

Clinical Communications

Budesonide/formoterol as maintenance and reliever therapy compared to fixed-budesonide/formoterol plus albuterol reliever for pediatric asthma: A cost-utility analysis in Colombia

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Clinical Implications

- This study supports the recommendation of the 2020 focused update of the National Asthma Education and Prevention Program asthma guideline regarding the use of budesonide/formoterol as single maintenance and reliever therapy as the preferred treatment in patients aged 5 to 11 years with asthma uncontrolled on inhaled corticosteroids.

Childhood asthma is a major public health problem in the United States as well as in many other low- and middle-income countries such as Colombia, which has a prevalence estimated at 10% to 12%.¹ One of the most frequent and effective strategies used to achieve asthma control in uncontrolled pediatric asthma with low to medium doses of inhaled corticosteroids (ICSs) is the addition of long-acting beta-2 agonists (LABAs).² Nevertheless, the strategy for administering the ICSs-LABA combination for children in this age group differs between the 2 most up-to-date asthma guidelines: the Global INitiative for Asthma recommends as the preferred treatment a fixed combination of low to medium doses of ICSs and LABAs as a daily controller with as-needed short-acting β_2 -agonists for symptom relief,² whereas the 2020 focused update of the National Asthma Education and Prevention Program asthma guideline recommends as the preferred treatment the combination of an ICS and formoterol as single maintenance and reliever therapy (SMART).³ We therefore compared the cost-effectiveness of budesonide/formoterol (bud/form) as SMART versus its administration as fixed-dose combination and short-acting β_2 -agonists as quick-relief therapy in pediatric patients aged 5 to 11 years with asthma uncontrolled on ICS.

We used a Markov simulation model with cycle length of 1 week and 3 mutually exclusive nonabsorbent states,⁴ labeled “no symptoms,” “suboptimal control, no exacerbation,” and “asthma exacerbation.” The time horizon was 12 months, and therefore the costs and effects were not discounted. The main outcome of the model was quality-adjusted life-years (QALYs). The model compared direct medical costs and disease outcomes from the perspective of the health care system in Colombia.

The following assumptions were made: (1) In the “no symptoms” health state, patients undergoing both therapies were treated with bud/form 80/4.5 μ g once a day. (2) In the “suboptimal control, no exacerbation” health state, patients

undergoing SMART were treated with bud/form 80/4.5 μ g 8 inhalations per day (7 as-needed inhalations per day in addition to their daily maintenance treatment) for 1 week (the duration of a cycle length). (3) In the “suboptimal control, no exacerbation” health state, patients undergoing the fixed-dose combination therapy were treated with 8 inhalations of albuterol per day in addition to their daily maintenance therapy with bud/form 80/4.5 μ g once a day for 1 week.⁵

Effectiveness data and transition probabilities were obtained from the ICSs-LABA branch of previous economic evaluations,⁶ and a randomized clinical trial.⁵ Utilities were derived from the pediatric asthma health outcome measure,⁷ and from a Colombian survey. Health states corresponding to “no symptoms,” “suboptimal control, no exacerbation,” and “asthma exacerbation” had utility values of 0.989, 0.705, and 0.275, respectively.

Resource utilization and costs were obtained from consensus of experts, a local cost study,⁸ and an official database provided by the Colombian Ministry of Health and Social Protection. For the cost calculations of the bud/form as SMART, in the “no symptoms” health state, we calculated the cost of 1 inhalation per day of bud/form 80/4.5 μ g, and in the “suboptimal control, no exacerbation” health state, we calculated the cost of 8 inhalations per day of bud/form 80/4.5 μ g for 1 week (the duration of a cycle length).⁵ Similarly, for the cost calculations of the fixed-dose combination therapy, in the “no symptoms” health state, we calculated the cost of 1 inhalation per day of bud/form 80/4.5 μ g, and in the “suboptimal control, no exacerbation” health state, we calculated the cost of 8 inhalations per day of albuterol in addition to their daily maintenance therapy with bud/form 80/4.5 μ g once a day, for 1 week.⁵

Costs were calculated in Colombian pesos and converted to dollars (US \$s) based on the average exchange rate for 2018 (US \$1 = 2956.55 Colombian pesos).⁹

The study protocol was approved by the local ethics board.

