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Cost effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting

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CS, NLS, PK, and PP are employees of Novartis. SHO was employed by Novartis at the time of development of this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Author contributions

All authors were involved in drafting, reviewing, and approving the manuscript. In addition, all authors were involved in the adaptation of the cost-effectiveness model.

Abstract

Objective: Omalizumab add-on to standard-of-care therapy has proven to be efficacious in severe asthma patients for whom exacerbations cannot be controlled otherwise. Moreover, evidence from different healthcare settings suggests reduced healthcare resource utilization with omalizumab. Based on these findings, we aimed to assess the cost effectiveness of the addition of omalizumab to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting.

Methods: A previously published Markov model was adapted using Brazil-specific unit costs to compare the costs and outcomes of the addition of omalizumab to standard-of-care therapy versus standard-of-care therapy alone. Model inputs were largely based on the eXpeRience study. Costs and health outcomes were calculated for lifetime-years and were annually discounted at 5%. Both one-way and probabilistic sensitivity analyses were performed.

Results: An additional cost of R\$ 280,400 for 5.20 additional quality-adjusted life-years was estimated with the addition of omalizumab to standard-of-care therapy, resulting in an incremental cost-effectiveness ratio of R\$ 53,890. One-way sensitivity analysis indicated that discount rates, standard-of-care therapy exacerbation rates, and exacerbation-related mortality rates had the largest impact on incremental cost-effectiveness ratios.

Limitations: Assumptions of lifetime treatment adherence and rate of future exacerbations independent of previous events might affect the findings. Lack of Brazilian patients in the eXpeRience study may affect the findings, although sample size and baseline characteristics suggest that the modelled population closely resembles Brazilian severe allergic asthma patients.

Conclusion: Results indicate that omalizumab as an add-on therapy is more cost-effective than standard-of-care therapy alone for Brazilian patients with uncontrolled severe allergic asthma, based on the World Health Organization's cost-effectiveness threshold of up to 3 times the gross domestic product.

Keywords: asthma, omalizumab, cost-effective, Brazil, costs, quality-adjusted life-years

Introduction

Over 330 million individuals have asthma worldwide¹, and Brazil has one of the highest prevalence rates of asthma in the world, ranging from 10% to 20%², with approximately 15 million asthma patients as estimated by the Pan American Health Organization in 2009³.

Although asthmatic patients are assisted with the currently available drugs in Brazil's federal public healthcare system, asthma-related outcomes continue to persist. Asthma continues to be one of the main causes of hospitalization in Brazil, with approximately 154,000 asthma-related hospitalizations reported in the last 5 years, imposing a huge social and economic burden⁴. During the same period, asthma was the cause of approximately 2500 deaths per year in Brazil, representing approximately seven avoidable deaths per day⁴.

Overall, 10% to 20% of asthma patients have severe asthma^{5,6}. According to the Global Initiative for Asthma (GINA) guidelines, severe asthma is defined as asthma that requires step 4 or 5 treatment with high-dose inhaled corticosteroids (ICS) plus a second controller medication (long-acting beta agonist [LABA], leukotriene modifier, theophylline, or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite therapy⁷. A cohort study conducted in Brazil among children with moderate to severe persistent asthma reported that in approximately 60% of patients, asthma remained uncontrolled despite treatment with ICS for 12 months⁸.

Patients with severe allergic asthma, belonging to GINA step 4, have frequent exacerbations that cannot be controlled even with the best available care^{9,10}. These patients are at a high risk of severe exacerbations, emergency room (ER) visits, hospital admissions, and death¹¹. Although patients with uncontrolled asthma represent a relatively small proportion of all asthma patients in Brazil, healthcare expenditure was approximately eight times higher in these patients (R\$503 [US \$125]) compared to those with controlled asthma (R\$64 [US \$16]), and was mostly driven by ER visits and hospitalization¹². This suggests that a considerable healthcare cost reduction can be achieved if disease control is improved in patients with uncontrolled asthma.

