Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma

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OBJECTIVES: To compare the cost-effectiveness of budesonide-formoterol in a single inhaler used as both maintenance and reliever medication versus clinician-directed titration of salmeterol-fluticasone as maintenance medication, plus salbutamol taken as needed, in controlling asthma in adults and adolescents.

METHODS: A Canadian economic evaluation was conducted based on the results of a large (n=2143), open-label, randomized, controlled effectiveness trial in which health resource use was prospectively collected. The primary outcome measurement was the time to the first severe exacerbation. Costs included direct medical costs (physician and emergency room visits, hospitalizations, asthma drug costs, etc) and productivity (absenteeism). The time horizon was one year, which corresponded to the duration of the clinical trial. Prices were obtained from 2005 Canadian sources. Both health care and societal perspectives were considered, and deterministic univariate sensitivity analyses were conducted.

RESULTS: In the clinical trial, budesonide-formoterol as maintenance and reliever treatment was superior to salmeterol-fluticasone with respect to the time to the first severe exacerbation, overall rate of exacerbations and use of as-needed reliever medication. The annualized rate of severe exacerbations was 0.24 events/patient in the budesonide-formoterol arm and 0.31 events/patient in the salmeterol-fluticasone arm (P=0.0025). From a health care perspective, the mean cost per patient-year was $1,315 in the budesonide-formoterol arm versus $1,541 in the salmeterol-fluticasone arm. From a societal perspective, the mean cost per patient-year was $1,538 in the budesonide-formoterol arm and $1,854 in the salmeterol-fluticasone arm. Budesonide-formoterol was dominant (more effective and less expensive) in the base case analysis from both perspectives. The results were robust under sensitivity testing.

CONCLUSIONS: The strategy that allows budesonide-formoterol to be used in a single inhaler as both maintenance and reliever medication proved to be more effective and less expensive than a strategy of clinician-directed titration of salmeterol-fluticasone with salbutamol as reliever therapy.

Key Words: *Asthma; Budesonide-formoterol; Comparison; Economic evaluation; Salmeterol-fluticasone*

Évaluation économique de l'association budésonide-formotérol comme traitement d'entretien et traitement d'appoint chez des patients atteints d'asthme modéré ou grave au Canada

BUT : L'étude avait pour but de comparer la rentabilité de l'association de budésonide et de formotérol dans un seul inhalateur, utilisée tant comme traitement d'entretien que comme traitement d'appoint avec celle de l'association de fluticasone et de salmétérol utilisée comme traitement d'entretien selon les indications du médecin et complétée par la prise de salbutamol au besoin, en vue de la maîtrise de l'asthme chez des adultes et des adolescents.

MÉTHODE : Une évaluation économique a été entreprise au Canada à partir des résultats d'un imposant (n=2143) essai comparatif, randomisé, ouvert, sur l'efficacité, dans lequel il y avait eu une collecte prospective de données sur l'utilisation des ressources en santé. Le principal critère d'évaluation était le temps écoulé avant la survenue de la première exacerbation grave. Nous avons tenu compte des coûts médicaux directs (consultations médicales et consultations à l'urgence, hospitalisations, médicaments antiasthmatiques, etc.) ainsi que de la perte de productivité (absences). L'horizon était de un an, ce qui correspondait à la durée de l'essai clinique. Les prix ont été obtenus de sources canadiennes de 2005. Le point de vue des soins de santé et celui de la société ont été pris en considération dans l'étude, et nous avons réalisé des analyses de sensibilité déterministes unidimensionnelles.

