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Title: Cost-effectiveness of the subcutaneous house dust mite allergen immunotherapy plus pharmacotherapy for allergic asthma: a mathematical model

To the editor:

Previous research suggests that allergen immunotherapy (AIT) may be cost-effective for the treatment of patients with allergic asthma (AA) (1,2). However, most evidence is based on randomized controlled trials and the use of policy-relevant outcomes like exacerbations and medication step down is lacking. Potential differences in the cost-effectiveness across populations have also been underexplored (1,3). Recently, in Allergy Journal Schmitt *et al* reported for the first time from German real-world data that AIT reduced the progression of asthma using GINA steps as severity categories (4). Also, Jutel et al. reported a 10.8% reduction in the prescription of AA medications and a 59.7% reduction of allergic rhinitis (AR) medications among pediatric patients who received subcutaneous immunotherapy (SCIT) (5). In Colombia, Sánchez et al. reported in a real-world study that 40% of patients with moderate-persistent allergic asthma treated with SCIT and inhaled

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corticosteroids (ICS) achieved a complete withdrawal of asthma medications after monthly administration of the SCIT during three years. However, no evidence regarding the potential economic implications of the SCIT exists in Colombia and Latin America. Under this same perspective, we evaluated the cost-effectiveness of SCIT plus ICS vs ICS for AA, in pediatric and adult patients with or without AR, from the perspective of the Colombian health care system using a mathematical modeling approach and parameters for multiple sources including observational studies. Model-based cost-effectiveness evaluations are advantageous because they allow the combination of multiple sources of evidence, extrapolation of results beyond the study length of clinical trials, and converting treatment effects into policy-relevant outcomes (1,3)

We developed a cohort state-transition model (Markov model) to simulate potential consequences in costs and health-related quality-of-life of the evaluated strategies in the clinical pathway of asthmatic patients over a 10-year time horizon, divided into incremental 3-month cycles (time where changes in health status are expected). Within the model, a hypothetical cohort (i.e., a group of individuals that could theoretically receive the evaluated strategies) of 1,000 8-year-old patients (at baseline) per strategy with moderate persistent AA (sensitized to house dust mites [HDM] with clinically relevant symptoms, as these are the main source of sensitization among patients with asthma in Colombia) was modeled to “transit” across different mutually exclusive health states (6–8). The amount of medication required for disease control was used as a proxy of asthma severity levels and defined the different health states: treatment with GINA Step-3 (medium dose of ICS + Salbutamol), Step-2 (low dose of ICS + Salbutamol), asthma in remission (complete withdrawal of medications), and any-cause death, which means the probability of death in Colombia due to any reason (Figure 1A). Each cycle has an associated cost and utility value. A population of patients with only AA was defined as the target population to be simulated in the base case scenario (i.e., primary scenario with the most probable set of assumptions and input values according to the decision problem addressed).

The effectiveness of strategies was measured by reductions in medication doses (Step-down/remission) and exacerbations and was incorporated in the model as treatment-specific probabilities of the occurrence of these events in the 3-month intervals within the time horizon. These probabilities reflect the effect of strategies in the samples used in the different sources from clinical

response data incorporated in the model. At the end of each cycle, the cohort is re-distributed across states based on transition probabilities and health-state and event-specific costs, and gains in utilities that are translated into quality-adjusted life-years (QALYs).

The intervention consisted of a monthly administration for 3-years of a regime of SCIT+ICS followed by ICS + rescue medications only (9). The comparator strategy (ICS) consisted of ICS + symptomatic medications during the overall time horizon. Different scenario analyses were performed considering AR as comorbidity and a cohort of adult patients (18 years) at baseline. Also, a scenario with combined therapy (ICS+LABA) was conducted to account for the other recommended treatment scheme in the GINA report. Benefits associated with the evaluated strategies were expressed as QALYs. Costs and QALYs were discounted at 5% per year. For more details about methods and analytical inputs see Appendix S1 and Table S1.

In the base case scenario, SCIT+ICS would avert a total of 847 exacerbations per 1,000 patients treated compared to the ICS strategy. This, together with savings in medications, would generate 0.37 additional QALYs (3.7 months) and an additional cost of \$828 per patient. These clinical gains are projected to come at a higher total cost of the SCIT+ICS intervention resulting from the additional cost of SCIT administration in the first three years of the model (76.6% of total SCIT+ICS costs). Only a small proportion of the SCIT+ICS total costs (5.2%) would be compensated through savings in costs of emergency department (ED) visits and hospitalizations. These results yielded an incremental cost-effectiveness ratio (ICER) below a willingness to pay (WTP) threshold of USD \$19,282 per additional QALY making the SCIT+ICS cost-effective (Table 1). In a population with AA+AR, the SCIT+ICS strategy would generate additional 0.41 QALYs (4.1 months) and \$673 costs per patient. This yielded an ICER 27.3% lower compared to the base case scenario suggesting 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 compared to the base case population (Table S2). Considering AR as a comorbid condition in this population resulted in an ICER 27.5% lower compared to adult patients with AA alone.

