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Journal

Annals of Allergy Asthma & Immunology, 95(6)

ISSN

1081-1206

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Publication Date

2005-12-01

Peer reviewed

Asthma-related exacerbations, therapy switching, and therapy discontinuation: a comparison of 3 commonly used controller regimens

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Background: Asthma control is the goal of therapeutic interventions. In observational studies, the use of short-acting β-agonists (SABAs) is a surrogate for symptoms and emergency department or hospital events for exacerbations.

Objective: To compare asthma exacerbations, medication switch, and use of SABAs among 3 treatment cohorts: fluticasone propionate and salmeterol as a single inhaler (FSC), fluticasone and salmeterol as separate inhalers (FP + SAL), and fluticasone propionate alone (FP).

Methods: Administrative claims data from approximately 10 million individuals from April 2000 to December 2002 were examined. Patients 15 years or older with claims for asthma, SABAs, and study medications were included in the study. Asthma-related medical and pharmacy claims were evaluated. Multivariate regression techniques were used to model the outcomes of interest, controlling for patient characteristics.

Results: The odds of a hospitalization or emergency department event were significantly lower for the patients receiving FSC (n = 1,013) compared with those receiving FP (n = 1,130) (odds ratio, 0.75; 95% confidence interval, 0.61–0.93) and those receiving FP + SAL (n = 271) (odds ratio, 0.69; 95% confidence interval, 0.51–0.95). Patients receiving FSC also had a significantly lower risk of switch or discontinuation of index medication and lower rates of postindex SABA use.

Conclusion: In this analysis, patients receiving FSC had lower rates of asthma-related symptoms and exacerbations as measured by SABA refills and hospitalization, respectively, when compared with patients receiving either FP or FP + SAL. This observational examination of medical and pharmacy claims data adds to the clinical reports that demonstrate the increased effectiveness of FSC when compared with FP or FP + SAL.

Ann Allergy Asthma Immunol. 2005;95:535–540.

INTRODUCTION

Asthma is a high-prevalence, high-cost disease, with a US lifetime prevalence of 30 million. In a 2002 report, approximately 10 million US citizens experienced asthma attacks or episodes, resulting in approximately 2 million emergency department (ED) events, 500,000 hospitalizations, and 4,600 deaths.[1] A goal of the National Asthma Education and Prevention Program (NAEPP) is to decrease the asthma-associated morbidity, including ED visits and hospitalizations.[2] During the past decade asthma-related morbidity has plateaued, but ED events and hospitalizations have not significantly decreased.[1]

In 1998, overall costs for asthma, including direct medical and indirect costs, were estimated to be $12.7 billion annually, twice the overall costs measured 10 years earlier.[3–5] Direct medical costs account for most total asthma costs (58%),[4] and most of the potentially avoidable expenses are attributed to asthma exacerbations.[6] Inappropriate therapy for asthma is often associated with high resource utilization.[7] The NAEPP guidelines for treatment of asthma place an emphasis on the use of inhaled corticosteroids (ICSs) for all severities of persistent asthma and the use of long-acting β-agonists (LABAs) when control is not achieved with ICSs alone as the preferred therapies.[2] Evidence suggests that adherence to adequate and appropriate treatment with ICSs diminishes the risk of exacerbations, potentially reducing asthma-related costs due to flares and the indirect costs related to disease morbidity.[8–10] Improved persistence with ICSs has been associated with reductions in hospitalizations, ED visits, and asthma mortality.[8–11]

The present study was designed to evaluate whether the better clinical outcomes noted in randomized trials that favored fluticasone propionate and salmeterol as a single inhaler (FSC) compared with fluticasone propionate alone (FP) and fluticasone propionate plus salmeterol dispensed as separate inhalers (FP + SAL) would be noted in observational studies.[12–14] Outcome parameters used to evaluate effectiveness of therapy included postindex exacerbations indicated by administrative claims for ED or hospital utilization, loss of

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Funding for this research project was provided by GlaxoSmithKline.
Received for publication December 2, 2004.
Accepted for publication in revised form February 16, 2005.

symptom control evaluated by the filling of prescriptions for albuterol or other short-acting β-agonists (SABAs), and switch or discontinuation of controller medication.