RÉSULTATS : Dans l'essai clinique, l'association budésonide-formotérol comme traitement d'entretien et comme traitement d'appoint s'est révélée supérieure à l'association fluticasone-salmétérol en ce qui concerne le temps écoulé avant la survenue de la première exacerbation grave, le taux global d'exacerbation et l'utilisation au besoin des médicaments d'appoint. Le taux annualisé d'exacerbation grave était de 0,24 événement/patient dans le groupe budésonide-formotérol et de 0,31 événement/patient dans le groupe fluticasone-salmétérol (P=0,0025). Du point de vue des soins de santé, le coût moyen par personne-année était de 1315 $ dans le premier groupe et de 1541 $ dans le second et, du point de vue de la société, le coût moyen par personne-année était de 1538 $ dans le premier groupe et de 1854 $ dans le second. L'association budésonide-formotérol s'est donc révélée dominante, c'est-à-dire plus efficace et moins coûteuse que l'autre, et ce, des deux points de vue dans l'analyse du scénario de référence. Les résultats se sont montrés robustes d'après les tests de sensibilité.

CONCLUSION : La stratégie fondée sur l'association de budésonide et de formotérol dans un seul inhalateur, utilisée tant comme traitement d'entretien que comme traitement d'appoint s'est montrée plus efficace et moins coûteuse que l'association de fluticasone et de salmétérol utilisée comme traitement d'entretien selon les indications du médecin et complétée par la prise de salbutamol au besoin comme traitement d'appoint.

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Asthma inflicts a large burden on patients, their families, health services and society in general (1). The Asthma Society of Canada reports that:

- asthma is the leading cause of absenteeism from school and is the third leading cause of work loss (1);
- every year in Canada, 146,000 emergency department visits are attributed to asthma (2);
- in 1994, 54,532 hospital admissions were attributed to asthma (3); and
- the total annual cost of asthma care is between $504 and $648 million annually (1990 dollars) (4).

Over the past 20 years, the understanding of asthma and its pathogenesis has rapidly evolved. Treatment strategies have also evolved, with most guidelines recommending a stepwise approach to care. The Canadian Asthma Consensus Guidelines (2003) (5) has recommended that very mild asthma be treated with short-acting beta$_2$-agonists (SABAs) taken as needed, and inhaled corticosteroids (ICSs) be introduced as the initial maintenance treatment. They also recommend that if asthma has not adequately been controlled by low doses of ICSs, long-acting beta$_2$-agonists (LABAs) should be considered as the first option for add-on treatment. Increasingly, fixed-combination products containing ICSs and LABAs have been used because they are convenient and may prevent patients from over-relying on their LABA and/or SABA at the expense of their ICS therapy.

Currently, in Canada, there are two ICS/LABA fixed combination products: budesonide-formoterol (Symbicort, AstraZeneca Canada Inc, Canada) and salmeterol-fluticasone (Advair, GlaxoSmithKline Inc, Canada). (The use of trade names is for product identification purposes only and does not imply endorsement.)

In clinical practice, patients are usually prescribed maintenance therapy (often an ICS/LABA fixed combination) and a separate SABA to be used as needed to relieve breakthrough symptoms. A modification of this treatment approach has recently been tested, which involves the use of budesonide-formoterol for both maintenance therapy and as-needed symptom relief, obviating the need for a separate rescue inhaler such as salbutamol. This is possible because of the rapid onset of action of formoterol, equivalent to that of salbutamol.

A 12-month, open-label study (6) had compared the effectiveness of budesonide-formoterol for maintenance plus reliever therapy with a regimen that used salmeterol-fluticasone as maintenance plus salbutamol for rescue. Health care resource use was collected prospectively as part of the clinical trial. Using the data from this clinical trial, an economic analysis was conducted using Canadian costs. In the present study, the objective of the economic evaluation was to compare the costs and consequences from both the health care and the societal perspectives of budesonide-formoterol as maintenance and reliever therapy versus salmeterol-fluticasone plus salbutamol.

METHODS

Study design

Full details of the study design, treatments and clinical assessments have been previously published (6), and are summarized below.