The scenario with ICS+LABA therapy and AA was associated with higher total costs of the evaluated strategies (Table 1), yielding an ICER 16.6% lower compared to the base-case scenario of pediatric patients with ICS as the controller therapy. A 23.3% reduction was projected for adult patients. In a scenario with 45.8% of patients with AA achieving medication step-down generated by the SCIT as reported by Zielen et al. (10) and a sustained effect over 3 years after discontinuation as reported by Stelmach et al. (11), the break-even point (i.e., a 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 15.0 and 11.7 years after SCIT cessation in pediatric and adult patients, respectively. For patients with AA+AR, this point would be reached at 11.4 and 9.5 years for pediatric and adult cohorts, respectively.

The utility values resulted in the highest change in the ICER (Figure 1B). In all evaluated analyses the SCIT+ICS remained cost-effective. Probabilistic sensitivity analysis indicated that SCIT+ICS was cost-effective in 95.2% of iterations, and in 88.7% of iterations was associated with a gain in QALYs. The SCIT+ICS showed an increased probability of being cost-effective as the WTP threshold increased (Figure S1).

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 and thus it can be used for the economic evaluation of asthma therapies in multiple contexts. 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 commonly used pharmacological treatments in the current practice and may base their decisions considering not only a clinical dimension. We also addressed the limitations of previous economic evaluations of AIT. According to Asaria et al. and Ehteshami-Afshar et al., the evaluation of possible differences in the cost-effectiveness of AIT across subpopulations remains one of the broader gaps in the literature. Population-based treatment decisions may potentially lead 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) (1,3). Furthermore, as in most of the model-based cost-effectiveness estimations, our results should be seen in light of the methodological assumptions defined in its development and the conceptual structure adopted. Mathematical models for medical-decision making are a simplified version of reality and therefore may not completely capture the complexity of the disease and the effects of interventions. Using parameters from real-world studies, for the first time our results suggest 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 in the context of the developing world, where asthma remains as a neglected disease.

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Conflicts of interests

Authors declare no conflict of interests

Author contributions

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

Legend of figures

Figure 1. A) Markov model diagram. Each health state is represented by a circle and arrows connecting two different states indicate possible transitions of the cohort. Arrows leading to their initial health state indicate that no transition was also possible. Patients start in the GINA step 3 state and could end in the Asthma in remission state. A decision tree was embedded in GINA step 3 and GINA step 2 states to represent the occurrence of asthma exacerbations (ED visits or hospitalizations) (See Appendix S1 for further details). B) Deterministic sensitivity analysis. Bars indicate the resulting incremental cost-effectiveness ratio and the associated relative change compared to the ICER in the base case scenario. GINA = Global Initiative for Asthma, ICER = Incremental Cost-Effectiveness Ratio, ED = Emergency Department.

Tables

Table 1. Results of the base case scenario and the scenario using combination therapy as controller strategy for asthmatic patients with or without allergic rhinitis

Outcomes	AA			AA + AR		
	SCIT + ICS	ICS	Difference	SCIT + ICS	ICS	Difference
ICS as controller therapy						
Clinical outcomes						
Total number of ED visits	733	1,152	-419	485	1,743	-1258
Total number of hospitalizations	736	1,165	-428	487	1,762	-1275
Total QALYs	6,794	6,420	374	6,807	6,389	418
Cost outcomes (discounted)						
Health states						
GINA Step 3	1.129.166	346.583	782.583	1.213.289	446.397	766.892
GINA Step 2	128.674	36.272	92.402	141.182	41.837	99.345
Asthma in remission [#]	41.884	14.331	27.553	41.884	14.331	27.553
Events						
ED visits	16.769	26.349	-9.581	11.086	39.856	-28.770
Hospitalizations	111.013	175.575	-64.562	73.393	265.574	-192.181
Total costs	1.427.506	599.110	828.396	1.480.835	807.995	672.840
ICER			2.216			1.610
ICS + LABA as controller therapy[†]						
	SCIT + ICS + LABA	ICS	Difference	SCIT + ICS + LABA	ICS	Difference
Cost outcomes (discounted)						
Health states						
GINA Step 3	2.398.107	1.852.215	545.891	2.482.230	1.952.030	530.200

