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Cost-effectiveness of omalizumab for the treatment of inadequately controlled severe allergic asthma in Chinese children

Hua Zhou, MD^a, Yanming Lu, MD^b, Bin Wu, PhD^c , and Datian Che, MD^a

^aDepartment of VIP, Shanghai Children's Hospital, affiliated with the School of Medicine, Shanghai Jiaotong University, Shanghai, China; ^bDepartment of Pediatrics, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China; ^cMedical decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China

ABSTRACT

Objective: The addition of omalizumab to standard therapy has proven to be efficacious in children with severe allergic asthma. The goal of this study was to assess the cost-effectiveness of adding omalizumab to standard treatment for asthma in Chinese pediatric patients.

Methods: A Markov model was constructed to project the health and economic outcomes in pediatric patients with severe allergic asthma. Model inputs were obtained from the literature. Cost and quality-adjusted life-years (QALYs) were measured over a five-year time horizon. One-way and probabilistic sensitivity analyses were conducted.

Results: For the base-case analysis, the addition of omalizumab to standard therapy yielded an incremental cost of \$49,047 for 0.232 incremental QALY, led to an incremental cost-effectiveness ratio of \$211,217/QALY. Sensitivity analyses were robust for these results.

Conclusions: This study found that the addition of omalizumab is not a cost-effective strategy compared with standard therapy for children with severe allergic asthma in China due to its high cost.

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Introduction

Asthma is characterized by chronic airway inflammation and has caused a substantial, global disease burden that is among the top 20 chronic conditions in the global ranking of disability-adjusted life years in children [1]. The Chinese all-age disability-adjusted life-years caused by asthma in 2010 was approximately one million [2,3]. The prevalence of asthma, percentage of acute asthma attacks and frequency of hospitalizations for asthma attacks are roughly 3%, 77% and 47% in Chinese children aged 0–14 years, respectively [4]; however, the use of therapeutic drugs at home remains insufficient [3]. In patients with asthma, approximately 20% have severe asthma, of which 20% is inadequately controlled [5]. Inhaled corticosteroids (ICS) and a long-acting beta-agonist (LABA) are prescribed for these patients; however, a considerable proportion remain poorly controlled and present with an increased risk of asthma exacerbation with a decline in lung function, leading to hospital admissions and unscheduled visits [6,7]. Uncovering novel

therapeutic options for this subgroup of patients is urgent because children with severe asthma have poor quality of life and require more health-care resources.

Inflammation commonly leads to the pathogenesis of asthma, and IgE-mediated responses are crucial for allergic asthma [5]. Higher mean immunoglobulin E (IgE) levels are found in a majority of pediatric patients with severe asthma compared to those with moderate or mild asthma, so there is a strong rationale for treating this population of patients with anti-IgE therapy. As the first approved humanized monoclonal anti-IgE antibody that binds IgE, omalizumab blocks the allergic cascade by preventing the interaction between IgE and its receptors on mast cells and basophils. Based on the results of a meta-analysis that pooled three clinical trials, omalizumab as an add-on to standard therapy is well-tolerated and reduces exacerbations (RR = 0.48, 95% confidence interval [CI]: 0.38–0.61) in children [8,9]; however, due to the high cost of omalizumab, the economic outcome of omalizumab as an add-on therapy is of major concern for children's parents or decision makers. Although

CONTACT Datian Che, MD  chedd@shchildren.com.cn  Department of VIP, Shanghai Children's Hospital, affiliated with the School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China; Bin Wu  wubin@renji.com  Medical Decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China.

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several economic studies evaluated the cost-effectiveness of omalizumab treatment for asthma [10–12], economic evaluations from the perspective of middle-income regions are lacking for asthmatic children.

Accordingly, the goal of this study was to conduct an economic evaluation to determine whether omalizumab as an add-on to standard therapy was cost-effective in Chinese children with severe allergic asthma.

