshold analysis to provide the break-even price of omalizumab for the base case. In addition, we performed a subgroup analysis in which the target population was assumed to suffer from particularly severe asthma, with exacerbations rate double that of the base case and a symptom-free rate half that of the base case.
### Table 1 – Clinical inputs and cost inputs in our economic model.

<table>
<thead>
<tr>
<th></th>
<th>Standard therapy group</th>
<th>Omalizumab add-on group</th>
<th>Responder subgroup</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate per person-week and risk ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Symptom-free rate</td>
<td>0.16</td>
<td>RR 1.68 (95% CI 1.48–1.91)</td>
<td>RR 2.03 (95% CI 1.49–2.81)</td>
<td>[13,14,25]</td>
</tr>
<tr>
<td>Mild exacerbation rate</td>
<td>0.067</td>
<td>RR 0.55 (95% CI 0.43–0.71)</td>
<td>RR 0.40 (95% CI 0.29–0.55)</td>
<td>[5,13,14,26]</td>
</tr>
<tr>
<td>Severe exacerbation rate</td>
<td>0.0069</td>
<td>RR 0.36 (95% CI 0.14–0.91)</td>
<td>RR 0.24 (95% CI 0.12–0.50)</td>
<td>[5,13,14,26]</td>
</tr>
<tr>
<td>Hospitalization rate</td>
<td>0.0015</td>
<td>RR 0.27 (95% CI 0.03–2.43)</td>
<td>RR 0.24 (95% CI 0.13–0.42)</td>
<td>[5,13,14,26]</td>
</tr>
</tbody>
</table>
| **Utility for initial and reproducibility analyses**
  |                        |                         |                    |        |
  | Symptom-free asthma          | 0.93 (1)               |                        | [18] and assumption |
  | Day-to-day asthma            | 0.76 (0.81)            |                        | [18,19] |
  | Mild exacerbation            | 0.65 (0.62)            |                        | [18,19] |
  | Severe exacerbation          | 0.52 (0.26)            |                        | [18,19] |
  | Hospitalization              | 0.52 (0.26)            |                        | [18,19] |
| Mortality                    |                        | 0.0155                  |                    | [21,22] |
| Proportion of responders     | 60.5%                  | 100%                    |                    | [3,4]  |
| **Direct cost ($)**          |                        |                         |                    |        |
  | Standard therapy cost per 4 wk for base case | 147                     |                        | Model case |
  | Standard therapy cost per 4 wk for sensitivity analysis | 274                     |                        | Model case |
  | Omalizumab cost per 4 wk, using 150-mg vial ($635/vial) | 1874                    |                        | [13,14] |
  | Omalizumab cost per 4 wk, using 75-mg vial ($318/vial)§ | 1686                    |                        | [13,14] |
  | Median unit cost of emergency department visit (interquartile range) | 79 (55–158)             |                        | QIP    |
  | Mean unit cost of hospitalization | 2203                    |                        | [23]    |
| Non-health care cost ($)     |                        |                         |                    |        |
  | Transportation cost per visit or hospitalization | 20 (10–40)              |                        | Assumption |

CI, confidence interval; RR, rate ratio relative to standard therapy group.

* Omalizumab add-on group indicates the total number of patients treated with omalizumab plus standard therapy.

† Responder subgroup indicates a subgroup of patients who derive great benefits from omalizumab plus standard therapy.

‡ Utility values inside and outside of parentheses are used as the primary utility set and the alternative utility set, respectively.

§ Omalizumab 75-mg vials are unavailable now in Japan and based on our assumption.

|| QIP indicates our department’s Quality Indicator/Improvement Project, which collects clinical and claims data from more than 200 hospitals in Japan.
Results

Table 1 shows symptom-free and exacerbation rates of the standard therapy group and rate ratios for the omalizumab add-on group and responder subgroup relative to the standard therapy group. Confidence intervals of the rate ratio under log-normal distribution were used as the range for probabilistic sensitivity analysis. Utility values and asthma-related mortality risks were shared among the two groups and the responder subgroup (Table 1). Omalizumab cost, standard therapy cost, and unit cost of health care resource use are also provided in Table 1.