The trial was a large, randomized, open-label, parallel-group, 12-month study conducted in 246 centres in 16 countries including Canada. Patients were 12 years of age or older with moderate to severe asthma. During the past 12 months, but not in the past two weeks before enrolment, patients either experienced at least one severe asthma exacerbation or, on their own initiative, temporarily (ie, for at least three days) increased the dose of an ICS due to a deterioration of their asthma. After a two-week run-in period, patients were randomly assigned to a treatment group with budesonide-formoterol 160 µg/4.5 µg (Symbicort 200) (each dry powder or metered dose inhalation contains 200 µg of budesonide and 6 µg formoterol fumarate dihydrate, which is equivalent to 160 µg of budesonide and 4.5 µg of formoterol fumarate dihydrate per delivered dose), two inhalations twice daily, plus additional inhalations as needed; or salmeterol-fluticasone 50 µg/250 µg, one inhalation twice daily, plus salbutamol as needed. After four weeks on a constant maintenance dose, treatment of patients in both groups was assessed by a physician and, as with normal clinical practice, titrated up or down accordingly to improve asthma control or to attain the lowest effective dose.

The primary variable of efficacy was the time to the first severe asthma exacerbation, defined as a deterioration in asthma leading to oral steroid treatment (at least three days), hospitalization or emergency room (ER) visit, or an unscheduled visit (ie, patient-initiated) leading to a change in asthma treatment. The mean and total number of severe exacerbations, number of patients with exacerbations and days with oral steroids due to exacerbations were also recorded.

Economic analysis

Because avoidance of exacerbations is a central goal in asthma management, an analysis of cost-effectiveness was conducted reporting the total cost per exacerbation avoided. Annualized exacerbation rates were obtained from the clinical trial. Total costs for each type of health care resource were determined by multiplying the unit cost by the number of units consumed (eg, physician visits). Total costs were then summed for each treatment arm and divided by the number of patient-years in each respective treatment arm to derive the mean cost/patient-year.

Resource use data were obtained from the trial and from an expert clinical panel. The number of physician visits, visits by other health care professionals, home care visits and days off work, and data on intake of study and rescue medications were collected from patient notebooks and transferred to case record forms at scheduled clinical visits. In the clinical trial, rescue salbutamol was available as Ventodisk (GlaxoSmithKline Inc, Canada) or Ventolin (GlaxoSmithKline Inc, Canada) metered dose inhaler (MDI). For the present evaluation, it was assumed that 1 µg of salbutamol delivered via a Ventodisk was equivalent to 1 µg of salbutamol delivered via an MDI. Data on concomitant medication were taken from the case record forms, while days in hospital were taken from reports of serious adverse events.

An expert panel estimated the type and dose for reported concomitant medications. For each of the categories of concomitant medication (eg, systemic glucocorticosteroid), physicians were asked to identify the drug most commonly used in Canada and the most common daily dose or dosing regimen.

Prices were obtained from a variety of appropriate sources, and were based on national or provincial (mostly Ontario) prices. Prices are reported in 2005 Canadian dollars, either from 2005 sources or by adjustment to 2005 prices using the Consumer Price Index (7).

Drug costs were obtained from the current Ontario Drug Benefit Formulary/Comparative Drug Index (8). Generic prices were used when available. All rescue salbutamol use was priced at

TABLE 1
Baseline patient characteristics

Characteristic	Budesonide-formoterol (n=1067)	Salmeterol-fluticasone (n=1076)
Female, n (%)	616 (57.7)	647 (60.1)
Age, years, mean (range)	45.3 (12–80)	45.1 (12–84)
ICS dose at entry, µg/day, mean (range)	887.5 (50–2000)	881 (40–3000)
Asthma duration, years, median (range)	13 (1–75)	12 (0–74)
Rescue bronchodilator, puffs/24 h, mean (range)	1.81 (0.0–9.5)	1.82 (0.0–9.7)
Preventive use of bronchodilator, puffs/24 h, mean (range)	0.83 (0.0–6.0)	0.83 (0.0–24.0)
FEV_1 prebronchodilator, % predicted, mean (range)	73.3 (39–115)	73.1 (28–100)
FEV_1 postbronchodilator, % predicted, mean (range)	82 (39–130)	81.7 (25–117)
Reversibility, % (range)	12.5 (–21–+95)	12.5 (–29–+95)