Methods

Analytics overview

A Markov model of asthma was developed to estimate the clinical and economic implications of different strategies for uncontrolled severe persistent allergic asthma. A diagram of this model is presented in Figure 1. The time horizon was set at five years and was in line with similar cost-effectiveness studies [13]. The model cycle length was one week, which allowed for the modeling of exacerbation as an independent health state [14]. The model was composed of four mutually exclusive health states: no exacerbation, exacerbation with an unscheduled visit, exacerbation with hospitalization and death. The characteristics of the population in this study were assumed to be comparable with a Chinese study that enrolled 1158 children with moderate-to-severe asthma [15]. The mean age of the children was approximately seven years old, with a range of 3 to 13 years.

The primary outcome measurements were quality-adjusted life-years (QALYs) and cost, which were annually discounted at 5%, in line with the Chinese guidelines for pharmacoeconomic evaluations [16]. Incremental cost-effectiveness ratios (ICERs),

presented as the cost per additional QALY gained, were calculated. When the ICER was lower than the three times the per capita gross domestic product (GDP) of China in 2017 per QALY gained (\$27 351/QALY), the intervention was cost-effective [17].

Treatment comparisons and efficacy

The treatment strategies in this study were based on the current Chinese guidelines for asthma [18] and are also in line with the Global Initiative for Asthma (GINA) treatment strategy [19]. Two competing alternatives were evaluated: standard treatment with high dose ICS + LABA (standard strategy) and add-on treatment with omalizumab (omalizumab strategy). Standard therapy was defined by Steps 3 and 4 of the GINA treatment strategy [19].

The efficacy and safety profile of omalizumab in Chinese patients with asthma was comparable to that of the global population [20]. Due to the absence of specific data for Chinese children, we assumed that the clinical data in this population were also similar with those of the other population, and the clinical inputs used in the study were extracted from clinical trials regardless of region. In a Japanese trial, the rate of asthma exacerbations per patient-year in the standard strategy group was 2.99 [6], and this rate was applied to our analysis because of the similar ethnicity groups. By including three randomized, controlled trials (1381 asthmatic children and adolescents) [21–23], one recent meta-analysis showed that the risk ratio (RR) of significant asthma exacerbations between omalizumab and the standard strategy was 0.69 (range: 0.32–0.80) [9], whose lower limit in range was extracted from a subgroup analysis who had better

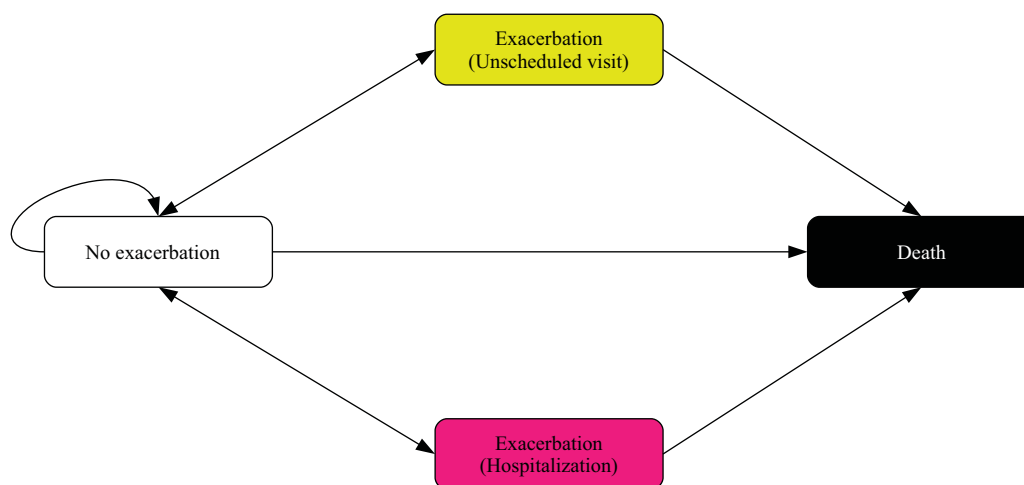


Figure 1. Diagram of the cost-effectiveness model structure. The description about transition probabilities could be found in the text and Table 1.