The results of the base-case analysis with the primary utility set are presented in Table 2. The mean lifetime discounted costs and QALYs were $43,000 and 16.00, respectively, for the standard therapy group and $114,100 and 16.10, respectively, for the omalizumab add-on group. The results produced an ICER of $755,200 per QALY, with the 95% CI ranging from $614,200 to $1,298,500 for the base-case analysis of the omalizumab add-on group relative to the standard therapy group.

In the base-case analysis with the alternative utility set, the ICER was $633,500 (95% CI $515,300–$1,054,500) per QALY gained (Table 2).

Sensitivity Analysis

A tornado diagram of one-way sensitivity analyses with the primary utility set is shown in Fig. 2. The results indicate that the ICER was sensitive to the risk of death from hospitalization ($550,700–$1,225,200), rate ratio for hospitalization ($678,500–$1,143,400), utility for symptom-free asthma ($625,500–$1,042,200), rate ratio for symptom-free asthma ($654,400–$878,400), discount rate ($612,700–$826,500), utility for day-to-day asthma ($675,700–$855,900), and omalizumab cost ($679,400–$755,200). The ICER decreased by 10% when the omalizumab cost was reduced by 10%. Threshold analysis identified a break-even price of $40 for a 150-mg vial of omalizumab. In the subgroup analysis of patients with particularly severe asthma, the ICER was $583,600 (95% CI $462,300–$1,308,900) per QALY gained.

The cost-effectiveness acceptability curve illustrates the cost-effectiveness probability of omalizumab over a range of willingness-to-pay (WTP) values (Fig. 3). For a WTP threshold value of $728,000, the cost-effectiveness probability of omalizumab was 51%.

EVPI for Response to Omalizumab

In the responder subgroup analysis with the primary utility set, the mean lifetime discounted costs and QALYs were $155,300 and 16.19, respectively, resulting in an ICER of $590,100 (95% CI $430,700–$858,600) relative to the standard therapy group (Table 2). The ICER (point estimate) for the responder subgroup was 22% lower than that for the omalizumab add-on group (i.e., the base-case analysis).

In the value of information analysis with the primary utility set, the individual EVPI was $4100 (95% CI $2500–$6000) at a threshold value of $45,000 per QALY. The population EVPI for total eligible patients with severe asthma (7200 patients) amounted to $28 million (95% CI $17 million–$42 million) per year.

Discussion

In the present study, we analyzed the cost-effectiveness of omalizumab add-on therapy relative to standard therapy alone, on the basis of clinical data from an RCT carried out in Japan. The results showed that omalizumab was not cost-effective given the existing evidence.
We demonstrated that the ICER was sensitive to omalizumab cost and that the cost-effectiveness was improved when omalizumab add-on therapy was targeted at responders or patients with particularly severe asthma. The best ways to improve the cost-effectiveness of omalizumab may include decreasing the price of omalizumab, restricting omalizumab therapy to a subgroup of patients with a higher risk of exacerbation, which has been recommended by the National Institute for Health and Clinical Excellence [12], and confining the intervention to previously predicted responders identified on the basis of pretreatment patient characteristics. Further research should be performed on omalizumab response prediction methods (e.g., genetic testing) to help physicians decide whether to begin omalizumab add-on therapy. The development of prediction methods for patients’ response to omalizumab will considerably improve the ICER. We calculated the EVPI for omalizumab response to estimate the value of further research for developing prediction methods, although the estimation of EVPI is uncommon in economic evaluations in which the ICER is far from the WTP threshold. Thus, caution is required to assess the quantitative results, and further studies should involve real testing value for responders. However, our findings suggest the importance of prediction methods.

