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Cost analysis of the use of inhaled corticosteroids in the treatment of asthma: a 1-year follow-up

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Abstract A retrospective cohort using pharmacy and medical claims was analysed to determine whether the differences in efficacy of various inhaled corticosteroids demonstrated in clinical trials lead to differences in costs of care observed in clinical practice. Subjects that had an ICD-9 (493.XX) code for asthma and a new pharmacy claim for inhaled fluticasone propionate 44 mcg (FP), beclomethasone dipropionate (BDP), triamcinolone acetonide (TAA), budesonide (BUD) or flunisolide (FLU) were identified and followed for 12 months. Annual asthma care charges (pharmacy and medical) over the 12-month observation period were significantly ($P < 0{\cdot}03$) higher in patients treated with BDP, TAA, BUD and FLU compared to FP, 24%, 27%, 34% and 45% respectively. In addition, patients treated with BDP, TAA, and FLU were associated with significantly ($P \leq 0{\cdot}005$) higher total healthcare (asthma + non-asthma) charges compared to patients on FP, 53%, 46% and 39% respectively. Asthma care and total healthcare charges remained lower for FP after including FP 110 mcg and excluding patients who were extreme cost outliers (± 2 SD from the mean) in a univariate sensitivity analysis. This analysis supports recent randomized control trials that FP offers a superior efficacy profile at lower asthma care as well as total healthcare charges compared to other inhaled corticosteroids. © 2001 Harcourt Publishers Ltd
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Keywords asthma; cost; inhaled corticosteroids; fluticasone; budesonide; triamcinolone; beclomethasone; flunisolide.

INTRODUCTION

Asthma care in the United States accounts for an estimated $US 12·6 billion annually with approximately $US 7·4 billion being direct medical costs. Of these direct medical expenditures approximately 40% are related to hospital care [emergency department (ED) or hospital encounters] (1, 2). Several studies have demonstrated that appropriate pharmacological intervention can reduce mortality and decrease hospitalization and ED utilization in people with asthma (3–6).

The National Asthma Education and Prevention Program's Expert Panel Report 2 (EPR 2) 'Guidelines for the Diagnosis and Management of Asthma' recommends inhaled corticosteroids as the primary treatment for the management of persistent asthma (7). The EPR 2 established criteria for starting and adjusting maintenance medications based on level of asthma severity. Inhaled corticosteroids are considered the most effective long-term control therapy for persistent asthma for all levels of severity. In addition, the EPR 2 recognized that inhaled corticosteroids potency varies on a microgram basis.

Since the publication of the EPR 2 in 1997, numerous clinical comparisons have demonstrated relative clinical differences between the marketed inhaled corticosteroids (8–15). In the majority of these studies, as well as studies in patients with rhinitis (15), a new generation inhaled corticosteroid, fluticasone propionate (FP), has demonstrated safety and efficacy advantages compared to the older generation ICS [beclomethasone (BDP), budesonide (BUD), triamcinolone (TAA) and flunisolide (FLU)] (9, 16–18). While no single approach to the assessment of potency of ICS relative to both safety and efficacy has been established, the EPR 2 ranks FP > BUD = BDP > TAA > FLU.

Randomized clinical trials are the highest level of evidence used to establish comparative differences in efficacy. However, the restricted selection criteria of a clinical trial and the structured protocol with inducements for maintaining compliance and frequent physician contact may decrease the generalizability of the results to clinical practice. In addition, clinical trials tend to be of short duration, usually $\leq$ 12 weeks. This short duration as well as the restrictive entry criteria limits cost-efficacy analyses derived from these studies. Retrospective cohort studies using linked administrative medical

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and pharmacy claims databases may be used to augment and validate the data from clinical cost-efficacy trials (19–22). Retrospective studies complement the efficacy studies with long term cost data that are generated in clinical practice settings. These cohort analyses using administrative claims may utilize large patient populations not feasible in clinical trials and may better reflect actual clinical practice conditions (19). For these reasons, retrospective database analysis may be more applicable for cost comparison investigations (19–24).