Omalizumab is an add-on therapy that has proven to be efficacious in patients with severe allergic asthma whose disease cannot be controlled otherwise^{9,10}. However, not all patients respond to omalizumab treatment, and the response status is best evaluated by the physician using the Global Evaluation of Treatment Effectiveness (GETE) questionnaire at 16 weeks of treatment¹³. Patients who respond to omalizumab add-on therapy have reduced exacerbation rates and ER visits and improved health-related quality of life (HRQoL) and symptom control compared to patients receiving optimal standard-of-care therapy^{9,14-16}.

The present analysis, therefore, aimed to determine the cost effectiveness of omalizumab as an add-on to the best available standard-of-care therapy from the Brazilian healthcare perspective. Inputs were obtained from the recently conducted largest, multinational, observational study, eXpeRience¹⁷, which showed reductions in healthcare resource utilization with add-on omalizumab treatment. This analysis would allow a comprehensive economic assessment of omalizumab in a real-world setting using clinical practice patterns.

Methods

Model structure

A previously published Markov model¹⁸⁻²⁰, which was developed in Microsoft Office® Excel, was adapted using Brazil-specific unit costs to compare the costs and outcomes from Brazil's public healthcare

perspective of high-risk asthma managed with standard-of-care therapy alone (ICS + LABA + rescue medication including oral corticosteroids [OCS] and short-acting beta agonist [SABA]) versus omalizumab added on to standard-of-care therapy. Six health states were included in this model: “day-to-day asthma symptoms with omalizumab add-on therapy” (GETE responders), “day-to-day asthma symptoms with standard-of-care therapy” (and omalizumab non-responders), “clinically significant non-severe (CSNS) exacerbation,” “clinically significant severe (CSS) exacerbation,” “death from all causes,” and “asthma-related death” (Figure 1) Exacerbations were modeled as events in this model since a patient could experience more than one exacerbation in a cycle of 3 months.

Patients started in the appropriate day-to-day asthma symptom state based upon their treatment. In subsequent model cycles, patients could change health states or remain in the same health state, depending on transition rates. Each cycle was of a 3-month duration, and the time horizon of the model was lifetime. The treatment duration with omalizumab was also set for lifetime. Costs and health outcomes were annually discounted at 5%.

Model inputs

Clinical data

The model included clinical data from the eXpeRience study²¹. This was a single-arm, open-label, observational registry, that enrolled patients from 14 countries in Europe, America, and Asia and followed them up for 2 years while they were on omalizumab treatment.

Modelled population

The present cost-effectiveness analysis included 416 of the 943 patients enrolled in the eXpeRience study for whom complete data were available and patients were taking omalizumab on the basis of response evaluation at 16 weeks. The modelled population was taken as a subset of study population to ensure that effects observed were wholly attributed to omalizumab, because the model follows the same patient when he/she was not taking omalizumab (one-year prior to baseline) and when he/she was taking omalizumab (until 2 years post baseline). With this approach, it was possible to attribute differences in outcomes to omalizumab treatment due to pre-post design allowing for participants to act as their own control. Furthermore, the criteria used to arrive at the modelled population do not unduly favor one over the other and hence there is no selection bias.

Table 1 shows that the baseline characteristics of the modelled population are not significantly different (at 5% level) from that of the eXpeRience study population except for baseline IgE levels. This is justified considering that IgE levels affect dosage of omalizumab and this analysis has used doses as per the modelled population. Therefore, impact of different IgE levels has been captured in calculation of drug costs.

Model assumptions

The Brazilian population with severe, allergic, uncontrolled asthma was assumed to be similar to the eXpeRience study population used in the analysis (average age: 45 years; male: 36%). All patients were assumed to adhere to therapy. Omalizumab responders (assessed using the GETE questionnaire) were identified at Week 16, and non-responders discontinued omalizumab treatment and continued on standard-of-care therapy for the rest of the model.

