

UNDERSERVED POPULATIONS

Cost-Utility Analysis of the Inhaled Steroids Available in a Developing Country for the Management of Pediatric Patients with Persistent Asthma

CARLOS E. RODRÍGUEZ-MARTÍNEZ, M.D., M.SC.,^{1,*}, MÓNICA P. SOSSA-BRICEÑO, M.D., M.SC.,² AND
JOSE A. CASTRO-RODRIGUEZ, M.D., PH.D.³

¹*Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia; Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque; Research Unit, Military Hospital of Colombia, Bogota, Colombia.*

²*Department of Internal Medicine, Clínica Reina Sofía, Bogota, Colombia.*

³*Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.*

Introduction. The choice among the different treatments available can have a great impact on the costs of asthma, **Objectives.** The objective of this study was to estimate the incremental cost-utility ratio of three inhaled corticosteroids (ICs): budesonide (BUD), fluticasone propionate (FP), and ciclesonide, compared to beclomethasone dipropionate (BDP) (the only IC included in the Compulsory Health Insurance Plan of Colombia), **Methods.** A Markov-type model was developed to estimate costs and health outcomes of a simulated cohort of patients less than 18 years of age with persistent asthma treated over a 12-month period. Effectiveness parameters were obtained from a systematic review of the literature. Cost data were obtained from a hospital's bills and from the national manual of drug prices. The study assumed the perspective of the national healthcare in Colombia. The main outcome was the variable "quality-adjusted life years" (QALY), **Results.** While treatment with BDP was associated with the lowest cost (£106.16 average cost per patient during 12 months), treatment with FP resulted in the greatest gain in QALYs (0.9325 QALYs). FP was associated with a greater gain in QALYs compared to BUD and ciclesonide (0.9325 vs. 0.8999 and 0.9051 QALYs, respectively) at lower costs (£231.19 vs. £309.27 and £270.15, respectively), thus leading to dominance. The incremental cost-utility ratio of FP compared to BDP was £19,835.28 per QALY, **Conclusions.** BDP is the most cost-effective therapy for treating pediatric patients with persistent asthma when willingness to pay (WTP) is less than £21,129.22/QALY, otherwise, FP is the most cost-effective therapy.

Keywords asthma, children, cost-effectiveness, developing countries, inhaled corticosteroids, quality-adjusted life years

INTRODUCTION

The prevalence of asthma has increased since 2001 in the United States (1) and is a major public health problem in many countries, such as Colombia, which has a prevalence estimated at 10–12% (2, 3). Inhaled corticosteroids (ICs) are at present considered the controller of first choice for the treatment of persistent asthma of any degree of severity (4). The economic burden of this disease is important in terms of both direct medical and indirect costs for patients and for healthcare systems (5). Due to the high prevalence of asthma and the elevated costs associated with its poor control, the choice among the different treatments available can have a great impact on the costs of the disease (6).

Although numerous asthma cost-effectiveness analyses have been reported (5–12), to the best of our knowledge, none has been conducted based on pediatric patients and costs in a Latin American health system. In addition, the majority of these studies did not take into account either the chronic and episodic nature of asthma or the fact that in the real world the clinical effectiveness of treatments for asthma can be compromised due to low adherence (13).

The objective of this study was to estimate the incremental cost-utility ratio of three ICs currently licensed in

Colombia for use in children with persistent asthma (budesonide (BUD), fluticasone propionate (FP), and ciclesonide), compared to beclomethasone dipropionate (BDP), which is the only IC included in Colombia's compulsory health insurance plan.

METHODS

Model Structure

We developed a Markov simulation model with three mutually exclusive nonabsorbent states (regular Markov chain) (14, 15). In this model, the following three distinct health states were defined: "no symptoms", "suboptimal control, no exacerbation", and "asthma exacerbation", based on the economic implications of each of these states (Figure 1).

In the same manner as the model developed by Price MJ et al. (7), due to the chronic, episodic nature of asthma, a cycle length of 1 week was considered appropriate for this model. Likewise, in accordance with the above-mentioned model, we did not include costs for treatment of adverse events in our cost-utility model.

Treatment Adherence

In order to incorporate treatment adherence into the model, first we calculated different adherence rates for each IC based on their frequency of administration (one vs. two

*Corresponding author: Carlos E. Rodríguez-Martínez, M.D., M.Sc., Avenida Calle 127, No. 20–78, Bogota, Colombia. Tel: (57-1) 2595500; E-mail: carerodriguezmar@unal.edu.co

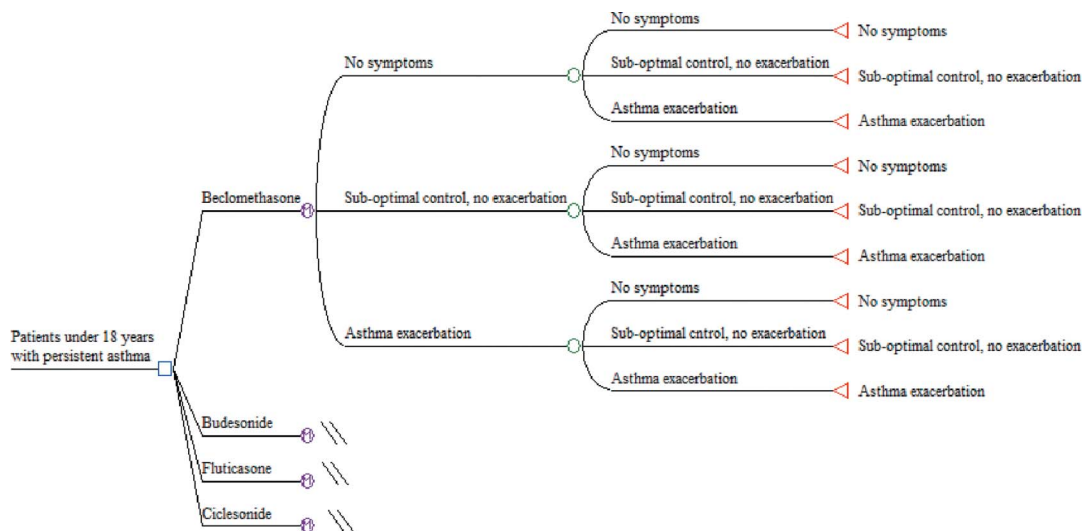


FIGURE 1.— Diagram of the Markov model for each treatment option.