The objective of this study was to determine whether the differences between the inhaled corticosteroids noted in laboratory and clinical efficacy trials are translated into differences in overall asthma care charges as measured by the effect that these treatments have on direct medical and pharmacy utilization. The objective of this study is to compare associated treatment charges for subjects taking ICS for the treatment of asthma in a managed care environment. Specifically, FP 44 mcg was compared to older generation inhaled corticosteroids; BDP, BUD, TAA and FLU, in patients who did not have a pharmacy claim for inhaled corticosteroid or leukotriene modifiers for 6 months prior to their first ICS pharmacy claim. Total asthma care charges and total healthcare charges were the outcomes of interest. These charges included asthma and non-asthma related pharmacy and medical charges.

METHODS

This was a retrospective administrative data analysis utilizing physician, hospital and pharmacy claims contained within the Pharmetrics Integrated Outcomes® database. The Pharmetrics Integrated Outcomes® database contains medical and pharmaceutical claims from over 20 managed healthcare plans across the United States, encompassing over 10 million lives for this period of study. For the purposes of this analysis, patients from only one plan were included in the study, as it was the only plan that covered the entire study period and included information on all five inhaled corticosteroids of interest.

Patient Identification

Patients aged 12–64 years were included if they had an International Classification of Disease, 9th Revision-Clinical Modification code (ICD-9-CM) for asthma (ICD-9-CM: 493.XX) and had continuous enrollment in a healthcare plan for at least 18 consecutive months around the index event. The index event was defined as an initial pharmacy claim for one of five inhaled corticosteroids: fluticasone propionate 44 mcg (FP), budesonide (BUD), triamcinolone (TAA), flunisolide FLU) or beclomethasone BDP. To ensure that the index prescription was in fact the first claim for an inhaled corticosteroid (ICS), patients were required to have a 6-month ICS-free period prior to the index date; they were further required to have at least two claims for the same agent in the 12 months following the index event. In addition, these patients could not have any leukotriene modifier (LTM) or salmeterol in the 6-month pre-index baseline period. Patients with cystic fibrosis (ICD-9-CM: 277) or chronic obstructive pulmonary disease (ICD9-CM: 491, 492, 493.2 or 496) were excluded from the study. Those with pharmacy claims for long-acting β-agonists or leukotriene modifiers, and patients over 45 years with more than one claim for ipratropium bromide were also excluded from the analysis.

This was an intent-to-treat analysis, thus patients who were switched to alternate therapies or those with overlapping claims of more than one ICS were analysed for the entire 12-month post-index period as a member of their original cohort. Because of the relative potency of FP, the base case analysis for this study was the comparison of FP 44 mcg to any strength of TAA, BDP, BUD or FLU.

Descriptive measures

Asthma-specific medical and pharmacy claims were captured for the 6-month pre-index period and the 12-month post-index period. Relevant medical encounters included: asthma-related hospitalizations, emergency department visits, outpatient visits and use of ancillary services. Charges associated with medical and pharmacy claims were calculated, as were total asthma-related charges. Overall medical charges were also calculated for pharmacy and medical encounters. Data captured in the 6-month pre-index period were used exclusively to risk adjust the cohorts. Since the pre- and post-periods were of different lengths, a pre–post univariate analysis was not performed.

A number of patient demographics were measured and subsequently used to adjust for differences between the cohorts using multivariate analyses. These include known determinants of increased medical utilization including patient age, gender and the presence of comorbid medical conditions. We further measured the use of oral steroid and short-acting β-agonists as a proxy for disease severity and these were also adjusted for in the multivariate models.

Analysis

Patient demographics for BDP, TAA, FLU and BUD were each independently compared to the reference cohort FP using t-tests for continuous variables and tests of proportions for dichotomous variables. Wilcoxon rank

sum tests were used to assess differences in unadjusted charges. To address differences in treatment cohorts that may have confounded any inter-group comparisons, multiple log-linear regression analysis was used to examine the effect of independent variables on the post-index (log-transformed) asthma-specific and total healthcare charges. Covariates included in the regression models were age, age squared, gender, pre-index asthma specific charges, co-morbid respiratory conditions, other co-morbidities (e.g. diabetes), and pre-index use of concomitant of oral corticosteroids and short-acting β-agonists. Adjusted mean charges were calculated using least squares mean and Duan's retransformation method are reported (25). All analyses were conducted using SAS Version 7·0 (26), and tests of significance were performed at an a priori $\alpha < 0{\cdot}05$.