Exacerbation rates

Costs and outcomes were calculated using the rates of clinically significant (CS) and CSS exacerbations with standard-of-care and omalizumab add-on therapies (Table 2). The exacerbation rates were

calculated using the number of exacerbations occurring by treatment group over a specific time and were adjusted by the years of exposure to obtain an annual exacerbation rate. These were proportionally applied to the quarterly cycles. The standard-of-care therapy group included in the analysis was defined as all patients in the eXpeRience study without a history of omalizumab treatment, with GETE response evaluation within 16 ± 1 weeks, and for whom complete data on exacerbations were available. This group included 416 patients. The omalizumab add-on therapy group was categorized into GETE responders ($n=312$) and GETE non-responders ($n=104$) at Week 16. CS exacerbations were then split between severe and non-severe exacerbations using the proportion that was observed in the study. CS asthma exacerbations that were not severe were assumed to be CSNS exacerbations.

Mortality data

Age-related mortality rates were calculated using Brazil's general population mortality rates based on population characteristics of the eXpeRience study (average age: 45 years; male: 36%). Asthma-related mortality was calculated by applying a rate of 2%, which describes the fatality rate associated with CSS exacerbations in asthma⁴. This rate was calculated based on hospitalized patients aged over 45 years. The risk of asthma-related death was applied to CSS exacerbations only, regardless of the treatment.

Utility data

For the "day-to-day asthma symptoms" state, utilities, which represent the strength of an individual's preference for specific health-related outcomes, were derived from the Asthma Quality of Life Questionnaire (AQLQ) values collected in the eXpeRience study. The AQLQ values were then mapped onto 5-dimension EuroQol (EQ-5D) questionnaire to derive utilities, using the mapping function developed at the University of Sheffield (Table 3)²². Furthermore, utility gain calculated in the QUALITX study²³, a 20-week, randomized, open-label study involving Brazilian patients (aged above 12 years) with severe, persistent, allergic asthma, which assessed the mean change from baseline in overall AQLQ score with omalizumab versus standard-of-care therapy, was used in the sensitivity analysis (Table 3).

A prospective study conducted in the UK provided EQ-5D scores for patients on OCS who were approximated to be in the CSNS exacerbation state (0.572) and for hospitalized patients who were approximated to be in the CSS exacerbation state (0.326)²⁴.

Resource use and cost data

The resource use data in terms of unscheduled general practitioner (GP) visits, hospital outpatient visits, ER visits, hospital admissions, and rescue medication were collected from the INNOVATE trial⁹, unlike the eXpeRience study, where the resource use data were recorded by the type of exacerbation (i.e., severe or non-severe). The components included under costs were exacerbation costs, routine visit costs, and drug costs. Brazil-specific unit costs were applied to the resource use data to calculate the costs in R\$. Unit costs of GP visit (R\$ 10), hospital outpatient visit (R\$ 10), and ER visit (R\$ 12.47) were obtained from SIGTAP²⁵. The hospitalization (in general ward) cost (R\$ 541.69) was based on average values spent on hospitalizations caused by asthma in the year 2014⁴. The SABA salbutamol (aerosol spray, 100 µg per dose) was considered as the rescue medication, and the cost for the exacerbation period was calculated according to the recommended dose for acute asthma exacerbations, based on the drug prescribing information. The unit cost of medication was based on the lowest acquisition cost in the year 2015 (R\$ 1.38/puff)²⁶.

Resource use related to severe and non-severe exacerbations was analyzed from the INNOVATE trial. Both types of exacerbations were reported to last for an average of 12.8 days²⁷. The exacerbation cost

was the same regardless of the treatment received. The average cost of a CSNS exacerbation was estimated to be R\$ 50.9 and that of a CSS exacerbation was estimated to be R\$ 75.09. For standard-of-care therapy, all patients were assumed to be receiving ICS and LABAs. However, patients were also receiving SABAs (64.2%) and OCS (30%) in the analyzed sample of the eXpeRience study (416 patients). The drug costs were taken from the Health Price Database of the Brazilian Ministry of Health (BPS, from Brazilian Portuguese, Banco de Preços em Saúde) based on the lowest acquisition price of the public health sector in Brazil in 2015. The total annual cost was estimated to be R\$ 1229. Drug costs for omalizumab were calculated using the dosing schedule from the eXpeRience study. The annual total costs, which included drug and administration costs, were R\$ 23,863 based on vial use and R\$ 21,795 based on mg used. A reduction of approximately 65% on drug acquisition cost was also considered. Because the payers' perspective was considered for the base case analysis, only direct medical costs were included.