doses per day) as reported (16) and applied the mathematical formula proposed by Tina-shah YC et al. (6) for adjusting the treatment effectiveness according to the level of therapeutic adherence. Second, assumptions regarding decrease of adherence to ICs over time were based on long-term treatment data for BUD. (17). Therefore, we assumed adherence rates of 88%, 62%, and 61% (3, 9, and 12 months after beginning treatment, respectively) for BUD and ciclesonide, and adherence rates of 77%, 54%, and 53% (3, 9, and 12 months after beginning treatment, respectively) for BDP and FP. Third, in addition to treatment effectiveness, we also adjusted costs according to this level of therapeutic adherence. Finally, the adherence-adjusted costs and effectiveness were incorporated into the model.

Time Elapsed for Reaching Full Effectiveness

Due to the fact that some ICs can take longer than others to reach full effect (18), we incorporated this source of variation into the model, using previously published articles (19, 20). We assumed that this time frame for reaching full effect using ciclesonide was similar to FP. The time frame for reaching full effect that was incorporated into the model for BDP, FP, BUD, and ciclesonide was 6, 4, 7, and 4 weeks, respectively.

SOURCES OF DATA

Disease Outcomes and Clinical Parameters

These were obtained from a systematic review of published randomized clinical trials and observational studies. Searches of computerized databases (MEDLINE, EMBASE, CENTRAL, and LILACS) and references cited in published literature identified the potentially applicable studies. The computerized search yielded 1570 citations, and a total of 55 studies were examined in full text for possible inclusion. For inclusion of data in the

model, participants in the studies needed to be under the age of 18 years with persistent asthma, and studies needed to include at least one of the four treatments analyzed in the model administered by metered-dose inhaler (MDI) and report at least one of the following outcomes: percentage of symptom-free days or probability of asthma exacerbation during the period of observation. Studies were excluded if they included patients with no clear diagnosis of asthma and patients over 18 years, if ICs were administered as dry powder inhalers, if BUD or BDP nebulizer suspension was used, if a combination of BDP and salbutamol in a single inhaler was used, or there was use of hydrofluoroalkane (HFA) as a propellant in the BDP MDI, because these were not available in Colombia at the time of the study. After applying these criteria, data from 24 publications were included in the model (21–44).

Data Inputs: Transition Probabilities

Transition probabilities were calculated following a methodology proposed by Briggs A. et al. (45) First, “baseline” transition probabilities were calculated by means of a weighted average of selected parameters of studies that included a placebo group and observational studies (21–29). Transitional probabilities for each of the three ICs were based on an adjustment to these baseline values according to the effectiveness of treatment of each IC relative to placebo. Second, transitional probabilities from the “sub-optimal control, no exacerbation” to the “asthma exacerbation” state for each IC were calculated multiplying baseline probabilities by the relative risk or the odds ratio for this outcome reported in the Cochrane meta-analysis that compares each IC with a placebo (30–32). This probability with respect to ciclesonide use was assumed to be the same as that of FP because this outcome is not reported in the Cochrane meta-analysis that compares ciclesonide with a placebo (33). Third, in order to calculate transition probabilities from the “sub-optimal control, no exacerbation” to the “no symptoms” state for

each IC, a weighted average of the outcome “symptom-free days” was synthesized from clinical trial information (21–24, 34–44). Fourth, in order to calculate the probability that the patients will continue in the “no symptoms” state for each IC, we assumed values 10% greater than transition probabilities from the “sub-optimal control, no exacerbation” to the “no symptoms” state. These assumptions were subjected to a thorough sensitivity analysis. Finally, to complete the remainder of the transitional probability matrix for each IC, we calculated the difference of one minus the sum of the probabilities in the same row (the sum of probabilities of each row must be equal to one).

Adjustments were made for studies with different time-frames. As it is possible to convert an instantaneous rate to a probability over a particular time period if the rate is assumed to be constant over that period, we calculated 1-week probabilities of the events based on instantaneous rates derived for these events (15, 45).

Data Inputs: Health Outcomes

Utility values for the three health states included in the model were based on a utility valuation survey of 76 parents of children with asthma in Colombia using standard gamble methodology (45). Parents were chosen as the most suitable patient-proxy respondents on the basis that many children with asthma would be too young to provide reliable responses.

The health state description comprised three domains, based on those reported in the Pediatric Asthma Health Outcome Measure (46): symptoms, emotions, and activity. Descriptions for the three domains were derived largely based on this study and validated by clinical experts.

The health state “no symptoms” had the highest utility value (0.989). Health states corresponding to “sub-optimal control, no exacerbation” and “asthma exacerbation” had utility values of 0.705 and 0.275, respectively. The number of QALYs was calculated as the utility value given to a particular health state multiplied by the length of time spent in that state.