GINA Step 2	317.353	125.601	191.751	329.861	131.166	198.695
Asthma in remission [#]	41.884	14.331	27.553	41.884	14.331	27.553
Events						
ED visits	16.769	26.349	-9.581	11.086	39.856	-28.770
Hospitalizations	111.013	175.575	-64.562	73.393	265.574	-192.181
Total costs	2.885.126	2.194.073	691.053	2.938.454	2.402.957	535.497
ICER			1.848			1.282

[#]Only costs resulting from visits to the general and specialized physician were considered. [†]Subcutaneous immunotherapy with either Salmeterol/Fluticasone or Formoterol/Budesonide. 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

References

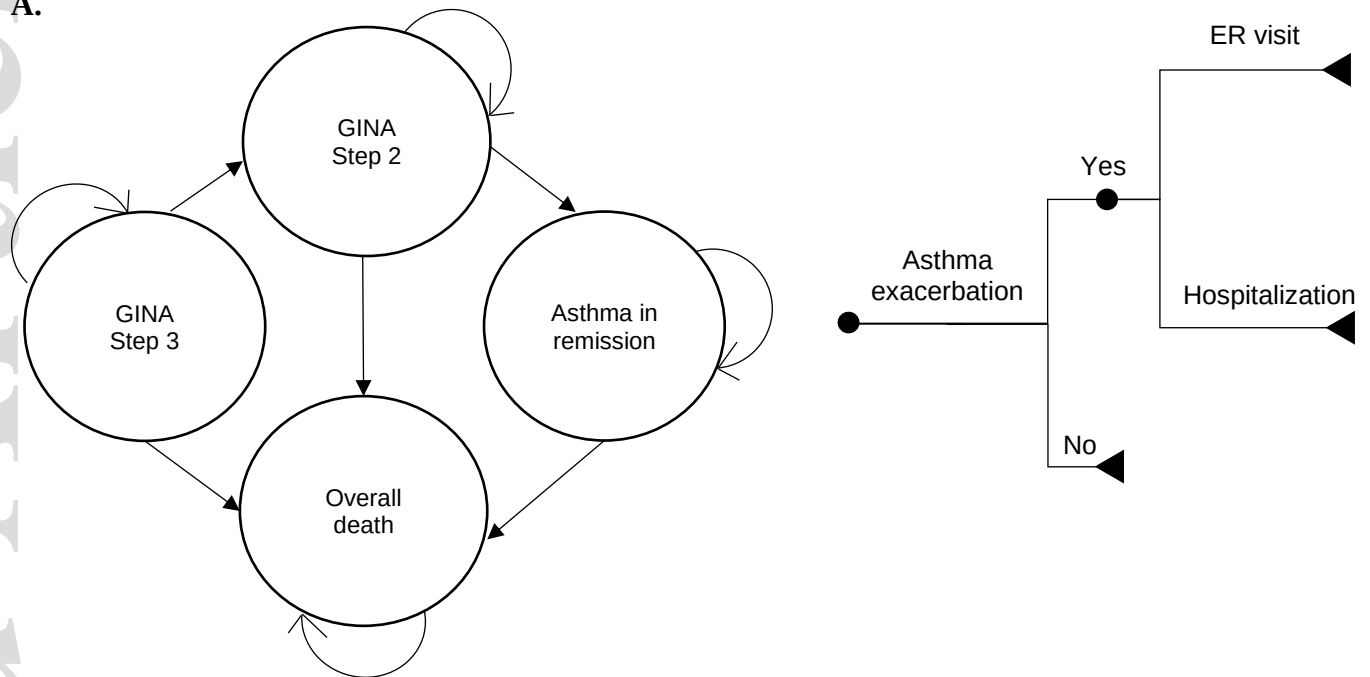
1. Asaria M, Dhami S, van Ree R, Gerth van Wijk R, Muraro A, Roberts G, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: A systematic overview. *Allergy*. 2018 Feb;73(2):269–83.
2. Simoens S. The cost-effectiveness of immunotherapy for respiratory allergy: a review. *Allergy*. 2012 Sep 1;67(9):1087–105.
3. Ehteshami-Afshar S, Zafari Z, Hamidi N, FitzGerald JM, Lynd L, Sadatsafavi M. A Systematic Review of Decision-Analytic Models for Evaluating Cost-Effectiveness of Asthma Interventions. *Value Heal*. 2019 Sep;22(9):1070–82.
4. Schmitt J, Wüstenberg E, Küster D, Mücke V, Serup-Hansen N, Tesch F. The moderating role of allergy immunotherapy in asthma progression: Results of a population-based cohort study. *Allergy [Internet]*. 2020 Mar 8 [cited 2020 May 22];75(3):596–602. Available from:

<https://onlinelibrary.wiley.com/doi/abs/10.1111/all.14020>

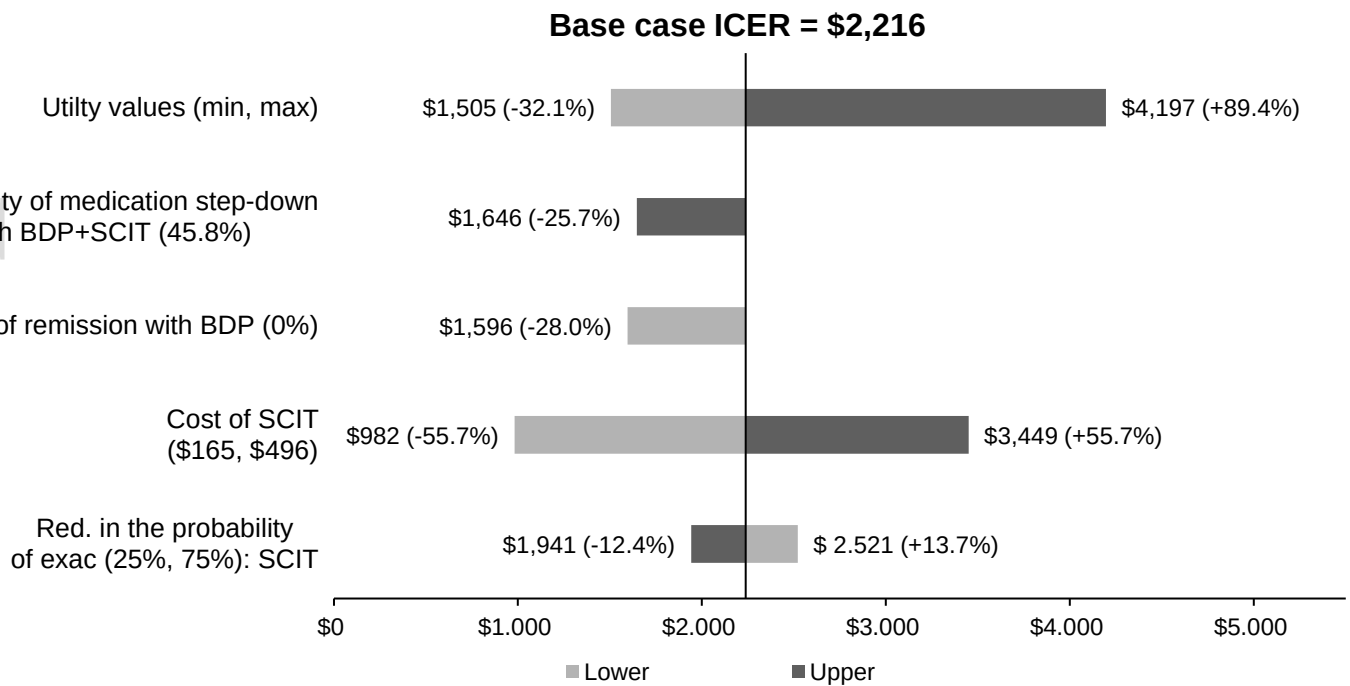
5. Jutel M, Brüggemann B, Richter H, Vogelberg C. Real-world evidence of subcutaneous allergoid immunotherapy in house dust mite-induced allergic rhinitis and asthma. *Allergy*. 2020 Mar 12;(January):all.14240.
6. Dennis R, Caraballo L, Garcia E, Rojas MX, Rondon MA, Perez A et al. Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study. *BMC Pulm Med*. 2012;12(1):17.
7. Buendía E, Zakzuk J, Mercado D, Alvarez A, Caraballo L. The IgE response to *Ascaris* molecular components is associated with clinical indicators of asthma severity. *World Allergy Organ J* [Internet]. 2015 [cited 2016 May 12];8(1):8. Available from: <http://www.waojournal.org/content/8/1/8>
8. Duenas-Meza E, Torres-Duque CA, Correa-Vera E, Suárez M, Vásquez C, Jurado J, et al. High prevalence of house dust mite sensitization in children with severe asthma living at high altitude in a tropical country. *Pediatr Pulmonol* [Internet]. 2018 Oct 1 [cited 2020 Dec 14];53(10):1356–61. Available from: <http://doi.wiley.com/10.1002/ppul.24079>
9. Tabar AI, Arroabarren E, Echechipía S, García BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol*. 2011 Jan;127(1):57-63.e3.
10. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: A randomized controlled trial. *J Allergy Clin Immunol*. 2010;126(5):942–9.
11. Stelmach I, Sobocińska A, Majak P, Smejda K, Jerzyńska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann Allergy, Asthma Immunol*. 2012;109(4):274–8.

Figure 1

A.

