Cost-effectiveness of subcutaneous house dust mite allergen immunotherapy plus pharmacotherapy for allergic asthma

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Abstract

Background: Current cost-effectiveness evaluations of the house dust mite (HDM) allergen immunotherapy fail to account for its effect on the reduction of exacerbations and medications while considering potential differences across patient populations. We aimed to evaluate the cost-effectiveness of subcutaneous immunotherapy (SCIT) plus inhaled corticosteroids (ICS) vs ICS for pediatric and adult patients with allergic asthma (AA) and AA with Allergic rhinitis (AR) from the health care system perspective. Methods: A Markov model with a 3-month cycle length and a 10-year time horizon was developed. A hypothetical cohort of eight years old patients with controlled (or partially controlled) AA was the base case population. Health states were: treatment with GINA Step-3, Step-2, medication-free asthma, and all-cause death. Effectiveness was measured by the reduction in medication doses and exacerbations. Scenario analyses were conducted considering allergic AR as a comorbid condition and an 18-years old cohort at baseline with or without AR. Results: In the base case, the SCIT+ICS would avert 847 exacerbations per 1,000 patients treated and generate additional 0.37 quality-adjusted life years (QALYs) and $836 costs per patient (SCIT+ICS=6.79 QALYs at a cost of $1,438/patient, ICS=6.42 QALYs at a cost of $601/patient). An incremental cost-effectiveness ratio (ICER) of $2,238 per QALY that fall below the willingness to pay threshold was obtained. The SCIT+ICS was also cost-effective among sub-groups of interest: adults win AA (ICER=$2,227) and AA+AR patients (8-years old cohort=$1,628, 18-years old cohort=$1,617). Conclusion: the SCIT+ICS can be cost-effective for pediatric and adult patients with AA with or without AR

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Conflicts of interests

Authors declare no conflict of interests

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Conception and design: DP, JZ, LC, NA, MC, EG. Model development and design: DP, MC, JZ. Interpretation of data: RD, MXR, MR, AP, GA, AGP, AB, LC, EG. Initial manuscript drafting: DP.

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Methods: A Markov model with a 3-month cycle length and a 10-year time horizon was developed. A hypothetical cohort of eight years old patients with controlled (or partially controlled) AA was the base case population. Health states were: treatment with GINA Step-3, Step-2, medication-free asthma and all-cause death. Effectiveness was measured by the reduction in medication doses and exacerbations. Scenario analyses were conducted considering AR as a comorbid condition and an 18-years old cohort at baseline with or without AR.

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Conclusion: the SCIT+ICS can be cost-effective for pediatric and adult patients with AA with or without AR

Keywords: allergen immunotherapy, asthma, cost-effectiveness analysis, economic evaluation

Abbreviations: SCIT (subcutaneous immunotherapy), ED (emergency department), WTP (willingness to pay), LABAs (long-acting beta2-agonists), healthcare resource utilization (HCRU), Inhaled corticosteroids (ICS), Allergic asthma (AA), Allergen immunotherapy (AIT), allergic rhinitis (AR), quality-adjusted life-years (QALYs), Global Initiative of Asthma (GINA), Colombian pesos (COP), American dollar (USD), randomized controlled trial (RCT), Beclomethasone Dipropionate (BDP), House Dust Mites (HDM), short acting beta agonists (SABA)

INTRODUCTION

As a high prevalent condition, asthma generates a substantial economic burden to the society and health care systems (1,2). Allergic asthma (AA) is the most frequent phenotype and is defined by the presence of sensitization to environmental allergens. Patients with AA experience a considerable burden in terms of poor health-related quality-of-life, productivity loss and healthcare resource utilization (HCRU) that increases with severity (3).

Inhaled corticosteroids (ICS) are the first line therapy recommended for the control of asthma symptoms due to their high anti-inflammatory effect. Despite its proven cost-effectiveness, their efficacy depends on its constant use over time and some patients remain with persistent symptoms resulting in adverse events in the long-term (4,5). New strategies with potential disease modifying effects should be evaluated in terms of their clinical and economic implications. Allergen immunotherapy (AIT) is the only therapy that can modify the

progression of allergic diseases by inducing immune tolerance (6). It is associated with reduction of HCRU and protective effect that can translate in potential cost-savings (7–9). Previous research suggests that AIT may be cost-effective for the treatment of patients with asthma (10,11). However, studies evaluating the cost-effectiveness of SCIT with HDM have been frequently based in randomized controlled trials (RCTs), and the use of relevant outcomes like exacerbations and medication step down is lacking. Potential differences in the cost-effectiveness across populations (e.g., children vs adults, patients with AA-only vs patients with AA and allergic rhinitis [AR]) have also been underexplored (10,12).