FEV_1 Forced expiratory volume in 1 s; ICS Inhaled corticosteroid

TABLE 2
Clinical and resource use trial outcomes

Event	Budesonide-formoterol (n=1064)	Salmeterol-fluticasone (n=1071)
Severe asthma exacerbations		
Number of patients, n (%)	159 (15)	204 (19)
Number of events, n	255	329
Events/patient-year, rate (95% CI)	0.24 (0.20–0.29)	0.31 (0.26–0.36)
Severe asthma exacerbations without unscheduled visit		
Number of patients, n (%)	132 (12)	167 (16)
Number of events, n	216	267
Events/patient-year, rate (95% CI)	0.19 (0.16–0.23)	0.23 (0.19–0.28)
Severe exacerbations with ER visits/hospitalization		
Number of patients, n (%)	31 (3)	46 (4)
Number of events, n	48	58
Events/patient-year, rate (95% CI)	0.04 (0.03–0.06)	0.05 (0.04–0.07)
Oral GCS treatment for at least three days		
Number of patients, n (%)	128 (12)	155 (14)
Number of courses, n	202	240
Total days of oral GCS, n	1980	2978

ER Emergency room; GCS Glucocorticosteroid

the cost of a generic salbutamol MDI. Drug costs were reported as the cost per claim, which was composed of the acquisition drug cost, a 10% markup, a $6.54 dispensing fee and a $2 patient co-payment, as per the Ontario Drug Benefit Formulary regulations. Physician fees were obtained from the 2005 Ontario Health Insurance Schedule of Benefits and Fees (9). The cost of outpatient nursing visits was obtained from the Workplace Safety and Insurance Board fee schedule for registered nurses (10). The cost of home care nursing visits was obtained from the Community Nursing Services Study and represents the average cost of for-profit and not-for-profit fees in Ontario (11). Hospitalization costs were obtained for asthma-related hospitalizations (Case Mix Group 146) from the Health Costing in Alberta 2004 Annual Report (12). Intensive care hospital days were assigned the average cost per day at the level of complexity (Plx) identified as Plx 4 (highest degree of Plx); general hospital days were assigned the average cost per day at the level of Plx identified as Plx 1 (lowest degree of Plx). ER visit costs were obtained from the Health Costing in Alberta 2004 Annual Report, which includes fully allocated costs with the exception of the cost of the ER physician (12). Physician fees (obtained from the 2005 Ontario Health Insurance Schedule of Benefits and Fees [9]) were added to the ER visit cost.

Hourly wages (average and minimum) were obtained from Statistics Canada (13). It was assumed that each workday was 8 h in duration.

The time horizon for this analysis was set at the duration of the clinical trial, which was one year. Consequently, discounting was not necessary. The evaluation was conducted from the health care and the societal perspectives. For the health care perspective, resources included physician visits, other health care professional services, hospitalizations, ER visits, home care and medication. The societal perspective included resources used in the health care perspective as well as the cost of time lost from work.

Univariate sensitivity analyses were conducted on four different parameters that varied:

- the mean number of severe exacerbations, ie, the rate of severe exacerbations (varied by using the upper and lower 95% CI of the hazard ratio) for budesonide-formoterol;
- the cost of salmeterol-fluticasone (assuming all patients were on the intermediate dose);
- the hourly wage (minimum instead of average); and
- the cost of hospitalization.

RESULTS

Efficacy and safety results have been previously presented (6).

Of the 2509 patients enrolled, 2143 were randomly assigned; 1067 to budesonide-formoterol and 1076 to salmeterol-fluticasone. (In Canada, 163 patients were enrolled and 146 patients were randomly assigned.) The baseline characteristics of the patients are shown in Table 1. There were no significant differences in age, sex, time since diagnosis or previous use of asthma medications between groups.

Budesonide-formoterol used as maintenance and reliever therapy was more effective than salmeterol-fluticasone plus salbutamol, as measured by the primary outcome. The risk reduction for the time to the first exacerbation was 25% (hazard ratio 0.75; 95% CI 0.61 to 0.93; P=0.0076). There was a 22% reduction in the mean number of exacerbations with budesonide-formoterol (hazard ratio 0.78; 95% CI 0.66 to 0.91; P=0.0025). The annualized exacerbation rates were 0.24 events/patient-year and 0.31 events/patient-year, respectively (Table 2).