Sensitivity analysis

Because FP 110 mcg is used as an alternative to FP 44 mcg using fewer inhalations per day, we assessed the impact of including FP 110 mcg on the total and asthma-specific economic endpoints. Furthermore, an additional comparison of FP 44/110 patients to the other cohorts with extreme outliers ($\pm$ 2SD from the mean) removed from the sample was conducted to ensure that the original results observed were not due to a few outliers skewing the data.

RESULTS

Demographics and baseline utilization

A total of 1956 patients met the inclusion/exclusion criteria. Of these, 131 were identified as new users of FP 44 mcg, 598 as new users of BDP, 91 as new users of BUD, 967 as new users of TAA and 169 new users of FLU. Daily dosage information was not available from the database and could not be determined. Baseline demographic characteristics were similar between cohorts (Table 1). Mean age ranged from 40 years in the FP 44 mcg cohort to 44 years in the FLU cohort. Each group had more women than men however, gender distribution was not significantly different between each comparison cohort and the FP cohort. Mean per patient monthly asthma-related treatment charges and total healthcare charges are reported in Table 1. Mean monthly baseline charges differed between the comparison groups and FP, with BUD having the greatest baseline mean monthly asthma charges of $66·25 while TAA had the lowest baseline mean asthma charges of $45·96. In addition, BUD had the largest mean monthly total healthcare charges of $465·64 while FLU had the lowest mean monthly total charges of $186·45. These baseline differences in charges, asthma medication utilization and comorbidities were included as covariates in the regression model.

All pre-index (baseline) and post-index (treatment) charges related to the treatment of asthma for each inhaled corticosteroids are reported in Tables 2 and 3. Compared to the 6-month pre-index baseline period, total monthly asthma charges in the 12-month post-index treatment period increased for TAA, BDP and FLU and decreased for FP and BUD. As expected, the unadjusted asthma medication charges increased in all five inhaled corticosteroid groups while hospitalization charges decreased in each group except for TAA which had a slight increase of 8% in inpatient care charges. This observation reflects what would be expected in a population of untreated asthmatics who subsequently receive anti-inflammatory treatment. However compared to the monthly pre-period charges, FP had the largest decrease

Table 1. Patient demographics

Parameter	FP	BDP	TAA	FLU	BUD
Total (*n*)	131	598	967	169	91
Average age, yrs (SD)	39·9 ($\pm$10·4)	40·8 ($\pm$11·6)	41·5 ($\pm$11·2)	44·0 ($\pm$11·4)	41·3 ($\pm$11·3)
Female (%)	70·2%	72·1%	72·1%	71·0%	70·3%
Co-morbidities*					
Upper respiratory infection	38 (29%)	135 (22·6%)	218 (22·5%)	26 (15·4%)	26 (28·6%)
Hypertension	8 (6·1%)	50 (8·4%)	93 (9·6%)	11 (6·5%)	14 (15·4%)
Depression	9 (6·9%)	19 (3·2%)	38 (3·9%)	5 (6%)	8 (8·8%)
Lower respiratory infection	3 (2·3%)	13 (2·2%)	30 (3·1%)	7 (4·1%)	8 (8·8%)
Diabetes	2 (1·5%)	19 (3·2%)	33 (3·4%)	2 (1·2%)	5 (5·5%)
Mean monthly asthma charges ($US)	49·07	56·85	45·97	48·34	66·25
Mean monthly total healthcare charges ($US)	325·95	281·00	265·74	186·45	465.64

FP: fluticasone 44 mcg; BDP: beclomethasone; TA: triamcinolone; BUD: budesonide; FLU: flunisolide.
*Less prevalent ($\leq$1%) co-morbid conditions: coronary artery disease, congestive heart failure, sepsis and peripheral vascular disease.

in asthma-related hospital charges, 62%, relative to BDP, FLN and BUD, 13%, 57% and 57% decreases respectively. In addition FP was observed to have the smallest increase in asthma related pharmacy charges, 172%, relative to BDP, TAA, FLN and BUD, 247%, 321%, 301% and 270% increases respectively. This overall decrease in inpatient care charges and the lower increase in monthly medication charges observed with FP 44 may account for the lower unadjusted differences in monthly asthma expenditures that favored the FP 44 cohort.