One-way sensitivity analysis

The model was tested for robustness using a sensitivity analysis. The following parameters were varied to analyze the impact of changes on the results: time horizon (20 years), different assumptions on discount rates (5% for costs and 0% for outcomes, no discounting), duration of omalizumab treatment (10 years), standard-of-care therapy exacerbation rate of 2 per year to 7 per year, utility values of omalizumab responders from the QUALITX study, considering mortality rate of 3.108% from a community-based study^{18,28} and of 0.5% in the hospitalized patients aged over 45 years in the Brazilian general population in 2014, obtained from the DATASUS (federal public healthcare system database)⁴ and cost of CSS exacerbation assumed to be R\$ 200 and R\$ 150 for CSNS exacerbation.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the uncertainty around the estimated values. The analysis was based on 1000 simulations. Parameters considered in the PSA were discounted at 5% for costs and quality-adjusted life-years (QALYs), 55 years of omalizumab treatment, and response evaluation at Week 16 based on good and excellent responders according to the GETE questionnaire.

Results

Base case results

Addition of omalizumab to standard-of-care therapy was associated with an incremental cost-effectiveness ratio (ICER) of R\$ 53,890 for each QALY gained (Table 4). Compared with standard-of-care therapy alone, for 100 patients, the number of CSNS exacerbations avoided with the addition of omalizumab to standard-of-care therapy was 2684, whereas the number of CSS exacerbations avoided was 2603 (including the number of asthma deaths).

Scenario analysis showed that the ICER was reduced by 60% when costs were discounted at 5% and outcomes at 0%. The utility values for omalizumab responders from the QUALITX study decreased the ICER by only 1%, indicating that the utility gain observed in the QUALITX and eXpeRience studies was similar. On the other hand, considering a mortality rate of 0.5% for asthma in the general Brazilian population (DATASUS 2014) increased the ICER by 45% as shown in the sensitivity analysis (Figure 2). Including an exacerbation rate of 2 per year with standard-of-care therapy also increased the ICER by 35% (Figure 2).

The results of the PSA showed that in all of the simulations, addition of omalizumab to standard-of-care therapy increased the amount of costs incurred and QALYs gained (Figure 3). Within the PSA, the average incremental cost was estimated at R\$ 280,268, and it varied between R\$ 244,697 and R\$

348,071, whereas the incremental QALYs were calculated to be 5.20, ranging between 4.44 and 6.72.

Discussion

An extensively published Markov model was adapted using Brazil-specific unit costs to estimate the economic value of omalizumab add-on therapy in the Brazilian healthcare setting. This cost-effectiveness analysis aimed to assess the impact of improved clinical and real-world outcomes observed with omalizumab add-on therapy on healthcare costs, and inform decision makers about the costs and benefits of omalizumab add-on therapy when making treatment choices. The estimated ICER of R\$ 53,890 per QALY in the base case analysis indicated that omalizumab add-on therapy is cost effective in Brazil (Brazilian gross domestic product [GDP] per capita: R\$ 43,529.38 [US \$11,208.08] as of 2013) compared with the cost-effectiveness threshold values established by the World Health Organization-Choosing Interventions that are Cost Effective method, developed on GDP per capita (less than GDP per capita: very cost effective, 1-3 × GDP per capita: cost effective, and more than 3 × GDP per capita: not cost effective)^{29,30}.

Cost-effectiveness analyses based on randomized controlled trials largely represent results obtained under constrained ecology of care, and the question of external validity always remains, implying that the relevance of the findings to real-world settings is uncertain. Hence, inputs for the present analysis were obtained from a large real-life study with good methodological quality based on the Downs and Black checklist^{17,31}.