Model-based cost-effectiveness evaluations allows the combination of multiple sources of evidence, extrapolating results beyond the study length of clinical trials and converting treatment effects into policy-relevant outcomes (10,12). In this study, we sought to evaluate the cost-effectiveness of SCIT + ICS vs ICS for pediatric and adult patients with AA and AA with AR in Colombia through a decision-analytic modeling approach and multiple data sources, including parameters from real-world studies.

METHODS

Analytic overview

A model-based cost-effectiveness analysis was conducted to estimate the ratio of incremental costs and health benefits between SCIT + ICS (intervention strategy) versus ICS (comparator strategy). A hypothetical cohort (1,000 patients per strategy) of pediatric patients (8-year-old at baseline) with a diagnosis of moderate persistent AA (sensitized to HDM with clinically relevant symptoms) without AR was defined as the target population to be simulated in the base case scenario. The SCIT+ICS strategy consisted of a monthly administration scheme for three years (a period in which the effect of SCIT is expected to be perceived) followed by ICS within a 10-year time horizon (13). The comparator strategy consisted in treatment with ICS + symptomatic medications during the overall time horizon. The 10-year time horizon was defined as a period in which the differences in long-term effects of SCIT+ ICS vs ICS in health outcomes and costs would be observed. Different scenario analyses were performed considering allergic rhinitis (AR) as a comorbid condition in the base-case population and a cohort of adult patients (18 years old at baseline) with and without AR to evaluate potential differences in cost-effectiveness estimations. The perspective of the health care system was adopted, and only direct-medical costs were used.

Benefits associated to the evaluated strategies were expressed as quality-adjusted life-years (QALYs). Costs and QALYs were discounted at 5% per year according to the Colombian guidelines for conducting economic evaluations (14). An exchange rate of $3,250 Colombian pesos (COP) per one American dollar (USD) was used to convert from 2018 COP to USD. A willingness-to-pay threshold (WTP) of $18,125 USD (i.e., three per capita Gross Domestic Product (GDP) of Colombia) per additional QALY was defined as the criteria for evaluating cost-effectiveness (14). The decision model was built using MS Excel 2018 (Microsoft, Redmond, WA).

Measures of effectiveness

The effect of the evaluated therapies was measured in terms of reduction in the probability of a moderate or severe exacerbation (as an event of emergency department visit – ED, or hospitalization, respectively), and the reduction or discontinuation of asthma medications (as an indicators of reduced disease severity and risk of exacerbations) (15). These outcomes reflect an improvement of health-related quality of life and a reduction in costs, and are thus considered robust metrics for relating clinical effectiveness to costs and QALYs (9,16,17).

Model structure

A Markov model was developed based on the stepwise approach proposed by the Global Strategy for Asthma Management and Prevention of the Global Initiative of Asthma (GINA) in which treatment steps are associated to different levels of asthma severity (18) (Figure 1). This conceptual structure was used to create a flexible and reproducible model accounting for relevant outcomes in clinical practice such as ED visits, hospitalizations and medication-step down that have not been widely used in previous HDM SCIT cost-effectiveness studies despite its recognized relevance for policy makers and clinicians (17,19). Furthermore, this model can be used to account for the different recommended treatment schemes within each GINA Step according to the target population to be simulated (12,18).

Four health states were defined: GINA Step 3, GINA Step 2, asthma without medications (complete withdrawn of all asthma medications) and any-cause death (absorbing Markov state). GINA Step 3 and GINA Step 2 states were defined as medium and low dose of ICS with salbutamol, respectively. An asthma-related death state was not included in the model due to the low frequency of this event in this level of disease severity. All-cause mortality probabilities were calculated based on vital statistics data of the Colombian National Administrative Department of Statistics (20). A Markov cycle of three months was used in the model as it is the minimum period of time in which asthma medications can be modified according to the clinical response of patients as recommended by the GINA report (18). A decision tree was embedded in the model to include exacerbations as events (Figure 1).