Treatment period utilization by cohort

Figure 1 presents the risk adjusted mean monthly asthma care and total healthcare charges for each cohort during the 12-month treatment period. From the regression model, compared to FP, all the other inhaled corticosteroids were associated with significantly higher ($P < 0{\cdot}03$) asthma care charges during the 12-month treatment period (Table 4). Beclomethasone patients were associated with 24% higher asthma care charges, BUD patients were associated with 34% higher asthma charges, TAA patients were associated with 45% higher asthma care charges and FLU patients were associated with 45% higher asthma charges compared to FP. In addition, BDP, TAA and FLU were associated with significantly ($P \leq 0{\cdot}005$) higher total healthcare charges, 53%, 43% and 39% respectively, compared to FP. However, total healthcare charges were not significantly different for BUD compared to FP.

A sensitivity analysis was performed comparing mean total asthma care expenditures for patients receiving FP 44 mcg or FP 110 mcg as compared to new users of all other inhaled corticosteroids (Table 5). Patients treated with FP (44 mcg or 110 mcg) continued to realize significantly lower asthma care charges as compared to any competing inhaled corticosteroid ($P < 0{\cdot}04$). Specifically, new users of FP (44 mcg or 110 mcg) had between 16% and 43% lower total asthma care expenditures after controlling for comorbid medical conditions, pre-index medication use and other patient demographics. In addition, asthma charges continued to be significantly lower with FP44/110 after the removal of extreme outliners ($\pm$ 2SD from the mean).

Table 2: Pre-index unadjusted mean monthly asthma-specific treatment charges*

Variable	FP (n = 131)	BDP (n = 598)	TAA (n = 967)	FLU (n = 169)	BUD (n = 91)
ER ($US)	1·11	1·63	1·14	1·29	0·56
Inpatient¶ ($US)	28·52	37·74	31·72	31·80	41·34
Ancillary‖ ($US)	0·56	1·48	0·70	0·69	0·48
Outpatient ($US)	13·44	10·29	7·24	5·96	17·77
Asthma medications ($US)	5·44	5·71	5·16	8·60	6·09
Total asthma ($US)	49·07	56·85	45·96	48·34	66·25

*Total per person monthly charges over the 6-month pre-period.
¶Includes surgical, facility, management and ancillary.
‖Non-clinician.
FP: fluticasone 44 mcg; BDP: beclomethasone; TAA: triamcinolone; BUD: budesonide; FLU: flunisolide.

Table 3. Post-index unadjusted mean monthly asthma-specific treatment charges*

Variable	FP (n = 131)	BDP (n = 598)	TAA (n = 967)	FLU (n = 169)	BUD (n = 91)
ER ($US)	0·61	0·94	0·95	1·74	0·21
Inpatient ¶($US)	10·95	32·78	34·37	13·83	17·91
Ancillary ‖($US)	0·43	0·30	0·99	0·63	0·56
Outpatient ($US)	8·57	9·86	9·37	8·88	9·33
Asthma medications ($US)	14·84	19·84	21·72	34·47	22·58
Average monthly ($US)	35·40	63·73	67·40	59·54	50·59

*Total pre person monthly charges over 12-month post-period.
¶Includes surgical, facility, management and ancillary.
‖Non-clinician.
FP: fluticasone 44 mcg; BDP: beclomethasone; TAA: triamcinolone; BUD: budesonide; FLU: flunisolide.