METHODS

Study Design, Sample, and Data Source

A retrospective cohort study design was used from a third-party payer perspective. Administrative claims data consisted of 3 commercial health plans, including a West Coast plan, an East Coast plan, a statewide regional plan, and a Southeast Medicaid plan. Total membership included more than 8 million lives among 3 commercial health plans and approximately 1.6 million additional members in the Medicaid plan. The data included all claims related to inpatient, outpatient, and prescription services and eligibility information for the members in those health plans. The study period was from April 2000 to December 2002. Within that period, the *index date* was defined as the first date a prescription for a study drug of interest was filled. A baseline or 12-month preindex period was observed and an individualized 12-month postindex period as determined by each patient's index date.

The inclusion criteria for this study were as follows: (1) at least 1 prescription between April through September 2001 for any of the following: FSC, FP, and FP + SAL dispensed separately and within 30 days of each other; (2) 1 or more SABA prescriptions in the preindex period; (3) age of 15 years or older as of April 1, 2001; (4) at least 1 principal or secondary medical diagnosis claim for asthma (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 493.xx) during the study period; and (5) continuous health plan eligibility during the study period. Patients were included in the 3 cohorts of interest based on asthma prescriptions dispensed between April and September 2001.

Exclusion criteria included any of the following: (1) any chronic obstructive pulmonary disease diagnosis (*ICD-9* code 491.xx, 492.xx, 494.xx, 496.xx) or any cystic fibrosis diagnosis (*ICD-9* code 277.xx) during the preindex period; (2) any ICS, LABA, or leukotriene receptor antagonists (LTRA) prescription in the preindex period; and (3) any alternative controller during the first 60 days after the index date.

Outcome Variables

The primary outcome of interest indicative of an asthma exacerbation or increase in symptoms was any *ICD-9* diagnosis claim for asthma associated with inpatient or ED care. Secondary outcomes included the number of SABAs dispensed during the postindex period or a switch or discontinuation of asthma index therapy. Discontinuation was defined as the first 60-day gap in the day's supply of index medication. The time to first switch or add-on of an alternative asthma controller medication was defined as the number of days from the index claim to a claim for any ICS, LTRA, LABA, theophylline, or cromolyn. Patients were required to use no additional or alternative controller for 60 days after the index event and were excluded if an alternative controller was dispensed during the initial 2 months. For the FP + SAL cohort, the time to switch or add-on of an alternative controller was measured as the number of days when the patient was supplied with both medications of interest.

Baseline Characteristics

Baseline characteristics included age, sex, health plan type, general comorbidities, and asthma-related comorbidities (allergic rhinitis, sinusitis, acute upper respiratory tract infection, tonsillitis, pharyngitis, pneumonia, and history of smoking). Variables measured during the preindex period included use of SABAs, ED services, and inpatient care services. In addition, we reported the percentage of patients with preindex asthma-related claims for pulmonary function testing and allergy skin testing as an indicator of compliance with guideline recommendations.

Statistical Analysis

Descriptive statistics were used to summarize all dependent and independent variables by cohort and to compare cohorts. Means and *t* tests were used for all continuous variables and percentages, and χ^2 tests were used for categorical variables. Two sets of analyses were conducted for each end point, comparing the FSC cohort to the FP cohort and the FP + SAL cohort, respectively. Logistic regression analysis was used to model asthma exacerbations, as measured by any asthma-related ED visits or hospitalization. Ordinary least squares regression was used to examine the relationship between asthma controller medication use at baseline and postindex SABA use. Cox proportional hazards regression techniques were used to model the risk of switching to another asthma medication from the index medication, the risk of discontinuing use of the index medication, and the risk of hospitalization or an ED visit. SAS statistical software, release 8.2 was used for all statistical analyses (SAS Institute Inc, Cary, NC).

RESULTS

A total of 2,414 patients met the inclusion and exclusion criteria. A total of 1,013 patients were in the FSC group, 1,130 in the FP group, and 271 in the FP + SAL group. The population was 62% to 64% female across cohorts, with a mean age ranging from 39 to 43 years. Comorbidities were significantly higher for the FSC cohort when compared with the other cohorts. Also, baseline SABA use was greater for the FSC cohort compared with those receiving FP (Table 1). During the preindex period, 5% (FSC), 7% (FP + SAL), and 6% (FP) of patients had an ED or hospital claim.