The budesonide-formoterol group required a mean daily dose of 562 µg (maintenance) plus 91 µg of (as-needed) budesonide, while patients in the salmeterol-fluticasone group used a mean of 583 µg of fluticasone (maintenance only).

TABLE 3
Descriptive statistics for study medication derived from information on inhalers

Treatment	Patients, n	Inhalers, n (mean ± SD)	Inhalers, n (median)
Total number of dispensed ICS inhalers			
Budesonide-formoterol group*	1062	12.7±6.0	12
Salmeterol-fluticasone group*	1069	11.6±3.9	12
Total number of dispensed salbutamol inhalers			
Budesonide-formoterol group†	11	1.5±0.8	1
Salmeterol-fluticasone group	1055	5.0±5.9	3
Total number of Ventodisk inhalations‡			
Budesonide-formoterol group†	6	33.0±31.7	25
Salmeterol-fluticasone group	507	326.7±431.0	170

**Data excluded patients who did not complete the trial or had missing data; †1% to 2% of budesonide-formoterol patients contravened the study protocol by also using salbutamol as reliever therapy; ‡Each Ventodisk (GlaxoSmithKline Canada) inhalation is equal to 200 µg of salbutamol. ICS Inhaled corticosteroid*

TABLE 4
Summary of total health care resource usage throughout the study*

	Budesonide-formoterol		Salmeterol-fluticasone	
Resource type	Patients, n	Group totals (days or visits)	Patients, n	Group totals (days or visits)
Patients	1058	361,335	1065	357,704
Days of hospitalization (intensive care)	1	9	1	5
Days of hospitalization (general care)	9	50	13	91
Emergency room visits	21	39	32	56
Visits to primary health care physician	163	318	186	361
Visits to specialist	110	164	129	230
Other health care visits	39	49	54	98
Home visits by physician	22	33	22	38
Home visits by other health care professionals	0	0	3	14
Days unable to perform usual activity	144	1355.5	135	1717.5

**Data excluded patients who did not complete the trial or had missing data*

Expressed as equivalent beclomethasone dipropionate doses, this represented 1019 µg/day (maintenance and as-needed) in the budesonide-formoterol group and 1166 µg/day (maintenance only) in the salmeterol-fluticasone group (6). At the end of the study, 68% of patients in the budesonide-formoterol group used a budesonide maintenance dose of 800 µg daily (delivered dose of 640 µg) while 31% received 400 µg daily (delivered dose of 320 µg). In the salmeterol-fluticasone group, 58% received the fluticasone dose of 500 µg daily, 27% received 1000 µg and 14% received 200 µg. It was assumed that the proportion of different strength of inhalers used throughout the trial corresponded to that reported at the end of the trial. Use of as-needed medication was lower in the budesonide-formoterol group (0.58 versus 0.93 inhalations/day; P<0.001).

TABLE 5
Unit costs

Medication*	Cost per unit, $	Cost per claim†, $
Budesonide-formoterol 160 µg/4.5 µg – 120 doses	78.00	90.34
Salmeterol-fluticasone 50 µg/100 µg – 60 doses	71.70	83.41
Salmeterol-fluticasone 50 µg/250 µg – 60 doses	85.80	98.92
Salmeterol-fluticasone 50 µg/500 µg – 60 doses	121.80	138.52
Salbutamol (generic) 100 µg – 200 doses	4.64	9.64
Prednisone 5 mg tablet (80 tablets)	0.009	5.33
Physician visits	**Cost per visit, $**	
GP (minor assessment)	17.30 (Ontario Schedule of Benefits and Fees, A001) (reference 9)	
Respirologist (partial assessment)	24.65 (Ontario Schedule of Benefits and Fees, A478) (reference 9)	
ER (partial assessment)	24.65 (Ontario Schedule of Benefits and Fees, A418) (reference 9)	
Other health care visits	**Cost per visit, $**	
Nurse (follow-up visit)	19.65 (data from reference 10)	
Home visits	**Cost per visit, $**	
District nurse	44.95 (data from reference 11)	
GP (house call assessment)	40.75 (Ontario Schedule of Benefits and Fees, A902) (reference 9)	
Hospitalizations/ER visit	**Cost per day/visit, $**	
Intensive care	1,793.16 (Health Costing in Alberta report) (reference 12)	
General care	969.00 (Health Costing in Alberta report) (reference 12)	
Visit (does not include physician fee)	120.36 (Health Costing in Alberta report) (reference 12)	
Work loss	**Cost per hour, $**	
Average wage, aged 15 years and older	18.90 (Statistics Canada) (reference 13)	
Minimum wage	7.45 (Statistics Canada for Ontario) (reference 13)	