Within the model the following transitions were possible: medication step-down (from GINA Step 3 to GINA Step 2), remission (from GINA Step 2 to asthma without medications) and death (from any health state). The following assumptions were considered: 1) patients start in the GINA Step 3 state and end in the asthma remission state, 2) transition from GINA Step 3 state to the asthma remission state was not allowed, 3) hospitalizations and ED visits were included in GINA Step 3 state, and only ED visits in the GINA Step 2 state, 4) transition probabilities of medication step-down and remission generated by the SCIT+ICS would be constant during the first five years, and a reduction in exacerbations during the complete time horizon, 5) the ICS strategy would generate medication-step-down and remission in the first two years of the time horizon, 7) no adverse events were considered in the model due to their relative low frequency and impact in terms of HCRU, costs and quality of life, 8) an exacerbation would require medical attention through ED or hospitalization.

Our model is based on the assumption that SCIT+ICS therapy generates higher disease remission and reduction of exacerbations compared to ICS without SCIT (21,22). As patients move among health states (i.e. as disease severity is reduced) they accumulate health-state and event-specific costs, and gains in utilities that are translated into QALYs. The negative effect of asthma exacerbations on quality of life was expressed through disutilities.

Inputs and data sources

Transition probabilities

Table 1 shows the parameters used in the decision model. A literature review was conducted to obtain effectiveness parameters and were subsequently validated with clinical experts. The probability of asthma remission for the ICS strategy was defined as the proportion of patients that discontinued all asthma medications in the control group of an observational study by Sánchez et al. in Colombia that included patients with moderate persistent asthma (23). Although authors do not specify the ICS used by patients, we assumed that the majority of patients were treated with Beclomethasone dipropionate (BDP) as it is the only IC covered by the Colombian health care system (24). The probability of medication step-down was obtained from the control arm of an RCT conducted by Zielen et al. in which the steroid-sparing effect of SCIT was evaluated and the proportion of patients achieving a controller medication step reduction was reported (25). This was the only study retrieved in our search that used the reduction in medication steps as an outcome to evaluate the steroid-sparing effect of SCIT + ICS and ICS. As authors used fluticasone propionate as the controller

treatment, we assumed similar effectiveness between BDP and fluticasone propionate (26). Probabilities of medication step-down and remission for the SCIT+ICS cohort were obtained from the study by Sánchez et al in which a sample of 122 patients received SCIT + ICS over a 3-year period and the proportion of patients with a reduction/complete withdrawn of asthma medications was reported (23). All initial probabilities were converted as rates using their periodicity and then re-expressed as probabilities with a 3-month interval (cycle length) (27)

Probability of asthma exacerbations

A post-hoc analysis was carried out to estimate the probability of an asthma exacerbation using a database of a population-based study by Dennis et al that reported that 43% (95% CI, 36.3-49.2) of patients with current asthma symptoms reported requiring an ED visit or hospitalization in the last year (28). Patients with 5-59 years of age with a physician diagnosed asthma or rhinitis were selected. The frequency of nocturnal symptoms (i.e., <2 nights/month, 2/month, 1-3 times/week and every night) was used to classify patients among different severity categories. A previous diagnosis of asthma or rhinitis by a physician was established as a selection criterion for a better approximation of patients that were undergoing pharmacological treatment and thus reflect the baseline scenario of routine care with ICS in Colombia.

Two logistic regression models (one for patients with asthma and other for patients with asthma and rhinitis) were constructed using patient demographics and categories of nocturnal symptoms frequency as predictors and the history of an ED visit/hospitalization as outcome (yes/no). Coefficients were converted to probabilities and the estimated parameter for the "1-3 times/week" category in the nocturnal symptoms variable (using the "<2/per month" as reference level) was assumed to reflect the baseline probability of an exacerbation in patients with moderate persistent asthma. The resulting probabilities were converted to rates and re-expressed as 3-month probabilities for inclusion in the model.

A 75.4% of reduction in the proportion of patients that reported unscheduled medical visits over a 9-month period reported by El-qutob et al. was used in the model to reflect the effect of SCIT+ICS in the reduction in the probability of asthma exacerbations (29). This parameter was applied to the estimated baseline probabilities of an asthma exacerbation of 0.331 and 0.465 for AA and AA+AR patients, respectively (Table 1).