Data Inputs: Resource Utilization and Costs

Each Markov-model health state has an associated cost, which is considered from the perspective of the national healthcare system in Colombia. Unit costs of all medications were taken from the national manual of drug prices based on the “Farmaprecios” 2007 guide (47).

Calculation of the daily cost of ICs was based on the estimated average daily dose appropriate for treating pediatric patients with mild-to-moderate persistent asthma according to current asthma guidelines (4, 48) and the relative use of available concentrations for each medication according to current market research.

Costs associated with the “no symptoms” and the “sub-optimal control, no exacerbation” health states were based on actual resource use as measured by an eight-item questionnaire that was filled out by three pediatric pulmonologists and verified with administrative data from care providers. The data collected on resource use were: the number of planned consultations with general practitioner,

pediatrician, or pediatric pulmonologist; the number of unscheduled medical visits; and the amount of asthma medication used (anti-inflammatory and/or reliever medications). Costs associated with the “asthma exacerbation” state were calculated based on a review of medical records of all patients aged less than 18 years discharged with a principal diagnosis of asthma (ICD-10 codes J450, J451, J458, J459, or J46X) between January 1 June 2007 and 30 June 2007 from Clinica Infantil Colsubsidio, a pediatric clinic located in the city of Bogota that receives patients from one of the most representative medical insurance companies in the city. Resource use and costs associated with 512 asthma exacerbations were evaluated in terms of medication usage, physician time, and, where appropriate, hospital costs. Median costs, together with interquartile range (IQR), were calculated for asthma exacerbations managed in different settings. Hospital-managed exacerbations involved management of asthma either in an emergency room alone or with subsequent management as an inpatient (in an asthma inpatient ward and/or in a pediatric intensive care unit). To reflect this, the cost associated with this health state was calculated as a weighted average of the costs of exacerbations managed in the emergency room and of those managed during an inpatient stay, based on the frequency of hospital admission observed in our review of medical records.

Costs were calculated in Colombian pesos (COP) and converted to UK pounds sterling (£) based on the average exchange rate for 2007 (1£ = 2957.98 COP\$) (49). Given that the model duration was one year, costs and effects were not discounted.

Sensitivity Analyses

A series of one-way, two-way, and multi-way sensitivity analyses (using a tornado diagram) and the effect of alternative model specifications were examined. In addition, a probabilistic sensitivity analysis using second-order Monte Carlo simulation was used to analyze uncertainty in the data. This probabilistic sensitivity analysis allowed us to generate confidence intervals around costs and effects. These were presented graphically on a cost-effectiveness plane to show the estimated joint distribution of incremental costs against incremental effects and evaluated using net benefit analysis (50). Subsequently a cost-effectiveness acceptability curve was derived from these data (51).

All analyses were performed with software (TreeAge Pro 2008, TreeAge Software, Williamstown, Mass).

RESULTS

The resulting transition probabilities (point estimates) of the Markov model from the “sub-optimal control, no exacerbation” to the “no symptoms” health state for placebo, BDP, BUD, FP, and ciclesonide were 31.4%, 81.7%, 71.5%, 82.8%, and 70.5%, respectively. The resulting transition probabilities from the “sub-optimal control, no exacerbation” to the “asthma exacerbation” state showed

TABLE 1.—Transition probabilities for patients with asthma treated with beclomethasone, budesonide, fluticasone, and ciclesonide.

Transition from	Transition to: No symptoms	Sub-optimal control, no exacerbation	Asthma exacerbation
No symptoms			
Basal	0.417	0.569	0.013
Beclomethasone	0.899	0.097	0.004
Budesonide	0.769	0.227	0.003
Fluticasone	0.910	0.087	0.002
Ciclesonide	0.776	0.221	0.002
Sub-optimal control, no exacerbation			
Basal	0.314	0.660	0.025
Beclomethasone	0.817	0.175	0.007
Budesonide	0.699	0.294	0.006
Fluticasone	0.828	0.168	0.004
Ciclesonide	0.705	0.291	0.004
Asthma exacerbation			
Basal	0.105	0.724	0.170
Beclomethasone	0.274	0.674	0.051
Budesonide	0.234	0.723	0.041
Fluticasone	0.278	0.694	0.027
Ciclesonide	0.237	0.729	0.034

that while BDP use was associated with the highest probability of asthma exacerbation, FP and ciclesonide use was associated with the lowest probability of asthma exacerbation (Table 1).

Of the total of 512 medical records of asthma exacerbations reviewed, 17.8% were exacerbations managed in the emergency department (ED), 81.2% in the asthma inpatient ward, and 1% in the pediatric intensive care unit. As expected, the value of the unit cost of hospitalization for asthma exacerbation was greater than the cost of treatment in the emergency department and the cost of unscheduled medical visits (Table 2). The weekly cost per patient associated with all three health states was lower for BDP than for the rest of the ICs (Table 3).

The base-case incremental cost-utility analysis showed that while treatment with BDP was associated with the lowest cost (£106.16 average cost per patient during 12 months), treatment with FP resulted in the greatest gain in QALYs (0.9325 QALYs on average per patient during 12

TABLE 2.—Values of unit costs (£, 2007).