**Data are from the Ontario Drug Benefit Formulary/Comparative Drug Index (8); †Includes markup, dispensing fee and patient co-payment. ER Emergency room; GP General practitioner*

Descriptive statistics for maintenance and as-needed asthma medication were also derived from collected inhalers (Table 3). Estimates of mean daily steroid dose based on collected inhalers were in agreement with the mean daily doses calculated from prescriptions and reported as-needed use.

For both treatment arms, relatively few patients used asthma medication other than study medication and oral steroids for exacerbations. Use of oral steroids due to severe asthma exacerbations was reported in 12% of budesonide-formoterol patients (1980 days of total use) and 14% of salmeterol-fluticasone patients (2978 days of total use). None of the differences in other drug uses between treatment groups was greater than 1%.

No clinically important differences between the two treatment groups were observed with respect to adverse events. Both budesonide-formoterol and salmeterol-fluticasone were well tolerated.

Health care resource use including hospitalization, ER visits, physician visits (general practitioner and specialist), other

TABLE 6
Total costs and mean cost per patient-year*

Resource	Budesonide-formoterol (n=1058), $	Salmeterol-fluticasone (n=1065), $
Hospitalization		
Intensive care	16,138.00	8,966.00
General care	48,450.00	88,179.00
Emergency room visits	5,655.00	8,121.00
Physician visits		
GP/FP	5,501.00	6,245.00
Specialist (respirologist)	4,043.00	5,670.00
Other health care visits	963.00	1,925.00
Physician home visits	1,345.00	1,549.00
Other health care home visits	0.00	629.00
Subtotal nondrug costs	82,095.00	121,283.00
Study drug costs		
Budesonide-formoterol	1,218,452.00	0.00
Salmeterol-fluticasone	0.00	1,320,040.00
Salbutamol MDI (generic)	217.00	66,846.00
Concomitant drug costs		
Prednisone	1,056.00	1,588.00
Subtotal drug costs	$1,219,724.00	1,388,474.00
Total health system costs	$1,301,820.00	1,509,757.00
Mean cost/patient-year	$1,315.00	1,541.00
Days of missed work		
Patient	204,952.00	259,686.00
Caregiver	15,876.00	47,295.00
Total societal costs	1,522,647.00	1,816,738.00
Mean cost/patient-year	1,538.00	1,854.00

**Data excluded patients who did not complete the trial or had missing data. FP Family physician; GP General practitioner; MDI Metered dose inhaler*

TABLE 7
Incremental cost-effectiveness ratio: Base case analysis

		Total cost per patient-year	
	Serious exacerbations per patient-year	Health care perspective, $	Societal perspective, $
Budesonide-formoterol	0.24	1,315.00	1,538.00
Salmeterol-fluticasone	0.31	1,541.00	1,854.00
Incremental difference	–0.07	–226.00	–316.00
Incremental cost-effectiveness ratio		Budesonide-formoterol dominates*	Budesonide-formoterol dominates