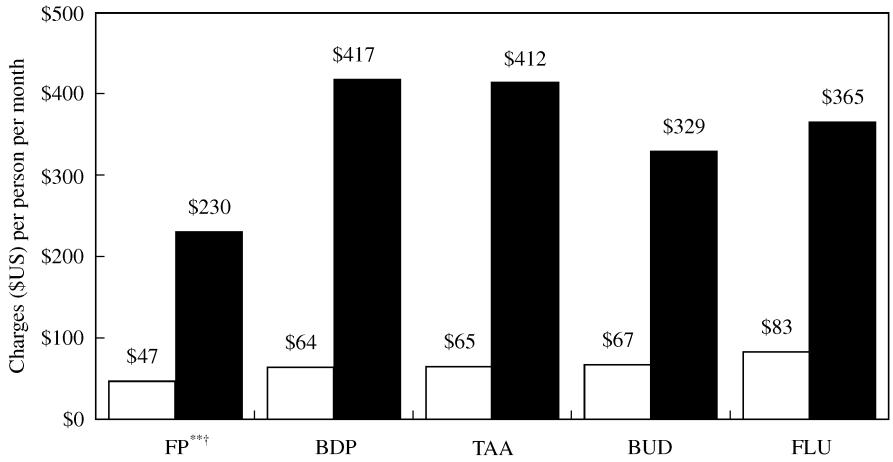

Fig. 1. Risk adjusted mean monthly asthma (□) and total healthcare charges (■) during the 12-month treatment period. *Least squares mean adjusting for age, gender, pre-index healthcare charges, co-morbid respiratory conditions, other co-morbidities (such as diabetes), and pre-index concomitant asthma medications (short actino β-agonists, oral corticosteroids and theophylline). $P < 0{\cdot}03$ for FP *vs.* BDP, TAA, FLU and BUD for asthma care charges, $P \leq 0{\cdot}005$ for FP *vs.* BDP, TAA and FLU for total heatlhcare charges.

Table 4. Parameter estimates of post-index asthma-specific charges: FP 44 mcg *vs.* individual inhaled corticosteroids

Variable	Reference	β-coefficient	Standard error	*P*
Intercept		5·09	0·32	0·0001
Beclomethasone	Fluticasone 44 mcg	0·24	0·11	0·0233
Budesonide	Fluticasone 44 mcg	0·34	0·15	0·0248
Flunisolide	Fluticasone 44 mcg	0·45	0·13	0·0005
Triamcinolone	Fluticasone 44 mcg	0·27	0·10	0·0087
Member age		0·010	0·015	0·5073
Use of oral corticosteroids or theophylline (pre-index)*	No oral corticosteroid or theophylline	0·15	0·055	0·0081
Use of oral corticosteroids and theophylline (pre-index)*	No oral corticosteroid or theophylline	0·62	0·10	0·0001
1 Albuterol prescription (pre-index)	No albuterol use	−0.29	0·068	0·0001
≥ 2 Albuterol prescriptions (pre-index)	No albuterol use	0·30	0·061	0·0001
Log asthma charges (pre-index)		−0·024	0·011	0·0224

Other non-significant model inputs included: age squared and individual co-morbidities (see Table 1).

DISCUSSION

The results of this clinical administrative claims analysis showed consistently lower asthma care charges for FP compared to all other inhaled corticosteroids. The findings remained even after including FP 110 mcg and excluding extreme cost outliers. In addition, these lower charges were also observed in total healthcare expenditures (asthma + non-asthma charges) when compared to BDP, TAA and FLU.

Previous clinical trials have demonstrated that FP is associated with better clinical outcomes and lower treatment related charges than alternative inhaled corticosteroids (7–10,13). The decision to use new therapeutic agents is usually based on potentially greater clinical benefit. Comparative clinical trials with the inhaled corticosteroids have confirmed that these inhaled corticosteroids do not produce the same clinical effect on a microgram to microgram basis (7–13). The differences in charges seen in this observational study may be related to not only the differences in how these inhaled steroids are used but suggest that the more potent inhaled corticosteroids may result in better clinical outcomes and reduced healthcare costs due to their improved safety and efficacy profiles.