response of omalizumab treatment [21–23]. The proportions of hospitalizations in children with exacerbation were 12.0% and 7.8% for the standard and omalizumab strategies [21–23], respectively. The case-fatality of hospitalization due to asthma exacerbation was 0.25% [24]. The current analysis did not consider the impact of adverse events because the risk of adverse events was similar between the two strategies [9]. The probability of transition to death in free exacerbation and exacerbation with unscheduled visits was estimated as the background mortalities and were obtained from the life tables of the World Health Organization (WHO) member states (2011) [25].

Estimates of health state costs and utilities

In this study, analyses were performed from a health-care perspective and included direct medical costs to the health-care system and patient, such as medication, number of patient visits and hospitalization due to exacerbation (Table 1). Indirect costs, such as productivity costs to patients or caregivers, were not considered. The Chinese Yuan was converted to US dollars using the following exchange formula: 1US\$ = CNY 6.5. The costs of the standard therapy were calculated based on the literature and included 155 outpatient persistent asthmatic children from 2012 to 2014 in four Chinese hospitals [26]. Based on the GINA guidelines, the costs of managing asthma were estimated over 12 weeks. Based on the administration schedule of clinical trials and Chinese expert opinion, omalizumab was administered every 2 weeks via a subcutaneous injection with a dose of 0.016 mg/kg/IgE (IU/ml) [22,23]. To estimate the dosage of omalizumab, we assumed that asthmatic children aged

seven years old in China had a body weight of 23.82 kg [27] and that total serum IgE was 335.5 (range: 33.6–1050.0) IU/mL [6]. The cost of omalizumab was based on the number of 150 mg vials available in China. The cost of omalizumab and its administration per unit were collected from local hospitals. Similar to a previous study, children on omalizumab treatment were assessed for their response at 16 weeks, and responders were separated from nonresponders [11]. The proportions of responders were derived from a previous report [11,28]. The costs of hospitalization and unscheduled visits resulting from asthma exacerbation were collected from previous Chinese economics studies [24,29].

The health state utility values for free exacerbation and exacerbation states were extracted from representative publications [24,29] that reported utility values in asthmatic children. We assumed that the utility values related to asthma in Chinese children were similar across different regions.

Analyses

The marginal costs and QALYs of omalizumab versus those of the standard strategy were measured and used to calculate the ICER value. The marginal cost included both drug and nondrug costs. The base-case results were generated using the expected values.

Serial deterministic sensitivity analyses were performed to test the robustness of the model outcomes for individual parameters. The clinical, utility and drug cost data were adjusted using their lower and upper boundaries of the 95% confidence interval when available. When such data were not available, we used $\pm 20\%$ of the base case input estimate.

Table 1. Model inputs.

Parameters	Expected values	Ranges	Source
Clinical inputs			
Body weight (kg)	23.82	20–150	[27]
Total immunoglobulin E level (IU/mL)	335.5	33.6–1050	[6]
Probability of exacerbation in standard strategy per week	0.056	0.029–0.06	[6]
HR of exacerbation of omalizumab versus standard strategy	0.69	0.59–0.8	[9]
Proportion of exacerbation requiring hospitalization in omalizumab strategy	0.078	0–0.142	[9]
Proportion of exacerbation requiring hospitalization in standard strategy	0.12	0.019–0.225	[9]
Case-fatality of hospitalization due to exacerbation	0.0025	0.0019–0.0031	[24]
Cost inputs (\$)			
Omalizumab per 150 mg	553.8	276.9–553.8	Local charge
Hospitalization per event	1391.5	989.4–2005.4	[24]
Administration of omalizumab per unit	3.08	2.31–5.38	Local charge
Standard treatment per week	10.9	10.2–11.5	[26]
Unscheduled visit per event	27.8	10.8–44.8	[29]
Utility inputs			
Free exacerbation in standard strategy	0.719	0.693–0.745	[11,28]
Free exacerbation in omalizumab strategy	0.767	0.747–0.787	[11,28]
Exacerbation requiring hospitalization in standard strategy	0.631	0.57–0.692	[11,28]
Exacerbation requiring hospitalization in omalizumab strategy	0.761	0.715–0.807	[11,28]
Disutility of exacerbation requiring unscheduled visit	0.15	0.1–0.2	[11,28]

Table 2. Clinical and cost-effectiveness results for the base case.