**Dominates refers to a strategy that is more effective and less costly*

TABLE 8
Summary of univariate sensitivity analysis results

Analysis	Results
Lower 95% CI (hazard ratio) for exacerbations and costs	Budesonide-formoterol dominates*
Upper 95% CI (hazard ratio) for exacerbations and costs	Equivalent
Cost of salmeterol-fluticasone reduced (assuming all 50/250 μg dose)	Budesonide-formoterol dominates
Minimum wage instead of average wage	Budesonide-formoterol dominates
Cost of hospitalization based on average cost of asthma-related admission	Budesonide-formoterol dominates

**Dominates refers to a strategy that is more effective and less costly*

health care visits and home care visits is reported in Table 4. Sick leave and caregiver time identified as 'days unable to perform usual activity' are also reported (Table 4).

Unit costs for resources are presented in Table 5.

Although the physician panel identified the most commonly used concomitant medications within a given class, the cost of concomitant medications (with the exception of prednisone, oral 5 mg tablets, and the occasional use of additional salbutamol in the budesonide-formoterol group) was not included in the analysis. All other concomitant medication use occurred with a low frequency (1% or less), and the majority of use occurred in the salmeterol-fluticasone group. Therefore, the decision to forego inclusion of costs of concomitant medication favoured the salmeterol-fluticasone group.

In the base case analysis, total costs were summed for the budesonide-formoterol treatment arm and the salmeterol-fluticasone treatment arm, and divided by the number of patient-years for each arm. From the health care perspective, drug costs represented 94% of the total costs in the budesonide-formoterol group and 92% of the total costs in the salmeterol-fluticasone group. Mean costs per patient-year are represented in Table 6.

An incremental cost-effectiveness ratio was calculated by dividing the incremental cost by the incremental benefit. From both the health care perspective and the societal perspective, budesonide-formoterol was the dominant treatment strategy compared with salmeterol-fluticasone, meaning that its use resulted in fewer exacerbations at a lower cost (Table 7). It was not appropriate to present incremental cost-effectiveness ratios in cases of equivalency or dominance. In the case of equivalency, the incremental difference would be zero, resulting in an undefined number; in the case of dominance (more effective, less costly), the double negative (numerator and denominator) becomes a positive result and leads to an incorrect interpretation of findings.

Several sensitivity analyses were conducted (Table 8). In the first sensitivity analysis, the annualized rate of exacerbations and the costs (excluding budesonide-formoterol and salmeterol-fluticasone) were varied using the upper and lower boundary of the 95% CI of the hazard ratio for the budesonide-formoterol arm (costs and consequences in the salmeterol-fluticasone group remained constant). Budesonide-formoterol remained dominant from both the health care and societal perspectives at the lower boundary. At the upper boundary, the incremental differences in costs and consequences, although still favouring budesonide-formoterol, were extremely small (0.02 fewer exacerbations per patient-year, and $6 less per patient-year from the health care perspective compared with $59 less per patient-year from the societal perspective). Consequently, this result at the upper boundary was judged to be equivalent.

In the second sensitivity analysis, all salmeterol-fluticasone 500 μg/50 μg inhalers were assumed to be salmeterol-fluticasone 250 μg/50 μg and assigned a cost of $98.92 per claim (reduced from $138.52 per claim). In a third scenario, the cost assigned

to absenteeism was set at the minimum wage ($7.45 per hour for Ontario), instead of the average wage. In a fourth scenario, the cost of hospitalization was calculated using the average asthma-related hospitalization costs from the Ontario Case Costing Initiative (14) multiplied by the number of hospitalizations (reported in the clinical trial), in effect reducing the impact of hospitalization in this analysis. Regardless of the changes, budesonide-formoterol continued to be the dominant strategy from both societal and health care perspectives.