Dewilde et al. [7] and Brown et al. [8] demonstrated that omalizumab therapy was cost-effective in patients with severe asthma. In contrast, Campbell et al. [9] presented an ICER of $287,200 and $172,300 per QALY gained in the base-case analysis and the responder scenario analysis (where nonresponders remained and received 16-week omalizumab therapy), respectively. Wu et al. [10] analyzed the relationship between HRQOL and lung function parameters and concluded that omalizumab, with an ICER of $821,000 per QALY gained, was not cost-effective. One possible explanation for the inconsistency between the results from the former three studies using Markov models and the present study may be the difference in model structure. Our model included the symptom-free state to distinguish non-exacerbation utilities of the omalizumab add-on group from those of the standard therapy group. Furthermore, there is a difference in how asthma-related death is linked with other states in the models. Campbell et al. [9], as in our study, linked asthma-related death with the hospitalization state, whereas Dewilde et al. [7] and Brown et al. [8] assumed that patients transitioned from the severe exacerbation state to asthma-related death at a 2.082% to 3.108% risk in their model, which did not include the hospitalization state. Considering that severe exacerbations were more frequent than hospitalizations, more patients should have died from asthma in the models of Dewilde et al. and Brown et al., compared with our model and that of Campbell et al., thus creating a bias in favor of omalizumab.
Another explanation is the difference in the price of a 150-mg vial of omalizumab.

**Strengths and Limitations**

Our study has several advantages compared with those reported in the literature. To the best of our knowledge, the present study is the first to explore the efficient use of omalizumab and assess the value of further research to eliminate the uncertainty associated with patients’ response to omalizumab. Another advantage is the first economic evaluation using clinical and cost outcomes of omalizumab from an Asian population. In Japan, medical fees for health care services are relatively low among Organisation for Economic Co-operation and Development countries [15]. Chronic diseases, such as asthma, that involve the repeated use of urgent health care services underscore the importance of conducting the economic evaluation of an expensive drug in the Japanese setting.

Our analysis also has assumptions and limitations. First, the input data for HRQOL utilities were derived from another study conducted outside Japan. The generalizability of HRQOL in asthmatic patients to other countries might be limited [18]. Considering this limitation, we presented the omalizumab- favorable scenario in which the alternative utility set had a broader utility range than that in previous studies, as recommended in the practical guide for economic evaluations that involve parameter uncertainties [29]. This means that our alternative utility set was the most favorable to omalizumab. Yet, omalizumab was not cost-effective. These ensure that our findings are rigorous. Second, our value of information analysis was based on structural uncertainties. Experts have been advocating how to handle this type of uncertainty [30]. There are, however, limited examples of working on this issue in economic evaluations of health interventions. Third, clinical data of the response to omalizumab were not available from the RCT in evaluating health interventions. Third, clinical data of the response to omalizumab were not available from the RCT in China, Korea, and Taiwan. Fourth, clinical data of the response to omalizumab were not available from the RCT in Japan. We advocate that data of responders should be collected alongside further clinical trials. Finally, we extracted clinical parameters of the overall patients treated with omalizumab and omalizumab responders from different clinical trials to estimate the EVPI for omalizumab response. Further research exploring EVPI more precisely by using clinical data from a single trial may be needed.

**Conclusions**

We conclude that omalizumab is not cost-effective in Japan given a WTP of $45,000 per QALY. Omalizumab, however, will remain in the market because it possesses a unique mechanism of action and provides great benefits to patients with severe asthma, particularly responders. The cost-effectiveness of omalizumab may be improved if omalizumab therapy could be confined to previously predicted responders. Future studies to investigate prediction methods for the identification of responders are of great value. Caution, however, is required in interpreting the EVPI for omalizumab response, given the assumptions and the structural uncertainties. We look forward to a reduction in the price of omalizumab, which will improve cost-effectiveness.

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