To assess the robustness of the model’s results, we performed deterministic sensitivity analyses and probabilistic sensitivity analysis using a second-order Monte-Carlo simulation.

Transition probabilities included in the model are presented in [Table E1](#) in this article’s Online Repository at www.jaci-inpractice.org.

The base-case incremental cost-utility analysis showed that compared with the fixed-dose combination therapy, the bud/form as SMART involved lower overall treatment costs (US \$1826.6 vs US \$3523.2 average cost per patient) and a greater gain in QALYs (0.8537 vs 0.8391 QALYs on average per patient). A position of dominance negated the need to calculate an incremental cost-effectiveness ratio ([Table 1](#)).

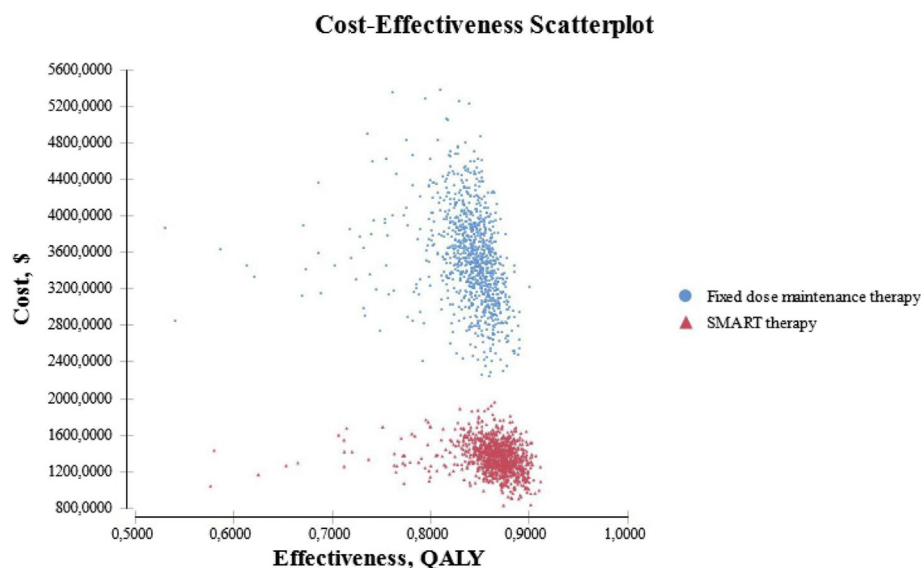
In the deterministic sensitivity analyses, our base-case results were robust to variations of all assumptions and parameters.

Parameter distributions used in the probabilistic sensitivity analysis are presented in [Table E2](#) in this article’s Online Repository at www.jaci-inpractice.org.

Based on the results of the probabilistic sensitivity analysis, in 77.0% of the iterations, the bud/form as SMART was associated with greater gain in QALYs and lower costs compared with the fixed-dose combination therapy ([Figure 1](#)).

TABLE I. Base-case cost-effectiveness analysis of bud/form as SMART vs fixed-dose combination for the treatment of pediatric patients with uncontrolled asthma on ICSs

Category	Strategy	Cost (US \$)	Incremental cost (US \$)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost/effectiveness
Absolutely dominated	Fixed-dose combination	3523.2	1696.6	0.8391	−0.0146	4198.6
Undominated	SMART	1826.6	—	0.8537	—	2139.6

**FIGURE 1.** Scatter plot of each iteration's cost and effectiveness values for each strategy in pediatric patients with uncontrolled asthma on ICSs. The X-axis shows the effectiveness, measured as QALYs; the Y-axis shows the costs measured in dollars (US \$, 2018). Each point represents 1 of the 10,000 trial runs, where each input was assigned a random value according to its probability density function.