Cost items	Unit costs	Lower value	Higher value
Anti-inflammatory medications^a			
Beclomethasone	0.07/day	0.02/day	0.12/day
Budesonide	0.71/day	0.13/day	1.28/day
Fluticasone	0.57/day	0.24/day	0.91/day
Ciclesonide	0.65/day	0.37/day	0.94/day
Medications for treating asthma exacerbations			
Salbutamol via pMDI	0.005/puff	0.004/puff	0.007/puff
Prednisolone × 5mg	0.08/tablet	0.07/tablet	0.09/tablet
Unscheduled medical visit	4.72	4.03	5.40
Treatment in the emergency department	83.71	27.32	176.79
Hospitalization for asthma exacerbation	181.31	63.88	10,362.70

Note: ^aCalculation of the daily cost of ICs was based on the estimated average daily dose appropriate for treating pediatric patients with mild-to-moderate persistent asthma according to current asthma guidelines and the relative use of available concentrations for each medication according to current market research.

months). FP was associated with a greater gain in QALYs compared to BUD and ciclesonide (0.9325 vs. 0.8999 and 0.9051 QALYs, respectively, on average per patient) at lower costs (£231.19 vs. £309.27 and £270.15, respectively, on average per patient), thus leading to dominance. The incremental cost-utility ratio of FP compared to BDP was £19,835.28 per QALY (Table 4).

Sensitivity Analyses

One-way, two-way, and multi-way sensitivity analyses (using a tornado diagram) showed that the cost of asthma exacerbation has the highest impact on the model outcome. As the cost of asthma exacerbation increases, the incremental cost-utility ratio of FP vs. BDP decreases, and the threshold value for the cost of asthma exacerbation at which FP dominates BDP (threshold value at which FP is associated with a greater gain in QALYs and at lower costs compared to BDP) is £1,060.85.

Parameter distributions used in the probabilistic sensitivity analysis are presented in Table 5. The results of the probabilistic sensitivity analysis are graphically represented as scatter plot for incremental cost-utility ratios in Figure 2, which shows that while BDP tends to be

TABLE 3.—Resource use and costs associated with model health states.

Health state	Resources costed	Weekly cost per patient (£)			
		Beclomethasone	Budesonide	Fluticasone	Ciclesonide
No symptoms	Study medication	0.53	4.97	4.02	4.59
Sub-optimal control No exacerbation^a	Study medication	1.45	5.88	4.94	5.50
Asthma exacerbation^b	Rescue medication and unscheduled medical visits.				
	Study medication, Rescue medication, Oral or parenteral corticosteroids, ED visit and hospitalization	259.36 2	263.79	262.85	263.41

Notes: ^a We assumed that patients in the “sub-optimal control, no exacerbation” health state needed salbutamol via pMDI two puffs every six hours during all the cycle length of 1 week and one unscheduled medical visit every two months.

^b We assumed that patients in the “asthma exacerbation” health state needed salbutamol via pMDI two puffs every 20 minutes for the first hour, two puffs every hour for the next 2 hours, two puffs every two hours for the next 6 hours, 2 puffs every four hours for the next 48 hours and finally 2 puffs every six hours for the remainder of the week. Additionally, we assumed that patients in this health state needed prednisolone 1mg/Kg/day for five days.

TABLE 4.—Base-case incremental cost-utility analysis of fluticasone, ciclesonide, and budesonide vs. beclomethasone.

Comparators	Cost (£)	Incremental cost	Utility ^a	Incremental utility	C/U ^b	ICUR ^c
Step 1: Rank by costs and compare utility with the next lowest cost comparator						
Beclomethasone	106.16		0.9262		114.62	
Fluticasone	231.19	125.03	0.9325	0.0063	247.92	19,835.28
Ciclesonide	270.15	38.96	0.9051	−0.0274	298.47	(Dominated)
Budesonide	309.27	78.07	0.8999	−0.0326	343.67	(Dominated)
Step 2: Compare the remaining comparators						
Beclomethasone	106.16		0.9262		114.62	
Fluticasone	231.19	125.03	0.9325	0.0063	247.92	19,835.28

Notes: ^aUtility measured as quality adjusted life of years (QALY).^bMean cost-utility ratio.^cIncremental cost-utility ratio.

TABLE 5.—Parameter distributions used in the probabilistic sensitivity analysis.

Probability distribution	Distribution parameters	
Beta distribution	Alpha	Beta
Probability of days without asthma symptoms		
– Beclomethasone	352	431
– Budesonide	298	417
– Fluticasone	817	987
– Ciclesonide	1025	1454
Lognormal distribution	Mean for ln (x)	SD for ln(x)
Cost of asthmatic exacerbations	13.0256	1.0068
Probability of asthma exacerbation		
– Beclomethasone, RR	−1.204	0.444
– Budesonide, RR	−1.406	0.277
– Fluticasone, OR	−1.832	0.385
– Ciclesonide, OR	−1.832	0.385
Uniform distribution	Minimum value	Maximum value
Frequency of unscheduled medical visits	4 per year	12 per year

associated with lower costs, FP tends to be associated with greater gain in QALYs. Based on the results from this simulation, the 95% uncertainty limits for cost per patient treated with BDP and FP were £34.17 to £359.86 and £139.36 to £384.40, respectively. Likewise, the 95% uncertainty limits for utilities per patient treated with BDP and FP were 0.8934 to 0.9581, and 0.9016 to 0.9624, respectively. In 12.9% of the iterations, FP was associated with greater gain in QALYs compared to BDP and with costs below a predefined willingness to pay (WTP) threshold of £9803.96 (threshold value based on local gross domestic product (GDP)—GDP per capita, proposed by the World Health Organization (WHO), to be used in developing countries).

The cost-effectiveness acceptability curve shows the probability of FP being cost-effective compared to BDP in a wide range of WTP thresholds: at £9803.96/QALY (corresponding to three times Colombia's GDP for 2008), FP had an 18% probability of being cost-effective; and at greater than £21,129.22/QALY, FP would be more cost-effective than BDP (Figure 3).