Health care resource utilization and costs

The considered costs were cost of medications, medical services (outpatient visits and specialized care) and ambulatory services (i.e., laboratory/image procedures). Costs *per year* were calculated by multiplying individual costs inputs with age-specific medication doses and medical services frequency considered to be appropriate to achieve disease control based in local and international clinical guidelines (18,30,31) (Table 1). For GINA Step 3 and GINA Step 2 states the recommended average daily dose of ICS (medium and low dose per day) for patients between 6-11 and >=12 years in the GINA report were used, respectively (5). The number of days with salbutamol use per month was obtained from a study by Sánchez et al and were multiplied with the daily dose of salbutamol used in the analysis (32). Frequency of outpatient, specialized care, ED visits and hospitalizations*per year* was obtained from a study by Florez et al (3).

The administration of nasal ICS in addition to loratadine was allowed for patients with AA+AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (30). For the GINA Step 3 and GINA Step 2 states, medium and low doses of nasal ICS were used, respectively. Loratadine was withdrawn in the GINA Step 2 state and no use of AR medications were allowed in the remission state. It was assumed that the reduction of AR medications was positively associated to the reduction of AA medications. Disaggregated cost inputs according to age group, health state and type of exacerbation are displayed in the Supplementary material 1.

A complementary scenario analysis was conducted by evaluating the use of SCIT as add-on therapy with a low dose of ICS + long acting β_2 agonists (LABAs) (i.e., formoterol/budesonide or salmeterol fluticasone) and

salbutamol. This scenario was conducted to account for other controller strategies recommended in the Step 3 of the GINA report that are frequently used in the clinical practice. A similar effectiveness between BDP and formoterol/budesonide or salmeterol/fluticasone was assumed. LABA medications were discontinued in the GINA Step 2 and AR medications were considered to be administered under the same scheme adopted in the base-case scenario. Costs and HCRU parameters were validated by clinical experts in the research staff. Unit cost parameters for all medications were obtained from the Drug Price Information System of the Colombian Ministry of Health and Social Protection (SISMED). Costs for the SCIT and other medical services were obtained from the Social Security Institute medical fee manual of 2001+30% as recommended by Colombian guidelines for economic evaluations (33,34).

Utility values

Previous EuroQol-5D utility values reported by Szende et al. for intermittent, mild, and moderate severity levels in Hungary were used (35). Utilities were assigned to the asthma without medication, GINA Step 2 and GINA Step 3 states in the model, respectively. Disutility associated to exacerbations were obtained from a previous study by Lloyd et al. that reported changes in baseline EuroQol-5D utility values in patients from the UK (36).

Sensitivity analysis

Deterministic analyses were performed by including in the model the upper and lower values of utility parameters, SCIT unit cost and the effectiveness of the SCIT + ICS in the reduction of the probability of an asthma exacerbation. The proportion of patients with at least one step reduction reported in the treatment arm of the RCT by Zielen et al was included as the maximum value of the probability of medication step-down with SCIT + ICS. An additional analysis was conducted by assigning a zero probability of asthma remission with ICS to account for a pessimistic value. All analyses were conducted in the base case scenario. Probabilistic sensitivity analysis was performed running 1,000 Monte Carlo simulations for non-redundant parameters. Commonly used mathematical distributions were assumed (Table 1).

RESULTS

Base case scenario

Compared to ICS alone, SCIT + ICS administered over three years in a 10-year time horizon would avert a total of 847 exacerbations per 1,000 patients treated. These results along with medication discontinuation would generate 0.37 additional QALYs (3.7 months) and additional $836 costs per patient. These clinical gains are projected to come at a higher total cost resulting from the additional cost of SCIT administration in the first three years of the model (76.7%). Only a small proportion of these costs (5.2%) would be compensated through savings in costs associated to ED visits and hospitalizations. These results yielded an ICER below a WTP threshold of $18,125 USD per additional QALY making the SCIT+ICS cost-effective (Table 2).