DISCUSSION

Economic evaluations have been criticized for being based on clinical trials of inadequate duration, for using intermediate outcomes or inappropriate comparators, and for making unrealistic assumptions (15). The present economic evaluation was based on a year-long clinical effectiveness trial in which health care resource use was prospectively collected. One of the outcomes in the clinical trial was avoidance of exacerbations. This represents an important end point in asthma because exacerbations represent periods in which patients have the greatest risk of emergency department visits, hospitalization and even death (16). In addition, asthma exacerbations inflict enormous amounts of emotional and financial stress, reduce the quality of life and hamper the ability to work. From a societal perspective, exacerbations are the leading cause of expenditures related to asthma, accounting for almost 50% of total costs (17). Furthermore, patients who have frequent exacerbations (generally believed to be approximately 20% of the total asthma population pool) incur 80% of the total direct costs of asthma (17). Thus, the study assessed in the present report was of adequate duration to measure a final outcome that is relevant from both a clinical and an economic perspective. Moreover, because health care resource use data were prospectively collected, few assumptions were made.

The strategy of using budesonide-formoterol in a single inhaler as maintenance and reliever therapy has proven to be a dominant strategy (more effective and less costly), not only in the base case analysis, but in all but one of the sensitivity analyses. These results are not surprising, because total costs were largely composed of drug costs and budesonide-formoterol therapy was less expensive than salmeterol-fluticasone therapy. Some may find that using budesonide-formoterol as reliever therapy is an expensive alternative to generic salbutamol, but the true comparison of interest is budesonide-formoterol maintenance and reliever therapy versus salmeterol-fluticasone plus salbutamol, not merely budesonide-formoterol versus salbutamol. The present analysis demonstrated that the benefits of using budesonide-formoterol as maintenance and reliever therapy were evident from both clinical and economic perspectives, and were not based on an inappropriate price comparison. Moreover, some patients neglect maintenance therapy with an ICS, and instead, rely heavily on the immediate benefits of SABAs. With the reported budesonide-formoterol strategy, patients are no longer able to do this. This is likely one of the reasons why asthma control was better in the budesonide-formoterol arm.

In Canada, publicly funded drug plans offer identical reimbursements for budesonide-formoterol and salmeterol-fluticasone. While both are LABAs in combination with ICSs, formoterol (but not salmeterol) acts as rapidly as salbutamol in relieving constricted airways. This allows a new description of beta-agonist in that formoterol could be described as a rapid-acting beta-agonist with a long duration. This description is in fact used in the most recent version of the Canadian Asthma Consensus Guidelines (5).

The generalizability of the present study is limited to patients with moderate to severe asthma, who require both an ICS and a LABA. These results cannot be extrapolated to patients with mild asthma or those who seek combination therapy before an adequate trial of ICSs alone. Because this analysis did not consider either of these two scenarios, any inference of these results should be avoided.

Finally, the results of the present analysis were based on a fully pooled international patient dataset in which Canada contributed 163 of the total number of patients enrolled. While reporting clinical effects in the aggregate is generally accepted as standard practice, some have expressed concern over the similar treatment of resource use (18). A post-hoc analysis of data from the Canadian-only patients confirmed the overall conclusions of the present evaluation. Results of the Canadian subset analysis, although not statistically significant because of the small sample size, revealed an even greater numerical difference in favour of the budesonide-formoterol strategy. Nevertheless, because the main outcome of this clinical trial was based on resource use, it is important to acknowledge this methodological issue as a potential limitation of the analysis.

CONCLUSIONS

The strategy of budesonide-formoterol in a single inhaler as maintenance and reliever therapy is dominant (ie, more effective and less expensive) over a strategy of clinician-directed titration of salmeterol-fluticasone as maintenance therapy plus as-needed salbutamol. These results were robust under sensitivity testing.

CONFLICT OF INTEREST: Elizabeth Miller is a consultant to the pharmaceutical industry, including AstraZeneca Canada. Dr Malcolm Sears has received research grants, honoraria and consultation fees from a number of pharmaceutical companies, with interests in the field of asthma including Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst, Novartis and Schering Plough, and holds the AstraZeneca Chair in Respiratory Epidemiology at McMaster University. Dr Andrew McIvor has received research funding, honoraria and research grants, and attended advisory boards for a number of pharmaceutical companies including AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Pfizer and Merck Frosst in the field of obstructive lung disease. Anna Liovas is an employee of AstraZeneca Canada.

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