After initiation of therapy, patients taking FSC had significantly lower asthma-related hospitalization and ED rates compared with the FP or FP + SAL groups. These events occurred in 3%, 8%, and 4% of FSC, FP + SAL, and FP patients, respectively. Odds ratios (ORs) associated with ED or inpatient care use during the postindex period for study parameters are included in Table 2. Patients receiving FSC were less likely to have an ED visit or be hospitalized compared with patients receiving FP (OR, 0.75; 95% confidence interval [CI], 0.61–0.93) or patients receiving FP +

Table 1. Baseline Demographics and Patient Characteristics

Characteristics	FSC	FP	FP + SAL
No. of patients	1,013	1,130	271
Female, No. (%)	651 (64.3)	703 (62.2)	173 (64.0)
Age, mean (SD), y	39 (17)*	40 (18)	43 (16)
No. of preindex SABAs, mean (SD)	2.99 (3.44)†	2.64 (3.32)	2.71 (3.38)
No. of preindex comorbidities, mean (SD)	1.39 (1.32)†	1.26 (1.42)	1.35 (1.29)
Patients with pulmonary function test claims, %	37†	23	31
No. of preindex oral cortocosteroids, mean (SD)	0.55 (1.43)*†	0.44 (1.27)	0.78 (1.89)
No. of preindex ED and inpatient claims, mean (SD)	0.06 (0.35)	0.09 (0.66)	0.10 (0.41)

Abbreviations: ED, emergency department; FP, fluticasone propionate; FP + SAL, fluticasone propionate and salmeterol from 2 separate inhalers; FSC, fluticasone propionate and salmeterol from a single inhaler; SABAs, short-acting β-agonists.
*Significant between FSC and FP + SAL cohorts at $P < .05$.
†Significant between FSC and FP cohorts at $P < .05$.

Table 2. Logistic Regression Model of ED or Inpatient Service Use During the Postindex Period*

Parameter	Patients using FSC or FP		Patients using FSC or FP + SAL	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.997 (0.991–1.004)	.39	0.99 (0.986–1.003)	.17
Female sex†	1.336 (1.074–1.662)	.009	1.28 (0.964–1.699)	.09
Plan A†	0.218 (0.154–0.307	<.001	0.251 (0.157–0.400)	<.001
Plan B†	0.224 (0.154–0.326)	<.001	0.243 (0.146–0.404)	<.001
Plan C†	0.190 (0.139–0.260)	<.001	0.219 (0.143–0.336)	<.001
No. of baseline ED visits	1.402 (0.916–2.146)	.12	1.688 (0.968–2.941)	.06
No. of baseline hospitalizations	1.028 (0.688–1.536)	.89	0.612 (0.290–1.295)	.20
No. of oral steroid claims	1.134 (1.051–1.224)	.001	1.027 (0.945–1.116)	.53
No. of cromolyn claims	0.954 (0.678–1.341)	.79	0.905 (0.617–1.327)	.61
No. of theophylline claims	0.982 (0.909–1.062)	.65	0.977 (0.892–1.070)	.62
No. of SABA claims	0.991 (0.960–1.024)	.60	0.997 (0.956–1.040)	.89
Any nebulizer claim†	0.267 (0.061–1.170)	.08	0.670 (0.184–2.440)	.54
Allergic rhinitis†	0.957 (0.742–1.233)	.73	0.836 (0.610–1.145)	.26
No. of comorbidities	1.351 (1.242–1.471)	<.001	1.273 (1.136–1.427)	<.001
FSC	0.754 (0.614–0.926)	.007	0.693 (0.506–0.948)	.02

Abbreviations: CI, confidence interval; ED, emergency department; FP, fluticasone propionate; FP + SAL, fluticasone propionate and salmeterol from 2 separate inhalers; FSC, fluticasone propionate and salmeterol from a single inhaler; OR, odds ratio; SABAs, short-acting β-agonists.
*Male is the reference group for female, plan D (Southeast Medicaid) is the reference group for other health plans, no nebulizer use is the reference group for any nebulizer use, no allergic rhinitis is the reference group for allergic rhinitis, and FP or FP + SAL is the reference group for FSC, depending on the model.
†Categorical variables.