Scenario analyses

In a population of patients with 8 years at baseline and AA+AR, the SCIT+ICS strategy would generate additional 0.41 QALYs (4.1 months) and $680 costs per patient (Table 2). This yielded an ICER 27.3% lower compared to the base case scenario suggesting an increased cost-effectiveness of the intervention in pediatric patients with AA+AR. Similar gains in QALYs and additional costs were obtained in a cohort of adult patients with AA compared to the base case population (Table 2). Considering AR as a comorbid condition in this population resulted in an ICER 27.4% lower compared to adult patients with AA alone

(Figure 2). This indicates that the SCIT+ICS would also be considered cost-effective in adult populations with or without AR.

The scenario with ICS+LABA therapy in a cohort of patients with 8 years at baseline and AA was associated to higher total costs of the evaluated strategies (Table 3). This yielded an ICER 16.0% lower compared to the base case scenario with ICS as the controller therapy. Similar results were projected for adult patients (Figure 2). In a scenario with a 45.8% of patients with AA achieving medication step-down generated by the SCIT as reported by Zielen et al. (25) and a sustained effect over 3 years after discontinuation as reported by Stelmach et al. (37), the break-even point (i.e., moment of time in which the total costs of the SCIT+ICS+LABA therapy would be lower to the costs associated to ICS+LABA) was estimated to occur at 17.0 and 10.7 years after SCIT cessation in pediatric and adult patients, respectively. For patients with AA+AR, this point would be reached at 10.8 and 8.7 years for pediatric and adult cohorts, respectively.

Deterministic and probabilistic sensitivity analyses

The utility values resulted in the highest change in the ICER (Figure 3). In all evaluated analyses the SCIT+ICS remained cost-effective. Probabilistic sensitivity analyses indicated that SCIT+ICS was cost-effective in 95.2% of iterations when compared to ICS and 88.7% of iterations were associated to a gain in QALYs. The SCIT+ICS showed an increasing probability of being cost effective as the WTP threshold increased (See supplementary material 2).

DISCUSSION

To our knowledge, this is the first study that evaluates the cost-effectiveness of HDM SCIT+ICS for patients with moderate persistent AA using medication step down and reduction of exacerbations as measures of clinical effectiveness. This analysis suggests that treatment with SCIT+ICS is a non-dominant but cost-effective therapy over ICS alone in pediatric and adult patients with AA with or without AR. The probabilistic sensitivity analysis confirmed the robustness of our model. Despite our observation of a reduction in costs per cycle after SCIT discontinuation, the magnitude of costs accumulated through the first three years led to a higher total cost associated to SCIT at the end of the time horizon. We consider that these results are driven by the substantial low cost of the IC defined in the case scenario (i.e., BDP) and thus, the resulting cost reduction did not compensate the initial additional costs associated to the SCIT. However, the resulting ICERs fell below the willingness to pay threshold per QALY of one to three GDP per capita of Colombia, making SCIT cost-effective in all scenarios defined.

Although our study was conducted using some parameters from the Colombian context, we consider that our results provide relevant inputs for the decision-making process in different contexts, especially in those where a significant pressure on health budgets exists. We developed a novel Markov model based on a guideline accepted in the clinical practice worldwide. Furthermore, Markov models are suitable for modelling chronic diseases like asthma that are characterized by varying symptomatic episodes of different severity over time (27). This aspect constitutes one of the major strengths of our study, as this may allow clinicians to obtain evidence regarding the economic implications of the SCIT as add-on therapy to the commonly used pharmacological treatments in the current practice and may base their decisions considering not only a clinical dimension (38).

A relevant aspect in our study was the inclusion of parameters from studies conducted in real-world settings. The efficacy of SCIT with HDM extracts in the reduction of symptoms and medications has been reported in previous experimental studies but its effectiveness in real-world settings is scarce (11,21,22). A previous observational study by Jutel et al. in Germany reported a 10.8% reduction in prescription of AA medications and a 59.7% reduction of AR medications among pediatric patients who received SCIT (39). Although the parameter for measuring the impact of SCIT in our study was the proportion of patients achieving

reduction/discontinuation of medication usage, our results coincide in the fact of a positive performance of SCIT in reducing the most important factor that determines the cost of illness.