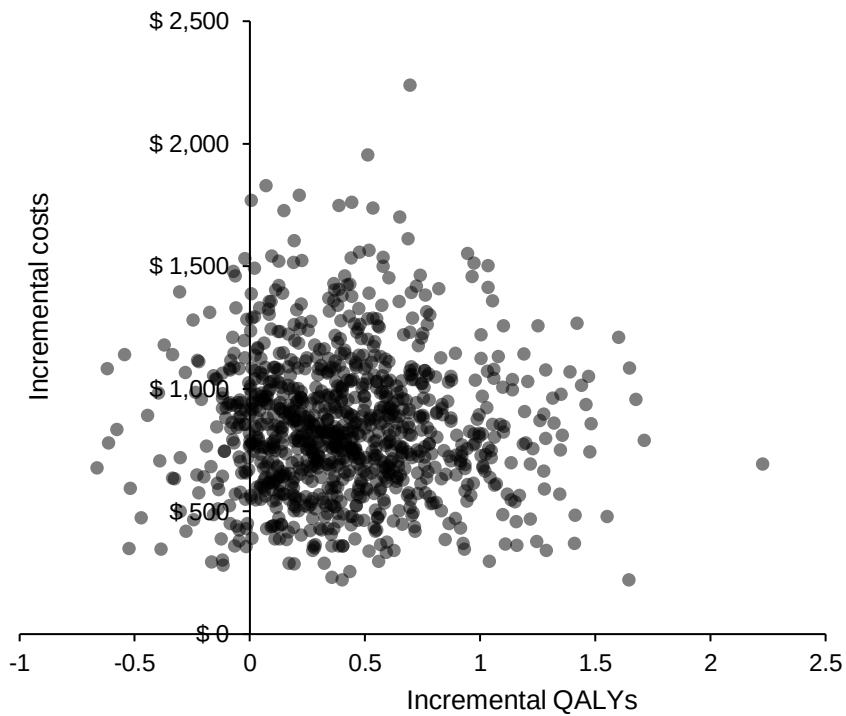


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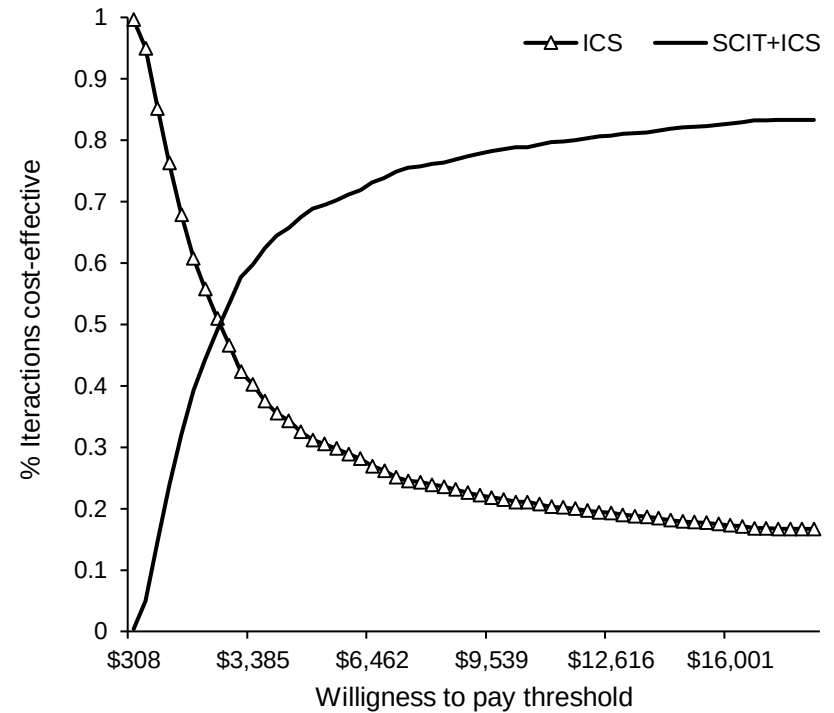


Supplementary figure 1. Probabilistic sensitivity analysis. A) Monte Carlo simulation. Each point in the plane presents one of the 1,000 different simulated ICERs for the base case scenario, B) Acceptability curves. ICS = Inhaled corticosteroids, ICS+LABA = Inhaled corticosteroids plus Long-acting B2 agonists, QALYs = Quality-adjusted life years