To our knowledge, this study is the first to incorporate real-world evidence in the economic evaluation of omalizumab in the Brazilian healthcare setting, and supports the findings from earlier randomized trials and previously published cost-effectiveness analysis of omalizumab in other jurisdictions. The present analysis used the long-term efficacy data from the eXpeRience study, in which omalizumab showed a continuous reduction in the number of exacerbations, thereby justifying the use of continuous treatment with omalizumab for GETE responders. Nevertheless, this analysis has several limitations. Firstly, it was assumed that patients were adherent to the standard-of-care and omalizumab add-on therapies throughout the lifetime horizon. However, in chronic illness, patients' persistence/adherence is generally poor, which questions this assumption. Assuming good treatment adherence for a longer period is reasonable considering omalizumab is administered in a hospital setting. Therefore, a patient will be less likely to miss an omalizumab dose than a standard-of-care therapy (ICS/LABA combination) as this is usually administered at home and requires the patient to take multiple doses in a day. The impact of this assumption does not unduly favor one over the other; rather it is conservative for omalizumab. Secondly, the model assumed that the rate of future events was independent of the events that occurred during previous cycles, which again contradicts the evidence available in the literature³²⁻³⁴. Thirdly, the eXpeRience study did not include any patients from Brazil. However, considering patients from America, Europe, and Asia were enrolled, it is plausible that this study population closely resembled the Brazilian population (Brazil is a remarkably heterogeneous country in terms of ethnicity, having descendants of Japanese, German, Arabic, African, Italian, Portuguese, Spanish, and South American origins). Moreover, the utility gain in patients included in the eXpeRience and QUALITX (a Brazilian study) studies was similar. Fourthly, the present study was based on the eXpeRience study that followed up patients for up to 2 years after omalizumab initiation. However, lifetime treatment duration with omalizumab was considered for the base case analysis since asthma is a chronic disease and shorter treatment durations were tested in the sensitivity analysis. Lastly, the resource use data during exacerbations were obtained from the INNOVATE trial, a randomized clinical trial which did not include any Brazilian patients. However, it was ensured that these resource use estimates were validated and

complemented by Brazilian experts to reflect the local practice. Additionally, the variations in the costs were tested in a sensitivity analysis, and no impact was observed on the ICER results.

A cost-effectiveness analysis of omalizumab as an add-on to standard-of-care therapy compared with standard-of-care therapy alone in patients with uncontrolled severe allergic asthma from the perspective of the Brazilian public healthcare system has also been previously published³⁵. However, this study was based on a randomized controlled trial and did not assess cost per QALY, as QALY data were not available. Rather, the study used cost per exacerbation avoided as an outcome and concluded that the acquisition cost of omalizumab treatment had a large impact on the results, suggesting that a reduction of 35% on the drug-acquisition cost should be applied to achieve a more favorable ICER. This study had a narrower perspective as it focused on exacerbations. It did not include other benefits relevant to asthma patients, e.g. reduced symptom burden, which are captured in the utility gain.

The cost-effectiveness of omalizumab addition to standard-of-care therapy in patients with severe allergic asthma has been evaluated under various international settings. European studies have shown that omalizumab is a cost-effective option, with the cost per QALY gained estimated between €23,880 and €56,091^{19,20,36,37}. Using data from the real-life, 1-year, randomized, open-label study ETOPA, omalizumab add-on therapy was shown to be a cost-effective option, with an estimated ICER of €31,209, in Canada¹⁸. In the US, the estimated ICER for omalizumab ranged from \$287,200 to \$821,000^{38,39}. The relatively low ICER calculated for omalizumab add-on therapy in Brazil, compared with European countries, Canada, and the US, is primarily due to the substantial differences in the price of omalizumab in these countries and also due to different sources and parameter inputs used, definition of standard-of-care therapy, and the assessed patient populations in these evaluations.