	Unscheduled visit (per patient-year)	Hospitalization (per patient-year)	Cost (\$)	QALYs	LYs	ICER(\$/QALY) ^a
Standard strategy	2.409	0.329	4935	3.227	4.991	–
Omalizumab strategy	1.773	0.150	53,982	3.460	4.997	211,217

^aComparing with standard strategy.

Probabilistic sensitivity analysis (PSA) was conducted by using Monte Carlo simulation with 1000 iterations; in each iteration, the value of each model input was changed at random, and the model outputs were extracted. The probabilities, proportions and utilities were sampled against a beta distribution; hazard ratio (HR) used a normal distribution, and costs used a log-normal distribution. The main presentation of the PSA was the cost-effectiveness acceptability curve.

Results

Cost-effectiveness results

In Chinese children with severe allergic asthma, the addition of omalizumab is expected to reduce unscheduled visits by 26.4% and hospitalizations per patient-year by 54.4% in comparison with the standard strategy (Table 2). Although life expectancies only have a paucity of change over a five-year time horizon, the addition of omalizumab provided an additional 0.232 QALYs, with incremental discounted costs of \$49 047. Thus, it was estimated that the ICER of omalizumab compared to that of the standard strategy was \$211 217 per QALY gained over a five-year time horizon.

Sensitivity analyses

One-way sensitivity analyses showed that the model results were robust to changes in these model inputs (Figure 2). The model outcomes were more sensitive to body weight because this parameter had the greatest impact on the ICER, suggesting that the omalizumab strategy would become more unfavorable as body weight increased. Other considerable influential variables included the total immunoglobulin E levels, utility of free exacerbation in the omalizumab and standard strategies, and cost of omalizumab. Other adjustments of these parameters, such as the probability of exacerbation and discount rate, had a paucity of impact on the model outcomes.

Compared to the standard strategy, the cost-effectiveness acceptability curves showed that the omalizumab strategy produced nearly zero probabilities of cost-effectiveness when the threshold was equal to \$27 351 (Figure 3).

Discussion

Reports of health benefits from the addition of omalizumab to standard therapy in clinical trials were well-received by pediatricians and parents of children with asthma; however, the widespread use of omalizumab is associated with a dramatic increase in health-care costs, which is a concern for clinicians and administrators. The need for a precise economic evaluation of omalizumab use in a clinical setting is necessary; however, there are only a few economic evaluations of omalizumab in children with asthma. To our knowledge, this was the first study to report the economic outcomes of omalizumab as an add-on therapy in children with uncontrolled, severe persistent allergic asthma in a middle-income region.

This economic analysis found that the addition of omalizumab improved the clinical outcomes of children with uncontrolled, severe persistent allergic asthma but at a greater cost to the Chinese health-care system. The ICER of omalizumab versus that of the standard strategy was more than \$200 000/QALY gained and was far higher than the Chinese willingness-to-pay threshold (\$27 351/QALY). This unfavorable finding is largely attributable to the higher costs associated with the acquisition of omalizumab, whereas the costs of other drugs in the standard strategy had less impact. One-way sensitivity analysis showed that when the price of omalizumab was reduced by 50%, the ICER of the omalizumab strategy decreased from \$211 217 to \$103 636 per QALY gained. Recently, the Chinese central government implemented a pilot project for negotiations involving innovative, expensive medicines that were outside of the National Formulary [30]. In this drug negotiation, the prices of expensive drugs, such as bevacizumab, were discounted more than 60%. The cost-effectiveness of omalizumab could be improved under a negotiated price. Although a higher discount rate could result in less favorable ICERs because costs related to omalizumab occur early and most economic and health benefits are realized in the future, discount rate had few impacts in the current analysis due to the short time horizon (five years) of the model.