A



B



Supplementary Table 1. Analytical inputs used in the economic evaluation

Model parameters	Base case value	Range for DSA [†]		Distribution	Reference
		Lower	Upper		
Transition probabilities (per 3-month cycle)					
ICS					
GINA Step 3 to GINA Step 2	0.025			Beta	(1,2)
GINA Step 2 to asthma in remission	0.041	0.000		Beta	(1)
SCIT+ICS					
GINA Step 3 to GINA Step 2	0.024		0.030	Beta	(1,2)
GINA Step 2 to asthma in remission	0.155			Beta	(1,2)
Frequency of asthma exacerbations					
Baseline probability of an asthma exacerbation in patients with AA	0.095			Beta	(3)
Baseline probability of an asthma exacerbation in patients with AA+AR	0.145				(3)
Reduction in probability of asthma exacerbation due to SCIT	0.504	0.252	0.756	Beta	(4)
Baseline rate of severe exacerbations per year	1.5			Lognormal	(5)
Baseline rate of moderate exacerbations per year	1.3			Lognormal	(5)
Length of a moderate exacerbation (days) [‡]	7.0			Lognormal	(6)
Length of a severe exacerbation (days) [‡]	10.2			Lognormal	(7)
Health state utilities					
GINA Step 3	0.630	0.400	0.860	Beta	(8)
GINA Step 2	0.700	0.500	0.900	Beta	(8)
Asthma in remission	0.890	0.790	0.990	Beta	(8)
Exacerbation-related disutilities					
Hospitalization	-0.200			Lognormal	(9)
ED visit	-0.100			Lognormal	(9)
Costs per year or event (2019 USD)					
Subcutaneous immunotherapy (\$27.6 per administration)	\$ 331.2	\$ 165.6	\$ 496.8	Gamma	(10)
GINA Step 3					
Pediatric patients (8-11y)	\$ 43,3			Gamma	(10,11)
Adults and adolescents (>=12y)	\$ 52,5			Gamma	(10,11)
GINA Step 2					
Pediatric patients (8-11y)	\$ 32,1			Gamma	(10,11)
Adults and adolescents (>=12y)	\$ 36,7			Gamma	(10,11)
Asthma without medications	\$ 19,9				
ED visit	\$ 23,2			Gamma	(10,11)
Hospitalization	\$ 152,6			Gamma	(10,11)

[†]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 with 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

References

1. Sánchez J, Cardona R, Sánchez A. Repercusión de la inmunoterapia con alérgenos luego de dos años de suspensión a pacientes con asma. *Rev Alerg México*. 2016 May 11;63(2):113.
2. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: A randomized controlled trial. *J Allergy Clin Immunol*. 2010;126(5):942–9.
3. Dennis RJ, Caraballo L, García E, Rojas MX, Rondon M a, Pérez A, et al. Prevalence of asthma and other allergic conditions in Colombia 2009–2010: a cross-sectional study. *BMC Pulm Med*. 2012;12(1):17.
4. El-Qutob D, Moreno F, Subtil-Rodriguez A. Specific immunotherapy for rhinitis and asthma with a subcutaneous hypoallergenic high-dose house dust mite extract: Results of a 9-month therapy. *Immunotherapy*. 2016;8(8):867–76.
5. Flórez-Tanus Á, Parra D, Zakzuk J, Caraballo L, Alvis-Guzmán N. Health care costs and resource utilization for different asthma severity stages in Colombia: a claims data analysis. *World Allergy Organ J* [Internet]. 2018 [cited 2018 Dec 1];11(1):26. Available from: <https://waojournal.biomedcentral.com/articles/10.1186/s40413-018-0205-4>
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (Update 2019) [Internet]. 2019. p. 1–162. Available from: www.ginasthma.org
7. Zakzuk J, Parra D, Salcedo Mejía F, Alvis-Zakzuk J, Buendía E, Caraballo L, et al. Out-Of-Pocket Health Expenditures In Patients With Uncontrolled Asthma From Colombia. *Value Heal*. 2016 May;19(3):A16.
8. Szende A, Leidy NK, Ståhl E, Svensson K. Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D. *Qual Life Res*. 2009 Mar 23;18(2):267–72.
9. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J*. 2007 Feb 3;16(1):22–7.
10. Ministerio de Salud y Protección Social. Acuerdo No. 256 de 2001 - Manual de Tarifas de la Entidad Promotora de Salud del Seguro Social. Bogotá - Colombia; 2001.
11. Ministerio de Salud y Protección Social. SISMED - Sistema de Información de Precios de Medicamentos [Internet]. 2019 [cited 2019 Nov 11]. Available from: <https://www.sispro.gov.co/central-prestadores-de-servicios/Pages/SISMED-Sistema-de-Informacion-de-Precios-de-Medicamentos.aspx>

Supplementary Table 2. Results of the scenario with adult patients and the scenario using combination therapy as controller strategy for asthmatic patients with or without allergic rhinitis