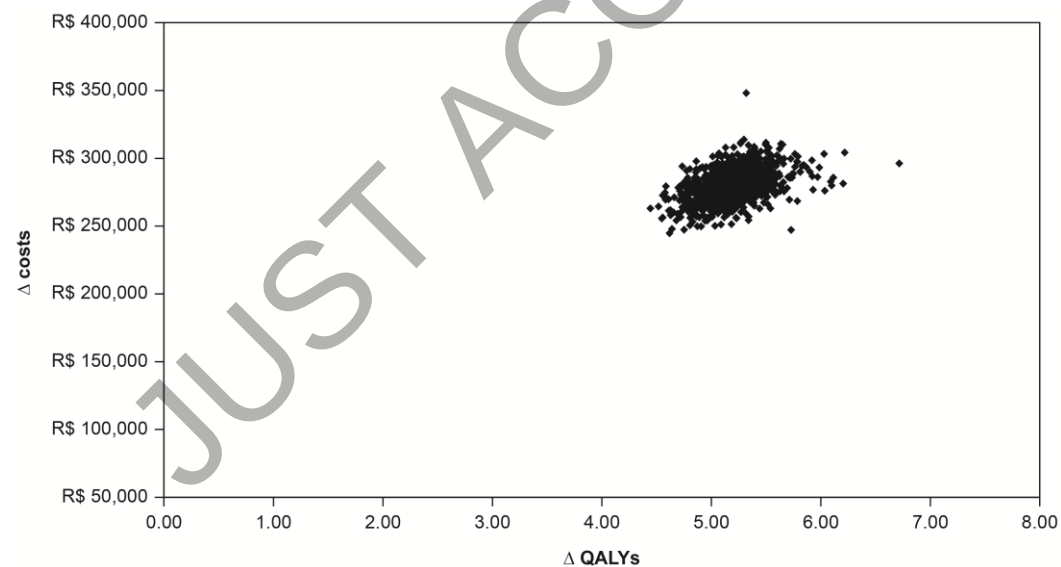
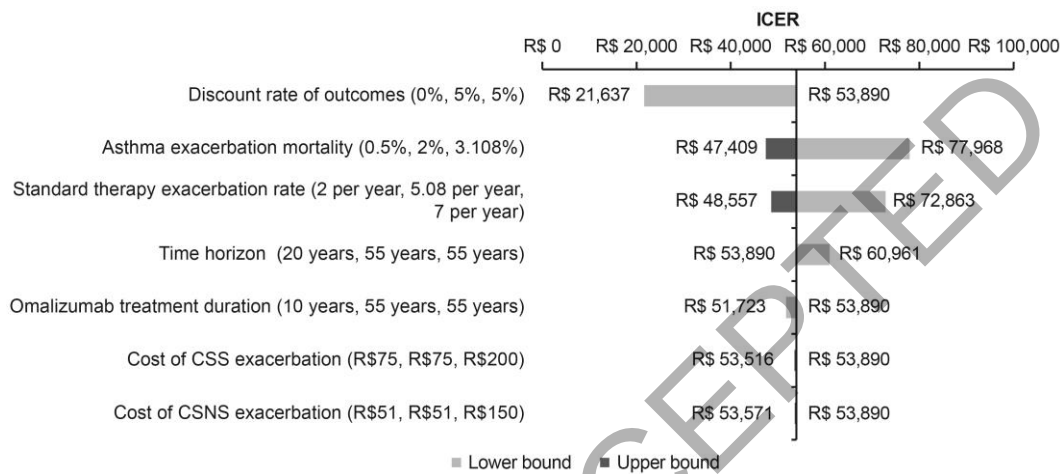
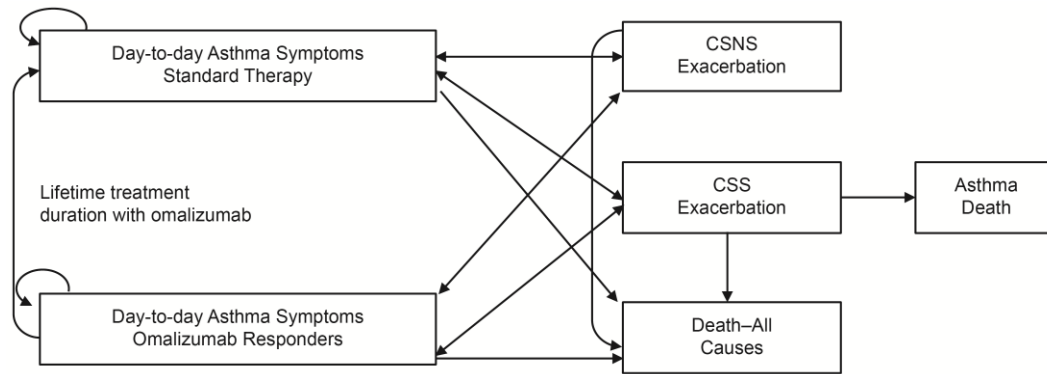
Conclusion