DISCUSSION

This study shows that when compared with the other three ICs licensed in Colombia, BDP is the most cost-effective therapy for treating pediatric patients with persistent asthma when WTP is less than £21,129.22/QALY; otherwise, FP is the most cost-effective therapy. When using a WTP of £9803.96/QALY, a threshold value recommended by the WHO to be used in developing countries (based on GDP per capita) (52), FP had an 18% probability of being cost-effective. The only variable that exhibited a significant effect on these results was the cost of asthma exacerbation.

To our knowledge, this report is the first to formally perform a comprehensive economic evaluation comparing ICs licensed in any low- to middle-income country for treating pediatric patients with persistent asthma. Although public funding of newer ICs such as BUD has been a common practice in more affluent countries (53), our results suggest that this practice could have significant

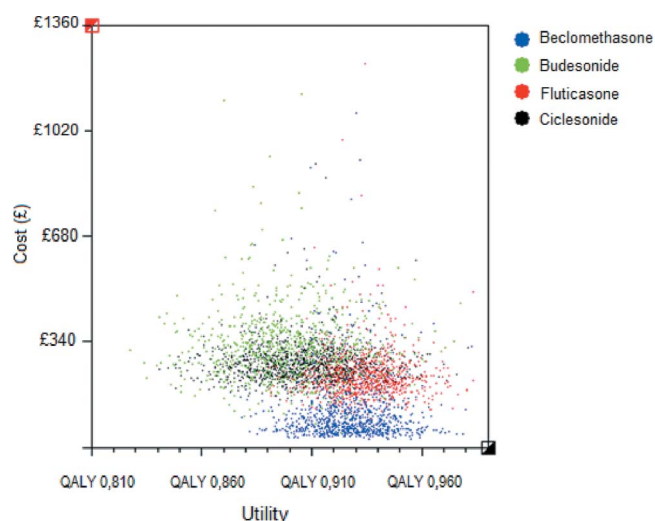


FIGURE 2.—Scatter plot for incremental cost-utility ratios (ICUR).

Each point represents one of the 10,000 Monte Carlo simulations and represents the mean incremental cost and utility of budesonide (BUD), fluticasone, and ciclesonide, compared to beclomethasone. QALYs: quality-adjusted life years.

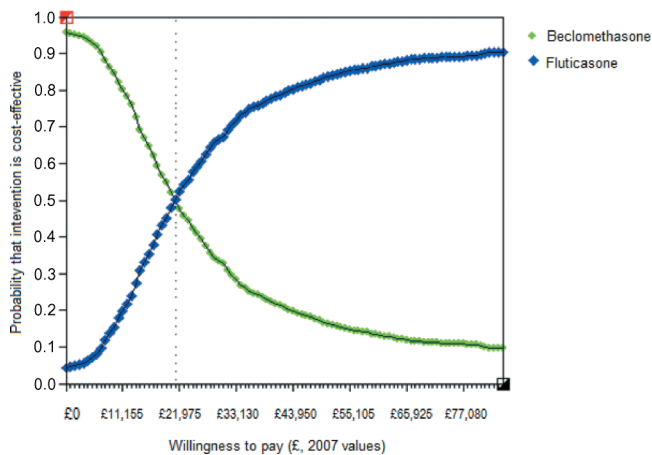


FIGURE 3.—Cost-effectiveness acceptability curve with fluticasone versus beclomethasone in pediatric patients with asthma.

The cost-effectiveness acceptability curve shows the probability of fluticasone propionate (FP) being cost-effective compared to beclomethasone dipropionate (BDP) in a wide range of willingness to pay (WTP) thresholds. At £9803.96/QALY (corresponding to three times Colombia's GDP for 2008), FP had an 18% probability of being cost-effective; and at greater than £21,129.22/QALY, FP would be more cost-effective than BDP.

cost of opportunity impact in Colombia and probably in other similar low- to middle-income countries. This is perhaps unsurprising, in view of the huge differences in medication costs and the results of two Cochrane's systematic reviews that compare the efficacy of these ICs in adults and in children (54, 55), concluding that although FP may lead to small additional improvements in certain measures (such as FEV₁ and PEF), in general all ICs at equipotent doses provide a similar level of asthma control.

Possible reasons for choosing ICs such as BUD, FP, or ciclesonide instead of BDP are time to response, potency, convenience, effectiveness, compliance, costs, and frequency of adverse side effects. There is some evidence that patients treated with FP exhibit an earlier response than those treated with BUD or BDP (19, 20). However, given that ICs generally are used for long-term therapy for asthma, the clinical significance of this early response is unlikely to be important (56). In relation to potency, FP has twice that of either BDP or BUD (57, 58). Likewise, FP demonstrates greater glucocorticoid receptor binding affinity and higher lipophilicity when compared to BDP and BUD (57). However, potential advantages in this respect are only important if they are not achieved at the expense of increased systemic drug availability, since a more potent IC may be related to more side effects. BDP is less efficiently inactivated by the liver than is BUD and FP, giving rise to more systemic adverse effects (59). Otherwise, ciclesonide has a higher security profile, since it is an agent that is inactive until it reaches its target site, the lung, where it is converted to its active form (60). Fortunately, these side effects of ICs are few and far between, and with a minimal economic impact. Among these systemic adverse effects, temporal deceleration of linear growth velocity may be the most important for children. The effect of ICs on linear growth in children with asthma may be confounded by poorly controlled

asthma, reduced growth rates before puberty, delayed puberty, and frequent use of growth-suppressing systemic steroids (61). Moreover, a recent study showed that the initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative (62). Finally, although all of the ICs are effective when taken twice daily, once-daily dosing may be equally effective for BUD and ciclesonide, and this frequency of dosing has been shown to have benefits in terms of improved compliance (16). It seems that when taken together, all the aforementioned factors translate to a slightly higher clinical efficacy for FP compared to other ICs (54, 55). However, taking into account differences in medication costs in Colombia, BDP has a better cost-effectiveness profile, at least at low levels of WTP.