Outcomes	AA			AA + AR		
	SCIT + ICS	ICS	Difference	SCIT + ICS	ICS	Difference
ICS as controller therapy						
Clinical outcomes						
Total number of ED visits	731	1,148	-417	483	1,736	-1253
Total number of hospitalizations	734	1,160	-427	485	1,755	-1270
Total QALYs	6,768	6,396	372	6,781	6,365	416
Cost outcomes (discounted)						
Health states						
GINA Step 3	1.189.473	418.884	770.589	1.273.309	518.333	754.976
GINA Step 2	137.636	41.338	96.298	150.095	46.883	103.212
Asthma in remission [#]	41.693	14.267	27.426	41.693	14.267	27.426
Events						
ED visits	16.829	26.440	-9.611	11.126	39.993	-28.867
Hospitalizations	110.808	175.208	-64.399	73.257	265.018	-191.761
Total costs	1.496.440	676.137	820.303	1.549.480	884.494	664.986
ICER			2.204			1.599
ICS + LABA as controller therapy[†]						
	SCIT + ICS + LABA	ICS	Difference	SCIT + ICS + LABA	ICS	Difference
Cost outcomes (discounted)						
Health states						
GINA Step 3	3.034.538	2.607.563	426.975	3.118.374	2.707.012	411.362
GINA Step 2	411.836	164.063	247.774	424.295	169.607	254.688
Asthma in remission [#]	41.693	14.267	27.426	41.693	14.267	27.426
Events						
ED visits	16.829	26.440	-9.611	11.126	39.993	-28.867
Hospitalizations	110.808	175.208	-64.399	73.257	265.018	-191.761
Total costs	3.615.705	2.987.541	628.164	3.668.745	3.195.897	472.848
ICER			1.688			1.137

[#]Only costs resulting of visits to general and specialized physician were considered. [†]Subcutaneous immunotherapy with either Salmeterol/Fluticasone or Formoterol/Budesonide. 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

Appendix S1: Methods

Modeled population

A hypothetical cohort (1,000 patients per strategy) of 8-year old patients at baseline with moderate persistent allergic asthma without allergic rhinitis and sensitized to house-dust mites (HDM) with relevant clinical symptoms was assumed in the base case scenario. Patients were considered to be sensitized only to HDM as these have been reported as the most prevalent and clinically relevant source of sensitization in patients with asthma in Colombia, with prevalences ranging from 60.2% to 87.9% (1–3). To evaluate the potential consequences of the evaluated strategies in an adult population, a cohort with 18years at baseline with or without allergic rhinitis was also simulated in a complementary scenario.

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 with different levels of asthma severity (4). 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 (4,5).

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 a 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 (6). A Markov cycle of three months was used in the model as it is the minimum time in which asthma medications can be modified according to the clinical response of patients as recommended by the GINA report (4). A 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. A decision tree was embedded in the model to include exacerbations as events.

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 relatively 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 (7,8). 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

A literature review was conducted to obtain effectiveness parameters and they 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 (9). 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 (10). 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 (11). 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 (12). 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 three years and the proportion of patients with a reduction/complete withdrawn of asthma medications was reported (9). All initial probabilities were converted as rates using their periodicity and then re-expressed as probabilities with a 3-month interval (cycle length) (13).

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 (1). Patients with 5-59 years of age with 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 the 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 the 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% reduction in the proportion of patients that reported unscheduled medical visits over 9 months 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 (14). 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 the 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 cost inputs with age-specific medication doses and medical services frequency considered to be appropriate to achieve disease control based on local and international clinical guidelines (4,15,16). 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 (17). The frequency of days with salbutamol use per month was obtained from a study by Sánchez et al and was multiplied with the daily dose of salbutamol used in the analysis (18). The frequency of outpatient, specialized care, ED visits, and hospitalizations *per year* was obtained from a study by Florez et al (19).

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 (15). 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 was allowed in the remission state. It was assumed that the reduction of AR medications was positively associated with the reduction of AA medications. Disaggregated cost inputs according to age group, health state, and type of exacerbation are displayed in Table S1.

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 Step 3 of the GINA report that are frequently used in clinical practice. 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 (20,21). An exchange rate of \$3,281 Colombian pesos (COP) per one American dollar (USD) was used to convert from 2019 COP to USD. A willingness-to-pay threshold (WTP) of USD \$18,282 (i.e., three per capita Gross Domestic Product (GDP) of Colombia) per additional QALY was defined as the criteria for evaluating cost-effectiveness.

Utility values

Previous EuroQol-5D utility values reported by Szende et al. for intermittent, mild, and moderate severity levels in Hungary were used (22). Utilities were assigned to asthma without medication, GINA Step 2, and GINA Step 3 states in the model, respectively. Disutilities associated with 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 (23).

Sensitivity analysis

Deterministic analyses were performed by including in the model the upper and lower values of utility parameters, SCIT cost per year ($\pm 50\%$), and the effectiveness of the SCIT+ICS in the reduction of the probability of an asthma exacerbation (Table S1). 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 (11). An additional analysis was conducted by assigning a zero probability of asthma remission with ICS to account for a pessimistic scenario. 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.