In a similar way, a previous population-based retrospective cohort study by Schmitt et al. evaluated the protective effect of AIT in asthma progression using the GINA treatment steps as a subrogate of disease severity in a real-world setting. Authors suggest that exposure to AIT is associated with a decreased risk of asthma progression from GINA Step 1 to Step 3 (HR 0.87 95% CI 0.80-0.95) and from GINA Step 3 to GINA Step 4 (HR 0.66 95% CI 0.60-0.74) (40). Although authors adopted a different definition of clinical effectiveness than that used in our study, their results highlight the protective effect of the SCIT in a real-world setting. In addition, our studies coincide with the use of a GINA-based conceptual framework for the simplification of the course of asthma.

We were able to obtain the probability of medication-step down and discontinuation of medications in patients with moderate persistent asthma that received SCIT from a real-world study in Colombia by Sánchez et al (23). In addition, we estimated the baseline probability of an asthma exacerbation using data form a population-based study by Dennis et al. that included a sample of 5,978 individuals in six cities in Colombia, and related the effect of the SCIT in this parameter using an observational study from El-Qutob et al. (28,29).

Our study addresses limitations previously identified economic evaluations of AIT. As stated by Asaria et al and Ehteshami-Afshar et al., the evaluation of possible differences in the cost-effectiveness of AIT across subgroups of patients remains one of the broader gaps in the literature. Population-based treatment decisions may potentially led to a loss of efficiency, as an intervention that is found to be cost-effective in a general population of patients may not be equally cost-effective among subgroups (or vice versa) (10,12). Our results indicate that the SCIT with either ICS or ICS+LABA would reach the highest cost-effectiveness in patients with AA+AR. We consider that these results were mainly driven due to the higher baseline probability of an asthma exacerbation compared to patients with AA only (0.465 vs 0.331) (28).

According to the latest guidelines on AIT for HDM mite-driven allergic asthma by the European Academy of Allergy and Clinical Immunology (EAACI), the reduction in asthma exacerbations and medications are considered relevant co-primary outcomes in the assessment of the efficacy of AIT (19). A previous study by Bruggenjurgen et al., evaluated the cost-effectiveness of HDM SCIT+ICS in the German setting through Markov models under the societal perspective (41). The study evaluated the strategies across different populations, but no attempt to reflect the clinical efficacy of SCIT either through a reduction of asthma medications or exacerbations was made. This aspect makes difficult to compare our estimated QALYs gains with those reported by the authors. In addition, relevant inputs in the model were retrieved only through consultation of experts and no detailed description of methods was conducted. Thus, it was defined as a low quality study by a previous systematic review (10).

A previous study by Reinhold et al. evaluated the economic implications of HDM SCIT+ICS in children with AA by a retrospective analysis of a clinical trial (65 patients). After three years, SCIT+ICS was found to be more expensive compared to ICS alone (7). Although authors considered medication step-down, they were unable to account for the effect of the SCIT in asthma exacerbations, neither were able to translate the clinical efficacy of the strategies through QALYs. Their estimations may thus underestimate the effect of the intervention in costs and QALYs.

This study has limitations and our results should be interpreted with caution. Firstly, utility estimations attributed to health states in the model were obtained from a survey conducted in Hungary, and they reflect the preferences for specific health states in that population (35). Utility parameters were associated with the greater uncertainty in our model as evidenced in the deterministic sensitivity analysis and this would have influenced the estimated QALYs gains. Nevertheless, the parameters used were retrieved from a population of patients across different GINA-defined disease categories using the EuroQol-5D instrument, one of the recommended health utility measures for the expression of clinical effectiveness in utility measures (42).

Secondly, given the limitations of information regarding the effectiveness of the alternatives under evaluation

in the reduction of exacerbations and medication dosage in Colombia, we relied on important assumptions regarding the effectiveness of SCIT and ICS. In the base case scenario we assumed that the BDP would be the main IC administered in this study, as it is the only IC covered by the Colombian health care system and has the highest market share (24). We consider that this assumption had an important influence in the estimated costs of the controller treatment in our model. As BDP has a considerably lower cost compared to other controller treatments, we potentially underestimated the costs of ICS in the base case scenario. However, we assessed this limitation in a complementary analysis using ICS+LABA as the controller treatment, where the SCIT also resulted cost-effective. Moreover, we could not take into account potential limitations and confounding variables in all the observational studies used as the main source of effectiveness parameters of the evaluated strategies. Nevertheless, we included the effectiveness parameters in the deterministic sensitivity analysis and results indicate that even under both conservative and optimistic values, the SCIT+ICS resulted cost-effective. These limitations could be minimized if there were more high-quality studies that reported the frequency of the selected measures of effectiveness for both treatment schemes in Colombia.