Our results are consistent with previous estimates of the impact of inhaled corticosteroid use on the cost of asthma care. Ozminkowski *et al*., analysing Marketscan data, reported that patients treated with inhaled corticosteroids had increases in asthma related costs but

Table 5. Results of sensitivity analysis on asthma-related charges*

Model	BDP		TAA		FLU		BUD	
	$\beta^{\dagger}$	*P*-value	$\beta^{\dagger}$	*P*-value	$\beta^{\dagger}$	*P*-value	$\beta^{\dagger}$	*P*-value
FP 44 mcg (base case)	0·24	0·0233	0·27	0·0087	0·45	0·0005	0·34	0·0248
FP 44/110	0·15	0·0275	0·18	0·0048	0·38	0·0002	0·27	0·0374
FP 44/110 (outliers removed‡)	0·16	0·0181	0·20	0·0017	0·43	0·0001	0·35	0·0058

*β-coefficient of variable (referent for all cohorts = FP) for log-linear regression of post period asthma-specific charges.
$^{\dagger}\beta$-coefficient = per cent increase in costs related to the drug of interest compared to FP.
‡Outliers = $\pm$ 2SD from the mean.
$\beta = \beta$-coefficient.
FP: fluticasone; BDP: beclomethasone; TAA: triamcinolone; BUD: budesonide; FLU: flunisolide.

reductions in overall healthcare costs (27). Lozano *et al*. reported from an administrative claims analysis that children with asthma had greater non-asthma related costs than children without a chronic illness (28). This suggests that the costs associated with asthma go beyond what usually is defined by an asthma ICD-9 code or asthma medication claim. Retrospective studies using claims data looking at the cost of asthma may take this into account by looking at all medical costs as well as the effect that asthma may have on the non-asthma related healthcare of the patient (28). Our study found that FP use was associated with lower asthma care charges as well as lower total healthcare charges compared to the other inhaled corticosteroids. This finding is important to third party payers as well as physicians who are concerned about the cost of asthma care.

Retrospective cohort studies using claims data have significant limitations. Reasons for physicians' choice of medication or severity of disease can not be determined using administrative claims. Multiple covariate analyses controlling for difference in baseline demographics; baseline costs, comorbid conditions, age, gender, and baseline use of asthma medication is a widely used technique in administrative claims-based research and is generally accepted as a reliable method for adjusting for disease severity (19–22). However, other factors not accounted for may affect outcomes such as misdiagnosis or misclassification of disease. If misclassification did occur, it should be equal between study groups. In addition, the results from retrospective cohort studies show the associations between drug and outcomes although causality is difficult to determine. Despite these limitations, these data provide important information on the overall cost of care associated with the use of the medications occurring in clinical practice.

The reluctance to use medications because of their acquisition costs is widespread and is seen in managed care plans that look at cost from silo perspectives and not from the total healthcare perspective. In this study the addition of all these inhaled corticosteroids increased asthma medication costs as expected. Based on average wholesale price of the recommended starting doses, the inhaled corticosteroid studied are comparably priced (range of $US 1·56–$US 1·85) except for FLU which has the highest average wholesale price of $US 2·53 per day (29). In this analysis FP 44 mcg was associated with lower adjusted asthma care (pharmacy and medical) charges compared to BDP, BUD, TAA and FLU. In addition, FP 44 mcg was also associated with lower asthma and non-asthma-related healthcare charges compared to BDP, TAA and FLU. This would translate into a yearly per patient savings between $199–$433 for asthma care charges and $1188–$2245 for total healthcare charges if all the patients were treated with FP 44 mcg. These costs savings suggest that decisions to select an inhaled corticosteroid based solely on the acquisition costs may result in higher asthma care costs as well as total health care costs. These findings are consistent with other studies that restricting formularies to older drug technologies as a cost savings measure may actually result in increased overall costs to a health plan (30–31).

The results of this study add further evidence to support the EPR 2 recommendations that lower microgram doses of FP may produce the same or greater benefit than other inhaled corticosteroids at comparable doses. In addition, the superior efficacy of FP compared to other ICS observed in clinical trials is confirmed with the lower costs for FP in this analysis, and supports the use of FP 44 mcg over other ICS in patients who were previously on short-acting β-agonists alone. These data suggest that FP should be considered as the initial inhaled corticosteroid for asthma controller therapy because of its greater cost-effectiveness.

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