Several studies have investigated the economic outcomes of omalizumab as an add-on to standard therapy for patients with uncontrolled allergic asthma

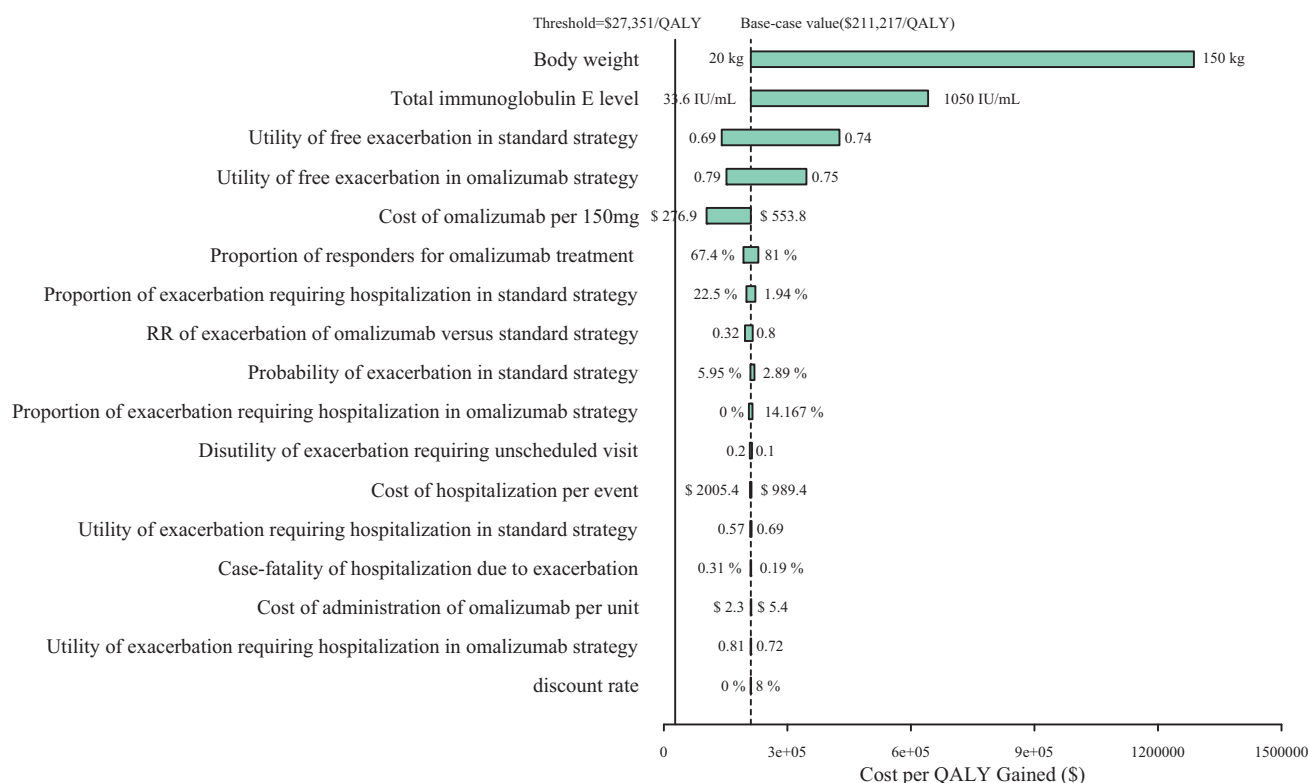


Figure 2. One-way sensitivity analyses of the omalizumab strategy in comparison with the standard strategy.