CONCLUSION

This analysis suggests that SCIT+ICS is cost-effective compared with ICS in the reduction of exacerbations and the discontinuation of rescue and controller medications in children and adult patients with moderate persistent symptoms with or without AR.

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TABLES

Table 1. Analytical inputs used in the economic evaluation

Model parameters	Base case value	Range for DSA$^+$	Range for DSA$^+$	Distribution	Reference
		Lower	Upper		
Transition probabilities (per 3-month cycle)	**Transition probabilities (per 3-month cycle)**				
ICS					
GINA Step 3 to GINA Step 2	0.025			Beta	(23,25)
GINA Step 2 to asthma without medications	0.041	0.000		Beta	(23)
SCIT+ICS					
GINA Step 3 to GINA Step 2	0.024		0.458	Beta	(23,25,37)
GINA Step 2 to asthma without medications	0.155			Beta	(23,25)
Frequency of asthma exacerbations					
Baseline probability of an asthma exacerbation in patients with AA	0.095			Beta	(43)
Baseline probability of an asthma exacerbation in patients with AA+AR	0.145				(43)
Reduction in probability of asthma exacerbation due to SCIT	0.504	0.500	0.900	Beta	(29)

Model parameters	Base case value	Range for DSA^{+}	Range for DSA^{+}	Distribution	Reference
Baseline rate of severe exacerbations per year	1.5			Lognormal	(3)
Baseline rate of moderate exacerbations per year	1.3			Lognormal	(3)
Length of a moderate exacerbation (days)$^{++}$	7.0			Lognormal	(18)
Length of a severe exacerbation (days)$^{++}$	10.2			Lognormal	(44)
Health state utilities					
GINA Step 3	0.630	0.400	0.860	Beta	(35)
GINA Step 2	0.700	0.500	0.900	Beta	(35)
Asthma without medications	0.890	0.790	0.990	Beta	(35)
Exacerbation-related disutilities					
Hospitalization	-0.200			Lognormal	(36)
ED visit	-0.100			Lognormal	(36)
Costs per year or event (2018 USD)					
Subcutaneous immunotherapy ($27.8 per administration)	$ 334.4	$ 22.3	$ 33.2	Gamma	(34)
GINA Step 3					
Pediatric patients (8-11y)	$ 43.2			Gamma	(33,34)
Adults and adolescents (>=12y)	$ 52.2			Gamma	(33,34)
GINA Step 2					
Pediatric patients (8-11y)	$ 32.1			Gamma	(33,34)
Adults and adolescents (>=12y)	$ 36.6			Gamma	(33,34)

Model parameters	Base case value	Range for DSA^{+}	Range for DSA^{+}	Distribution	Reference
Asthma without medications	$ 20.1				
ED visit	$ 23.3			Gamma	(33,34)
Hospitalization	$ 154.0			Gamma	(33,34)

$^{+}$Values are reported only for those parameters used in the deterministic sensitivity analyses. When only an upper or lower value is reported indicates that an extreme-value univariate analysis was conducted. $^{++}$Indicates the amount of time under treatment required to control symptoms associated to a moderate exacerbation. The duration of a severe exacerbation results of adding the duration of a moderate exacerbation with 3.2 days of length of stay considered as the mean time for an asthma-related hospitalization. DSA=Deterministic Sensitivity Analyses, ICS=Inhaled corticosteroids, SCIT+ICS=Subcutaneous Immunotherapy and Inhaled corticosteroids, GINA=Global Initiative for Asthma

Table 2. Outcomes of the base case scenario and the scenario of patients with allergic asthma and allergic rhinitis