References

1. Dennis R, Caraballo L, Garcia E, Rojas MX, Rondon MA, Perez A et al. Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study. *BMC Pulm Med*. 2012;12(1):17.
2. Buendía E, Zakzuk J, Mercado D, Alvarez A, Caraballo L. The IgE response to *Ascaris* molecular components is associated with clinical indicators of asthma severity. *World Allergy Organ J* [Internet]. 2015 [cited 2016 May 12];8(1):8. Available from: <http://www.waojournal.org/content/8/1/8>
3. Duenas-Meza E, Torres-Duque CA, Correa-Vera E, Suárez M, Vásquez C, Jurado J, et al. High prevalence of house dust mite sensitization in children with severe asthma living at high altitude in a tropical country. *Pediatr Pulmonol* [Internet]. 2018 Oct 1 [cited 2020 Dec 14];53(10):1356–61. Available from: <http://doi.wiley.com/10.1002/ppul.24079>
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (Update 2019) [Internet]. 2019. p. 1–162. Available from: www.ginasthma.org
5. Ehteshami-Afshar S, Zafari Z, Hamidi N, FitzGerald JM, Lynd L, Sadatsafavi M. A Systematic Review of Decision-Analytic Models for Evaluating Cost-Effectiveness of Asthma Interventions. *Value Heal*. 2019 Sep;22(9):1070–82.
6. Departamento Administrativo Nacional de Estadística (DANE). Vital statistics: birth and deaths forecasting. 2018.
7. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010 Aug 4;(8).
8. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. *Allergy Eur J Allergy Clin Immunol*. 2017;72(12):1825–48.
9. Sánchez J, Cardona R, Sánchez A. Repercusión de la inmunoterapia con alérgenos luego de dos años de suspensión a pacientes con asma. *Rev Alerg México*. 2016 May 11;63(2):113.
10. Romano G, Y A, López-Delgado N. Análisis de impacto presupuestal de beclometasona, budesonida, ciclesonida, deflazacort, fluticasona (propionato), formoterol, formoterol + budesonida, ipratropio bromuro, metilprednisolona, mometasona, montelukast, omalizumab, prednisolona, salbutamol y. Bogotá, Colombia; 2017.
11. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: A randomized controlled trial. *J Allergy Clin Immunol*. 2010;126(5):942–9.
12. Lasserson TJ, Cates CJ, Lasserson EH, White J. Fluticasone versus “extrafine” HFA-beclomethasone dipropionate for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2006 Apr 19;(2).
13. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford University Press; 2006. 237 p.
14. El-Qutob D, Moreno F, Subtil-Rodriguez A. Specific immunotherapy for rhinitis and asthma with a subcutaneous hypoallergenic high-dose house dust mite extract: Results of a 9-month therapy. *Immunotherapy*. 2016;8(8):867–76.
15. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950–8.
16. Ministerio de Salud y Protección social - Colciencias. Guía de práctica clínica Para el diagnóstico, atención integral y seguimiento de niños y niñas con diagnóstico de Asma. Bogotá - Colombia; 2013. 242 p.
17. Erick Bateman. Global Strategy for Asthma Management and Prevention. Glob Initiative Asthma [Internet]. 2016

[cited 2019 Oct 22];1–147. Available from: www.ginasthma.org

18. Sanchez J. Clinical differences between children with asthma and rhinitis in rural and urban areas. *Colomb Med*. 2018 Jun 1;49(2):169–74.
19. Flórez-Tanus Á, Parra D, Zakzuk J, Caraballo L, Alvis-Guzmán N. Health care costs and resource utilization for different asthma severity stages in Colombia: a claims data analysis. *World Allergy Organ J* [Internet]. 2018 [cited 2018 Dec 1];11(1):26. Available from: <https://waojournal.biomedcentral.com/articles/10.1186/s40413-018-0205-4>
20. Ministerio de Salud y Protección Social. SISMED - Sistema de Información de Precios de Medicamentos [Internet]. 2019 [cited 2019 Nov 11]. Available from: <https://www.sispro.gov.co/central-prestadores-de-servicios/Pages/SISMED-Sistema-de-Informacion-de-Precios-de-Medicamentos.aspx>
21. Ministerio de Salud y Protección Social. Acuerdo No. 256 de 2001 - Manual de Tarifas de la Entidad Promotora de Salud del Seguro Social. Bogotá - Colombia; 2001.
22. Szende A, Leidy NK, Ståhl E, Svensson K. Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D. *Qual Life Res*. 2009 Mar 23;18(2):267–72.
23. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J*. 2007 Feb 3;16(1):22–7.