The fact of demonstrating that a treatment strategy that ensures that patients receive not only an immediate increase in anti-inflammatory therapy but also rapid and sustained relief is not only more effective but also less costly when compared with a more fixed strategy is in good agreement with the periodic fluctuation in symptoms and airway inflammation that are characteristics of asthma.⁵

To our knowledge, there is only 1 study evaluating the clinical effects of bud/form as SMART in children aged 4 to 11 years with asthma uncontrolled on ICS.⁵ Bisgaard et al⁵ found that when compared with fixed-dose budesonide and a fixed combination of bud/form (plus terbutaline for rescue medication), bud/form as SMART significantly prolonged the time to first exacerbation. In addition, secondary outcomes were also significantly better with bud/form as SMART when compared with the other 2 strategies.⁵

Despite the limitation that most input-effectiveness parameters were derived from a single randomized clinical trial published several years ago, we can conclude that in Colombia, a low- and middle-income country, when compared with a fixed-dose combination, the use of bud/form as SMART in children aged 5 to 11 years with asthma uncontrolled on ICS is a dominant strategy because it involves a greater gain in QALYs

at lower total treatment costs. This finding supports the recommendation of the 2020 focused update of the National Asthma Education and Prevention Program asthma guideline for treating these patients with bud/form as SMART as the preferred strategy.

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TABLE E1. Baseline transition probabilities for bud/form in SMART vs fixed-dose combination for the treatment of pediatric patients with uncontrolled asthma on ICSs

Transition from	Transition to:		
	No symptoms	Suboptimal control, no exacerbation	Asthma exacerbation
No symptoms			
SMART	0.749	0.229	0.020
Fixed-dose combination	0.804	0.140	0.056
Suboptimal control, no exacerbation			
SMART	0.470	0.430	0.098
Fixed-dose combination	0.505	0.227	0.268
Asthma exacerbation			
SMART	0.361	0.516	0.121
Fixed-dose combination	0.388	0.282	0.330

TABLE E2. Parameter distributions used in the probabilistic sensitivity analysis

Probability distribution	Distribution parameters	Distribution parameters
Beta distribution	Alpha	Beta
Probability from no symptoms to no symptoms with SMART	99.25	33.08
Probability from no symptoms to suboptimal control with SMART	303.76	961.90
Probability from no symptoms to asthma exacerbation with SMART	391.98	19207.02
Probability from suboptimal control to no symptoms with SMART	211.53	238.53
Probability from suboptimal control to suboptimal control with SMART	227.57	301.66
Probability from suboptimal control to asthma exacerbation with SMART	360.70	3319.93
Probability from asthma exacerbation to no symptoms with SMART	255.64	454.47
Probability from asthma exacerbation to suboptimal control with SMART	193.08	181.10
Probability from asthma exacerbation to asthma exacerbation with SMART	351.88	2580.45
Probability from no symptoms to no symptoms with fixed-dose combination	77.596	18.916
Probability from no symptoms to suboptimal control with fixed-dose combination	343.860	2112.282
Probability from no symptoms to asthma exacerbation with fixed-dose combination	377.544	6364.313
Probability from suboptimal control to no symptoms with fixed-dose combination	197.495	193.584
Probability from suboptimal control to suboptimal control with fixed-dose combination	308.972	1052.141
Probability from suboptimal control to asthma exacerbation with fixed-dose combination	292.532	799.005
Probability from asthma exacerbation to no symptoms with fixed-dose combination	244.412	385.515
Probability from asthma exacerbation to suboptimal control with fixed-dose combination	286.918	730.521
Probability from asthma exacerbation to asthma exacerbation with fixed-dose combination	267.670	543.451
Health states QALYs		
No symptoms	3.411	0.037
Suboptimal control, no exacerbation	117.295	49.080
Asthma exacerbation	289.725	763.820
Gamma distribution	Alpha	Lambda
Cost of no symptoms state	16	15.686
Weekly cost of suboptimal control state with SMART	16	1.965
Weekly cost of suboptimal control state with fixed-dose combination	16	9.815
Cost of exacerbation state	64	0.125