Outcomes	AA	AA	AA	AA + AR	AA +
	SCIT + ICS	ICS	Difference	SCIT + ICS	ICS
Pediatric patients	Pediatric patients	Pediatric patients	Pediatric patients	Pediatric patients	Pediatr
Clinical outcomes					
Total number of ED visits	733	1,152	-419	485	1,743
Total number of hospitalizations	736	1,165	-428	487	1,762
Total QALYs	6,794	6,420	374	6,807	6,389
Cost outcomes (discounted)					
Health states					
GINA Step 3	1,137,087	346,364	790,724	1,218,917	443,452
GINA Step 2	129,390	36,345	93,045	141,547	41,758
Asthma without medications	42,297	14,470	27,828	42,297	14,470
Events					
ED visits	16,907	26,569	-9,662	11,178	40,188
Hospitalizations	112,048	177,203	-65,155	74,077	268,036
Total costs	1,437,731	600,950	836,780	1,488,016	807,903
Adult patients					
Clinical outcomes					
Total number of ED visits	731	1,148	-417	483	1,736
Total number of hospitalizations	734	1,160	-427	485	1,755
Total QALYs	6,768	6,396	372	6,781	6,365
Cost outcomes (discounted)					
Health states					
GINA Step 3	1,195,697	416,656	779,041	1,277,246	513,388
GINA Step 2	138,093	41,269	96,824	150,202	46,662
Asthma without medications	42,104	14,404	27,699	42,104	14,404
Events					
ED visits	16,964	26,654	-9,690	11,215	40,317
Hospitalizations	111,835	176,822	-64,987	73,936	267,459
Total costs	1,504,693	675,805	828,888	1,554,704	882,231

AA = allergic asthma, AR = allergic rhinitis, ICS =Inhaled corticosteroids, SCIT+ICS = subcutaneous immunotherapy and inhaled corticosteroids, ED = emergency department, QALYs = quality-adjusted-life years, ICER = incremental cost-effectiveness ratio, GINA = Global Initiative for Asthma

Table 3. Outcomes of the scenario of patients with allergic asthma and allergic rhinitis using combination therapy as comparator

Outcomes	AA SCIT + ICS + LABA^{+}	AA ICS	AA Difference	AA + AR SCIT + ICS + LABA^{+}	AA + AR ICS	A D
Pediatric patients						
Cost outcomes (discounted)						
Health states						
GINA Step 3	2,371,426	1,810,865	560,561	2,453,256	1,907,953	54
GINA Step 2	312,770	123,234	189,536	324,927	128,647	19
Asthma without medications	42,297	14,470	27,828	42,297	14,470	27
Events						
ED visits	16,907	26,569	-9,662	11,178	40,188	-2
Hospitalizations	112,048	177,203	-65,155	74,077	268,036	-1
Total costs	2,855,449	2,152,341	703,108	2,905,734	2,359,294	54
Adult patients						
Cost outcomes (discounted)						
Health states						
GINA Step 3	2,990,450	2,545,545	444,905	3,071,999	2,642,277	42
GINA Step 2	404,592	160,641	243,951	416,701	166,034	25
Asthma without medications	42,104	14,404	27,699	42,104	14,404	27
Events						
ED visits	16,964	26,654	-9,690	11,215	40,317	-2
Hospitalizations	111,835	176,822	-64,987	73,936	267,459	-1
Total costs	3,565,945	2,924,066	641,879	3,615,956	3,130,491	48

$^{+}$Subcutaneous immunotherapy with either Salmeterol/Fluticasone or Formoterol/Budesonide. AA = allergic asthma, AR = allergic rhinitis, SCIT = subcutaneous immunotherapy, ICS = inhaled corticosteroids, LABA = long acting β^2agonists, ED = emergency department, QALYs = quality-adjusted-life years, ICER = incremental cost-effectiveness ratio.

FIGURE LEGENDS

Figure 1. Decision-analytic model. A) Markov model diagram. B) Decision tree diagram for exacerbations. The decision tree was included within GINA step 3 and GINA step 2 states to represent the occurrence of asthma exacerbations. GINA = Global Initiative for Asthma.

Figure 2 . Estimated incremental cost-effectiveness ratios (ICERs) for all scenarios. Bars indicates the therapy used as comparator. ICS = Inhaled corticosteroids, ICS+LABA = Inhaled corticosteroids plus Long-acting B_2 agonists, QALY = Quality adjusted life year.

Figure 3. Deterministic sensitivity analysis. Bars indicate the resulting incremental cost-effectiveness ratio (ICER) and the associated relative change compared to the ICER in the base case scenario.

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