[12,28]; our findings are consistent with the results of these previous reports. For children aged 6–11 years in the United Kingdom, omalizumab add-on therapy led to an increase of more than £30 000/QALY compared with the standard therapy alone for the overall population or subgroups [11,28]; however, the addition of omalizumab could become cost-effective if the patient access scheme discounted price used at the UK National Health Service was implemented. One-way sensitivity analyses showed these UK-based findings to be robust across a wide range of alternative proposals. A greater number of economic studies have been performed in adults and indicate that omalizumab is not a cost-effective alternative in the majority of countries. The ICERs of omalizumab as an add-on therapy for allergic asthma ranged from €23 880/QALY in Italy to \$287 200/QALY in the United States [12]. These studies also found that a reduction in the price of omalizumab resulted in a considerable decrease in the ICER. One recent study found that the addition of omalizumab was more cost-effective than the standard therapy alone for adult patients with uncontrolled, severe allergic asthma in a middle-income setting [31]. This Brazilian study found that omalizumab as an add-on therapy could result in an increase of 5.20 QALYs, with an increment of R\$280 400, and yield an ICER of R\$53 890 that was lower than the local willingness-to-pay threshold.

The economic results were more unfavorable toward omalizumab, assuming the increased weight and total immunoglobulin E levels, resulting in higher ICERs due to the requirement for increased omalizumab dosages. Two main issues arise: first, whether a small dosage of omalizumab, such as a 75 mg prefilled syringe, could be available for children in China, and second, whether the cost could be paid per patient instead of per vial. The first issue is essentially an industrial question that may be related to production costs and can be resolved by adding the costs related to prefilling syringes. Omalizumab is available as 75 and 150 mg prefilled syringes, and the price of 75 mg per vial is approximately half that of 150 mg per vial. We are hopeful that a small dosage of omalizumab could be approved for Chinese children, as a small dosage could save money by preventing the waste of unused omalizumab when only a 150 mg per vial was available. One example is if a child required the administration of omalizumab 200 mg, but only 150 mg per vial was available, they would be required to pay for two vials of omalizumab. If the 75 mg per vial was available, they could pay for one high dosage of omalizumab (150 mg per vial) and one small dosage of omalizumab (75 mg per vial). Another issue is intrinsic to the reimbursement process. We need to implement new payment programs, such as the value-based payment model [32].