Our results agree with previous studies done in adults and children (12, 63), which have found that asthma treatment with FP is associated with greater clinical efficacy as well as with lower costs when compared to BUD. However, Trakas K et al. (64) found that in adults with moderate to severe asthma, BUD was a more cost-effective alternative than BDP and FP. Nevertheless, our findings are not easy to compare to those of previous studies because of differences in type of model (decision tree vs. Markov model), population analyzed (adults vs. pediatric patients), source of clinical parameters (based on a single study vs. a systematic review of the literature), time horizon of the study, and adjustment of the effectiveness and cost of each treatment for its respective rate of adherence.

The present study has many strengths. First, since asthma is a chronic, episodic disease, the disease is best modeled using a Markov model rather than a decision tree. Second, we took into account the effect of the different time frames for reaching full effect for all the comparators. Finally, we took into account the effect of incomplete and failing adherence to therapy that typically occurs when treating chronic diseases such as asthma. None of the previous studies accounted for all these factors simultaneously. Consequently, we believe that the present study provides a more complete overview of the cost-effectiveness of the use of ICs for the treatment of pediatric patients with persistent asthma in a developing country.

Our model also has some limitations. First, the base-case analysis was run for 12 months instead of a complete lifetime. However, because there is compelling evidence that asthma treatment in children with ICs does not alter the natural history of the disease, and has little influence in the final adult height (62), we judged a 12-month period to be long enough to determine the major health and economic consequences of taking ICs in pediatric asthmatics. Second, resource utilization and cost data were obtained from a single clinical center and may not be representative of the whole country. However, these data were obtained from a pediatric clinic that receives patients from one of the most important and representative medical insurance companies in the city. Moreover, costs were subject to wide sensitivity analyses. Finally, the perspective used was the

national healthcare system in Colombia, and thus only direct medical costs were considered in the model. Although the exclusion of indirect costs representing the loss of productivity of parents/caregivers may be biased against newer ICs since treatment with these medications is likely to decrease these costs because of their lesser associated probability of asthma exacerbations, and their inclusion is likely to be sufficient to maintain incremental cost per QALY gained of FP at unacceptable levels.

CONCLUSIONS/KEY FINDINGS

In conclusion, the present analysis shows that when compared with the other three ICs licensed in Colombia, BDP is the most cost-effective therapy for treating pediatric patients with persistent asthma when WTP is less than £21,129.22/QALY; otherwise, FP is the most cost-effective therapy. From the perspective of the national healthcare in Colombia, these findings suggest that compared to BDP, newer ICs currently licensed for use in pediatric patients with persistent asthma in Colombia show an incremental cost-utility ratio outside the range of some well-accepted medical interventions in developing countries and have a significant opportunity cost, and resources could probably be used better elsewhere. Alternatively, since the QALY has been called into question lately (65), and some health systems do not use cost-per-QALY thresholds any more, our analysis could provide an input into price negotiations for newer ICs (FP) in Colombia and probably in other similar low- to middle-income countries (66).

ACKNOWLEDGMENTS

We would like to thank Carlos Crespo-Palomo, José Manuel Rodríguez-Barrios, Darío Londoño MD, MSc, Federico Augustovski MD, MSc, and Jorge A Diaz R Q.F. MSc, for their helpful guidance in the preparation of this article. We also thank Mr. Charlie Barret for his editorial assistance.

DECLARATION OF INTEREST

Carlos E. Rodriguez-Martinez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorships of Merck Sharp & Dome and AztraZeneca. He has also received payments from GlaxoSmithKline, AztraZeneca, MSD, and Grunenthal for the development of educational presentations. Jose A. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorships of AztraZeneca, GlaxoSmithKline, Merck Sharp & Dome, and Novartis.

REFERENCES

- Centers for Disease Control and Prevention (CDC). Vital signs: Asthma prevalence, disease characteristics, and self-management education-