SAL (OR, 0.69; 95% CI, 0.51–0.95). The regression analysis in Table 2 indicates that female sex, health plan type, oral corticosteroid use, and baseline comorbidities were also significantly associated with postindex ED and hospital use. In addition, the Cox proportional hazard model demonstrated that patients receiving FSC were associated with a 21% lower risk of an asthma-related ED or hospitalization compared with patients receiving FP (hazard ratio [HR], 0.79; 95% CI, 0.67–0.93) and 27% lower risk than those receiving FP + SAL (HR, 0.73; 95% CI, 0.57–0.95).

Multiple linear regression was used to predict postindex SABA use. Patients in the FSC group had 0.32 fewer postindex SABA prescription compared with those in the FP group ($P = .01$) and had 0.53 fewer postindex SABA prescription than those in the FP + SAL group ($P = .01$). Preindex SABA use and health plan type were significantly associated with postindex SABA use in both models. The use of SABA decreased by 22% in the FSC group, 6% in the FP group, and 1% in the FP + SAL group.

Cox proportional hazards techniques were used to examine switching behavior and discontinuation of index medication (Fig 1). Patients receiving FSC had a 36% lower risk of discontinuation of controller medication compared with those receiving FP (HR, 0.64; 95% CI, 0.58–0.71) and a 26% lower risk of discontinuing index therapy when compared with dual therapy with FP + SAL (HR, 0.74; 95% CI,

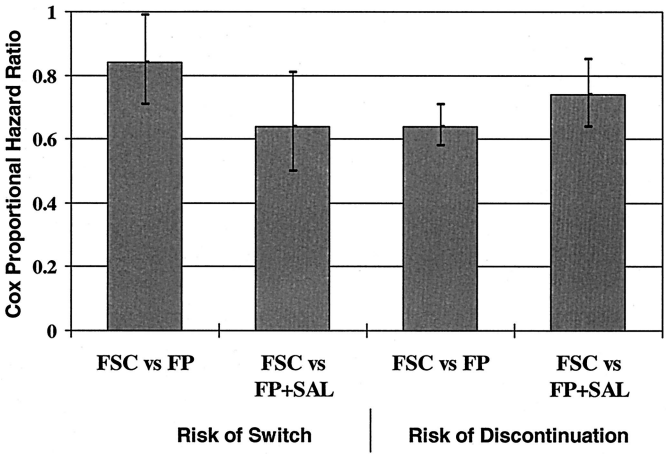

Figure 1. Risk of postindex switch and discontinued use of study medication. FSC indicates fluticasone propionate and salmeterol as a single inhaler; FP, fluticasone propionate alone; and FP + SAL, fluticasone and salmeterol as separate inhalers.

0.64–0.85). Younger patients and those with higher preindex SABA use were more likely to discontinue therapy. The risk of switching from index medication for patients in the FSC group was 16% lower than the risk for FP patients (HR, 0.84; 95% CI, 0.71–0.99) and 36% lower than the risk for patients receiving dual therapy with FP + SAL (HR, 0.64; 95% CI, 0.50–0.81).

DISCUSSION

Results from this study indicate that patients receiving FSC experienced fewer asthma-related ED or inpatient hospitalization events compared with patients receiving FP or FP + SAL. The number of SABA refills, a surrogate for asthma symptom control, also was lower for patients receiving FSC. Furthermore, patients taking FSC were less likely to switch to an alternative controller therapy. Consistent use of inhaled corticosteroids has been associated with improved outcomes.[9] These results support previous clinical trial findings that demonstrate the superiority of FSC compared with therapy with FP, SAL, or FP + SAL.[12–14]

Asthma exacerbations that result in asthma-related ED visits or hospitalization episodes are one of the major cost drivers for asthma.[4,6] Most clinical trials are not powered to detect changes in the rates of exacerbations. The Childhood Asthma Management Program,[15] Formoterol and Corticosteroids Establishing Therapy trial,[16] and OPTIMA[17] are exceptions. Observational studies such as the present investigation are used to enhance the data gathered from clinical trials. It can be argued that the relative lack of restrictive entrance criteria makes results from these examinations more easily generalized to the average asthma patient. The results of the present study are consistent with the results of randomized clinical trials.