The study suggests omalizumab as add-on therapy to be a cost-effective option over standard-of-care therapy alone for treatment of patients with uncontrolled severe allergic asthma in the Brazilian healthcare setting.

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Tables

Table 1

Variable	Experience Population (N=925)	Model Population (N=416)
Age group		
< 12 years	2 (0.2%)	2 (0.5%)
12-17 years	51 (5.5%)	21 (5.0%)
18-64 years	796 (86.1%)	366 (88.0%)
> 65 years	76 (8.2%)	27 (6.5%)
Gender		
Male	325 (35.1%)	147 (35.3%)
Female	600 (64.9%)	269 (64.7%)
Positive skin-prick test/RAST for perennial aeroallergens	816 (88.2%)	373 (89.7%)
History of allergy to seasonal aeroallergens present	587 (63.5%)	259 (62.3%)
Smoking History		
Never smoked	719 (78%)	337 (81%)
Ex-smoker	173 (19%)	68 (16%)
Current smoker	30 (3%)	11 (3%)
Age, years		
Mean	45.0	45.3
SD	15.0	14.6
Body weight, kg		
Mean	75.5	75.5
SD	17.7	16.7
Baseline IgE level, IU/mL		
Mean	323.1	265.0
SD	460.9	191.3
Duration of allergic asthma, years		
Mean	19.4	19.6
SD	13.6	13.6

Table 2

Therapy	Time point	N	CS exacerbations, number (rate)	CSS exacerbations, number (rate)
Standard-of-care therapy	12 months before omalizumab initiation	416	2112 (5.08)	934 (2.25)
Omalizumab overall	Week 16	416	175 (1.37)	43 (0.34)
	Month 8	416	128 (0.85)	35 (0.23)
	Month 12	416	119 (0.86)	23 (0.17)
	Month 18	416	123 (0.59)	28 (0.13)
	Month 24	416	124 (0.60)	32 (0.15)
Omalizumab responders	Week 16	312	91 (0.95)	20 (0.21)
	Month 8	312	73 (0.65)	18 (0.16)
	Month 12	312	62 (0.60)	16 (0.15)
	Month 18	312	59 (0.38)	14 (0.09)
	Month 24	312	62 (0.40)	11 (0.07)

Table 3

Source	Standard-of-care therapy	Omalizumab	
		Complete control and marked improvement – Responder	All
eXpeRience study	0.608 (n=37)	0.821 (n=21)	0.810 (n=25)
QUALITX study	0.510 (n=37)	0.729 (n=58)	0.673 (n=78)
Sensitivity analysis inputs based on the QUALITX study	0.608	0.827	0.771

Table 4

Per patient	Total costs (R\$)	QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY
Standard-of-care therapy	15,340	5.64	R\$ 280,400	5.20	R\$ 53,890
Standard-of-care therapy + omalizumab	295,740	10.84			
Number of events per 100 patients	CSNS		CSS		Number of asthma deaths
Standard-of-care therapy	4681		3637		74
Standard-of-care therapy + omalizumab	1997		1087		22
Events avoided with omalizumab	2684		2551		52