- United States, 2001–2009. *MMWR Morb Mortal Wkly Rep* 2011; 60:547–552.
- Dennis RJ, Caraballo L, García E, Rojas MX, Rondon MA, Pérez A, Aristizabal G, Peñaranda A, Barragan AM, Ahumada V, Jimenez S. Prevalence of asthma and other allergic conditions in Colombia 2009–2010: A cross-sectional study. *BMC Pulm Med* 2012; 13:12–17.
- García E, Aristizabal G, Vasquez C, Rodriguez-Martinez CE, Sarmiento OL, Satizabal CL. Prevalence and factors associated with current asthma symptoms in school children aged 6–7 and 13–14 years old in Bogota, Colombia. *Pediatr Allergy Immunol* 2008; 19:307–314.
- GINA Report. Global Strategy for asthma management and prevention, global initiative for asthma. 2011. Available at: <http://www.ginasthma.org>. Accessed September 17, 2012.
- Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost effectiveness of budesonide/formoterol for maintenance and reliever therapy versus salmeterol/fluticasone plus salbutamol in the treatment of asthma. *Pharmacoeconomics* 2006; 24:695–708.
- Tina Shih YC, Mauskopf J, Borker R. A cost-effectiveness analysis of first-line controller therapies for persistent asthma. *Pharmacoeconomics* 2007; 25:577–590.
- Price MJ, Briggs AH. Development of an economic model to assess the cost-effectiveness of asthma management strategies. *Pharmacoeconomics* 2002; 20:183–194.
- O'Connor RD, Nelson H, Borker R, Emmett A, Jhingran P, Rickard K, Dorinsky P. Cost effectiveness of fluticasone propionate plus salmeterol versus fluticasone propionate plus montelukast in the treatment of persistent asthma. *Pharmacoeconomics* 2004; 22:815–825.
- Sheth K, Borker R, Emmett A, Rickard K, Dorinsky P. Cost-effectiveness comparison of salmeterol/fluticasone propionate versus montelukast in the treatment of adults with persistent asthma. *Pharmacoeconomics* 2002; 20:909–918.
- Johansson G, Price MJ, Sondhi S. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/100µg vs. fluticasone propionate 100µg in adults and adolescents with asthma. III: Results. *Pharmacoeconomics* 1999; 16(Suppl 2):15–21.
- Stempel DA, Stanford RH, Thwaites R, Price MJ. Cost-efficacy comparison of inhaled fluticasone propionate and budesonide in the treatment of asthma. *Clin Ther* 2000; 22:1562–1574.
- Wang L, Hollenbeak CS, Mauger DT, Zeiger RS, Paul IM, Sorkness CA, Lemanske RF Jr, Martinez FD, Strunk RC, Szeffler SJ, Taussig LM; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the pediatric asthma controller trial. *J Allergy Clin Immunol* 2011; 127:161–166.
- Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med* 1994; 149:S69–S76.
- Rubio-Terrés C, Echevarría A. Modelos de Markov: Una herramienta útil para el análisis farmacoeconómico. *Pharmacoeconomics – Spanish Research Articles* 2006; 3:71–78.
- Briggs A, Sculpher M. An introduction to Markov modeling for economic evaluation. *Pharmacoeconomics* 1998; 13:397–409.
- Mallol J, Aguirre V. Once versus twice daily budesonide metered-dose inhaler in children with mild to moderate asthma: Effect on symptoms and bronchial responsiveness. *Allergol et Immunopathol* 2007; 35:25–31.
- Johansson G, Carlsen KH, Mowinckel P. Asthma drug adherence in a long term clinical trial. *Arch Dis Child* 2000; 83:330–333.
- Phillips K, Osborne J, Lewis S, Harrison TW, Tattersfield AE. Time course of action of two inhaled corticosteroids, fluticasone propionate and budesonide. *Thorax* 2004; 59:26–30.
- Hoekx JC, Hedlin G, Pedersen W, Sorva R, Hollingworth K, Efthimiou J. Fluticasone propionate compared with budesonide: A double-blind trial in asthmatic children using powder devices at a dosage of 400 µg/day. *Eur Respir J* 1996; 9:2263–2272.
- Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997; 156:688–695.
- Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1–3 years. *Arch Dis Child* 1993; 69:351–355.

22. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2 to 5 year-old asthmatic children. *Am J Respir Crit Care Med* 2000; 162:1500–1506.
23. Lönnkvist K, Hellman C, Lundahl J, Halldén G, Hedlin G. Eosinophil markers in blood, serum, and urine for monitoring the clinical course in childhood asthma: Impact of budesonide treatment and withdrawal. *J Allergy Clin Immunol* 2001; 107:812–817.
24. Gelfand EW, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: Efficacy and safety in asthma. *J Pediatr* 2006; 148:377–381.
25. Katz Y, Lebas FX, Medley HV, Robson R. Fluticasone propionate 50mcg BID versus 100mcg BID in the treatment of children with persistent asthma. *Clin Ther* 1998; 20:424–437.
26. Gleeson JGA, Price JF. Controlled trial of budesonide given by the Nebuhaler in preschool children with asthma. *BMJ* 1988; 297:163–166.
27. Boner AL, Piacentini GL, Bonizzato C, Dattoli V, Sette L. Effect of inhaled beclomethasone dipropionate on bronchial hyperreactivity in asthmatic children during maximal allergen exposure. *Pediatr Pulmonol* 1991; 10:2–5.
28. Benito-Fernández J, Onis-González E, Alvarez-Pitti J, Capapé-Zache S, Vázquez-Ronco MA, Mintegi-Raso S. Factors associated with short-term clinical outcomes after acute treatment of asthma in a pediatric emergency department. *Pediatr Pulmonol* 2004; 38:123–128.
29. Kattan M, Mitchell H, Eggleston P, Gergen P, Crain E, Redline S, Weiss K, Evans R 3rd, Kaslow R, Kerckmar C, Leickly F, Malveaux F, Wedner HJ. Characteristics of inner-city children with asthma: The national cooperative inner-city study. *Pediatr Pulmonol* 1997; 24:253–262.
30. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005; (1), Art. No. CD002738. DOI: 10.1002/14651858.CD002738.pub2.
31. Adams N, Bestall J, Jones PW. Budesonide versus placebo for chronic asthma in children and adults. *Cochrane Database Syst Rev* 1999; (4), Art No. CD003274 DOI: 10.1002/14651858.CD003274.
32. Adams NP, Bestall JC, Lasserson TJ, Jones PW, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005 (4), Art. No. CD003135. DOI: 10.1002/14651858.CD003135.pub3.
33. Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008 (2), Art. No. CD006217. DOI: 10.1002/14651858.CD006217.pub2.
34. Pedersen S, Garcia Garcia ML, Manjra AL, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160mcg/day and fluticasone propionate 176 mcg/day in children with asthma. *Pediatr Pulmonol* 2006; 41:954–961.
35. Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200mcg/day with inhaled beclomethasone dipropionate 400mcg/day in mild and moderate asthma. *Arch Dis Child* 1993; 69:206–211.
36. Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Van Essen-Zandvliet E, Arora S, Szeffler SJ; Pediatric Study Group. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: An open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002; 109:e92.
37. Springer C, Avital A, Maayan CH, Rosler A, Godfrey S. Comparison of budesonide and beclomethasone dipropionate for treatment of asthma. *Arch Dis Child* 1987; 62:815–819.
38. Szeffler SJ, Warner J, Staab D, Wahn U, Le Bourgeois M, van Essen-Zandvliet EE, Arora S, Pedersen S; Pediatric Study Group. Switching from conventional to extrafine aerosol beclomethasone dipropionate therapy in children: A 6-month, open-label randomized trial. *J Allergy Clin Immunol* 2002; 110:45–50.
39. Yiallourous PK, Milner AD, Conway E, Honour JH. Adrenal function and high dose inhaled corticosteroids for asthma. *Arch Dis Child* 1997; 76:405–410.
40. Francis RS. Long-term beclomethasone dipropionate aerosol therapy in juvenile asthma. *Thorax* 1976; 31:309–314.
41. Varsano I, Volovitz B, Malik H, Amir Y. Safety of 1 year of treatment with budesonide in young children with asthma. *J Allergy Clin Immunol* 1990; 85:914–920.
42. Vermeulen JH, Gyurkovits K, Rauer H, Engelstatter R. Randomized comparison and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir Med* 2007; 101:2182–2191.
43. von Berg A, Engelstatter R, Minic P, Srćekovic M, Garcia Garcia ML, Latoš T, Vermeulen JH, Leichtl S, Hellbardt S, Bethke TD. Comparison of the efficacy and safety of ciclesonide 160mcg once daily vs. budesonide 400mcg once daily in children with asthma. *Pediatr Allergy Immunol* 2007; 18:391–400.
44. Garcia Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6 to 14-year-old patients with mild asthma: The MOSAIC study. *Pediatrics* 2005; 116:360–369.
45. Briggs A, Claxton K, Sculpher M. Decision modeling for health economic evaluation. New York: Oxford University Press, 2006.
46. Chiou CF, Weaver MR, Bell MA, Lee TA, Krieger JW. Development of the multi-attribute pediatric asthma health outcome measure (PAHOM). *Int J Qual Health Care* 2005; 17:23–30.
47. Catálogo Farmacéutico Nacional. Available at: <http://www.medicentro.com.co/CATALOGO-FARMA.htm>. Accessed September 17, 2012.
48. British Guideline on the Management of Asthma. A national clinical guideline. British Thoracic Society. Scottish Intercollegiate Guidelines Network. Available at: <http://www.sign.ac.uk/pdf/sign101.pdf>. Accessed September 17, 2012.
49. Banco de la República, Colombia. Series estadísticas. Tasa de cambio. Santa Fe de Bogotá: Banco de la República; 2009. Available at: http://www.banrep.gov.co/series-estadisticas/see_ts_cam.htm. Accessed September 17, 2012.
50. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: Issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Med Care* 1994; 32:150–163.
51. Briggs AH, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: Choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002; 22:290–308.
52. Commission on Macroeconomics and Health, World Health Organization (WHO). Macroeconomics and Health: Investing in Health for Economic Development. Geneva: World Health Organization, 2001.
53. Acceso a medicamentos esenciales: compras corporativas nacionales y implicancias para el nivel regional y local. Available at: <http://www.eurosocialesalud.eu/files/docs/00064.pdf>. Accessed September 17, 2012.
54. Adams N, Lasserson TJ, Cates CJ, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2007 (4), Art. No. CD002310. DOI: 10.1002/14651858.CD002310.pub4.
55. Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. *Cochrane Database Syst Rev* 2008 (2), Art. No. CD007031. DOI: 10.1002/14651858.CD007031.
56. Sabin T, Gurumurthy P, Shilpa P, Jayaraj BS, Basavana Gowda H, Mahesh PA. Quality of life assessment in asthmatic patients receiving fluticasone compared with equipotent doses of beclomethasone or budesonide. *Lung India* 2005; 22:86–91.
57. Kelly HW. Establishing a therapeutic index for the inhaled corticosteroids: Part I. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 102:36–51.
58. Phillips GH. Structure-activity relationships of topically active steroids: The selection of fluticasone propionate. *Respir Med* 1990; 84(Suppl A):19–23.
59. Shaw RJ. Inhaled corticosteroids for adult asthma: Impact of formulation and delivery device on relative pharmacokinetics, efficacy and safety. *Respir Med* 1999; 93:149–160.
60. Anselmo M. Pediatric asthma controller therapy. *Paediatr Drugs* 2011; 13:11–17.
61. Allen DB. Safety of inhaled corticosteroids in children. *Pediatr Pulmonol* 2002; 33:208–220.
62. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC; CAMP Research Group. Effects of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012; 367:904–912.

63. Barnes NC, Thwaites RMA, Price MJ. The cost-effectiveness of inhaled fluticasone propionate and budesonide in the treatment of asthma in adults and children. *Respir Med* 1999; 93:402–407.
64. Trakas K, Oh PI, Einarson TR, Shear NH. A health economic analysis of fluticasone propionate, budesonide, and beclomethasone dipropionate for the treatment of moderate to severe asthma. *Value Health* 1998; 1:62.
65. Neumann PJ. What next for QALYs? *J Am Med Assoc* 2011; 305:1806–1807.
66. UK Secretary of State for Health Department of Health. A new value-based approach to the pricing of branded medicines-a consultation. Available at: http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122760. Accessed September 17, 2012.