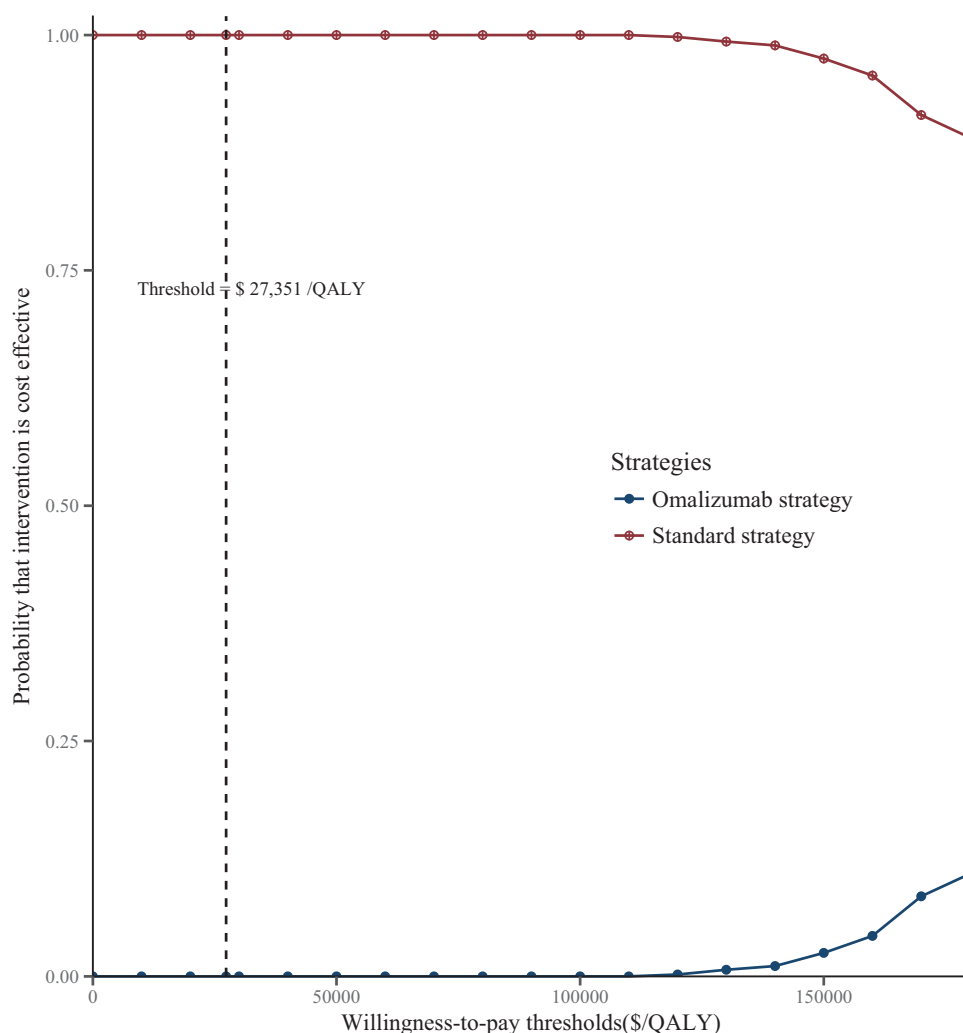


Figure 3. Cost-effectiveness acceptability curves for the omalizumab strategy in comparison with the standard strategy.

There are some limitations to our study—first, the perspectives of health-care were adopted and we did not consider indirect costs, such as the loss of productivity. One Chinese study found that parents of children with asthma lost approximately 10 days of working hours annually [33]. When the indirect benefits of omalizumab as an add-on therapy are considered, its cost-effectiveness may be improved. Second, we did not evaluate other new competing therapies for asthma, such as mepolizumab and reslizumab, because they have not been approved in China [34,35]. Third, our analysis did not consider a bronchial thermoplasty, which was comparable with omalizumab with an indirect treatment comparison [36]; however, there is no evidence regarding the efficacy of this procedure in children [37]. Fourth, a previous study found that the addition of omalizumab might be cost-effective in some subgroups, such as people experiencing an exacerbation that resulted in hospitalization, but our analysis did not evaluate the cost-

effectiveness of omalizumab treatment in subgroup cohorts because treatment efficacy of omalizumab only had a paucity of impact on the economic outcomes even when the RR decreased to the lowest boundary (0.32) in sensitivity analyses. Finally, we did not carry out a budget impact analysis of omalizumab as an add-on therapy with the standard treatment. Recent published data showed that the prevalence of asthma was approximately 3.0% in Chinese children aged 0–14 years [4]. Due to the large population size and high prevalence of asthma in China, the financial burden of covering omalizumab is likely high.

In summary, these results showed that omalizumab as an add-on therapy is not cost-effective compared to current standard treatments; this conclusion is based on the generally accepted Chinese cost-effectiveness threshold of \$27 351 per QALY gained. These findings were consistent regardless of changes in the adjustment of parameters within the model. In conclusion, Chinese children with uncontrolled, severe persistent

allergic asthma are recommended the standard treatment with ICS plus LABA until a reduction in the price of omalizumab allows it to be a more cost-effective treatment strategy.

Disclaimer

The views expressed are those of the authors. The funding agencies played no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Disclosure statement

None of the authors have anything to declare.

Ethics approval

This economic analysis was based on a literature review and modeling techniques; this study did not require approval by an Institutional Research Ethics Board.

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ORCID

Bin Wu  <http://orcid.org/0000-0002-4867-929X>

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