Asthma exacerbations negatively affect the quality of life of asthma patients and increase the risk of subsequent asthma-related ED events and hospitalization. The observed lower risk of this asthma-related morbidity in the FSC cohort may be due to the greater efficacy noted in the clinical trials[12–14] and increased compliance noted in observational studies.[18,19] The less frequent observation of switching controller medication seen with FSC may reflect patient preference associated with both the better outcomes and ease of administration. Patients taking FSC are more persistent with their medications than patients dispensed FP or FP + SAL[18,19] and in this study appear to achieve better clinical outcomes. The results of this study combined with the clinical trial literature demonstrating better outcomes with the combination of an ICS plus a LABA is reassuring in light of the data from the Asthma Care Research Network.[20]

Clinical studies have established the superior efficacy of FSC compared with either FP or SAL alone,[12–13] montelukast,[21,22] or the combination of montelukast and FP.[23,24] Users of FSC had reduced postindex albuterol use in each of these studies. This study of claims data is consistent with results published in clinical trials. Albuterol use may reflect lack of control of the symptoms of asthma and serves as a surrogate marker in observational studies and clinical trials for an increase in asthma symptoms. The present analysis reveals a significantly greater reduction in SABA use with FSC than the comparators.

Both clinical and observational studies, such as the present report, support the continued implementation of the NAEPP guideline recommendations for the treatment of asthma. These guidelines state that for patients with symptoms of asthma not controlled with ICSs alone or for patients with moderate to severe persistent asthma the preferred treatment is the use of an ICS combined with a LABA.[2] Better adoption of these treatment algorithms may result in decreases in variation in practice and potentially reduce the morbidity associated with uncontrolled asthma.[25,26] Evidence provided suggests that both increased adherence[18,19] and decreased risk of changing therapy noted with FSC may enhance the clinical outcomes in addition to the superiority noted with FSC in clinical trials. Further, the complexity of treatment involved with dual inhalers in the FP + SAL cohort may result in selective discontinuation of the prescribed therapy, which may lead to increased exacerbations. Patients in this study were continuously enrolled in a single health plan. All of the medications studied were formulary to ensure that switch or discontinuation was not due to changes in formulary status. Further the FSC cohort with the lowest rate of switch or discontinuation had the best clinical outcomes, suggesting that improved clinical status does not encourage discontinuation.

This study presents asthma exacerbation data using observational claims data from actual patients and validates and generalizes results observed in controlled clinical trials. One of the limitations of using claims data to compare alternate therapies is the potential for selection bias, since patients are not randomized to control and treatment groups as practiced

in clinical trial design. In claims-based studies, steps must be taken to ensure that observed treatment effects are not due to underlying characteristics of the study populations. Two multivariate models were used to control for a variety of preindex measures that reflect asthma severity. Logistic models demonstrated decreased hospital and SABA use and increased refill rates with FSC, and the Cox models demonstrated a lower HR for hospitalization, medication switch, or discontinuation. All observational analyses that use claims have the inherent limitation that the intent of the data is for billing purposes and not a measure of response to therapy. That stated, these data sets are used by the National Committee for Quality Assurance to measure quality.[27] Claims data have no universally accepted measure of disease severity. The regression models are therefore used to adjust for baseline differences. Although one cannot be certain that all ED events are associated with the diagnostic claim of interest, the frequency of events are consistent with those reported by the Centers for Disease Control and Prevention.[1] In addition, patients treated with FSC were required to pay only 1 copay, and patients treated with FP + SAL were commonly charged 2 copays. Refill persistence data for these 2 regimens[18] demonstrate that FSC is dispensed approximately 75% more than the regimen for FP + SAL, making the difference in total number of copays less than 1 per year between these 2 cohorts.

The current study adds to the body of literature that demonstrates greater control and decreases in exacerbations in patients undergoing therapy for asthma using FSC compared with FP and FP + SAL in separate inhalers. This observational analysis indicates that the use of FSC monotherapy results in lower rates of asthma exacerbations when compared with other commonly used therapeutic regimens.

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