Original Article

Comparative Effectiveness of Budesonide-Formoterol Combination and Fluticasone-Salmeterol Combination for Asthma Management: A United States Retrospective Database Analysis

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What is already known about this topic? Results of prior studies have suggested that patients with asthma who initiate budesonide-formoterol combination therapy may have a lower asthma exacerbation rate compared with those who initiate the fluticasone-salmeterol combination, a possible explanation for lower fills of additional asthma controller medication and lower short-acting β_2-adrenergic-agonist prescription claims.

What does this article add to our knowledge? This study adds a US perspective to the data of real-world comparative effectiveness for 2 of the most commonly used inhaled corticosteroid–long-acting β_2-adrenergic agonist medications (budesonide-formoterol combination therapy and fluticasone-salmeterol combination therapy) for the treatment of moderate-to-severe persistent asthma.

How does this study impact current management guidelines? Asthma management imposes heavy demands on available health care resources. This study provides patients, providers, and payers with real-world comparative effectiveness data on 2 of the commonly prescribed asthma therapies.

BACKGROUND: Comparative effectiveness of the budesonide–formoterol fumarate dihydrate combination (BFC) and the fluticasone propionate–salmeterol combination (FSC) therapy on asthma exacerbation has not been assessed in real-world settings in the United States.

OBJECTIVE: To compare exacerbation rates and health care utilization for patients with asthma who initiate BFC versus FSC therapy.

METHODS: This retrospective cohort comparative effectiveness study queried medical and pharmacy data for patients with asthma from a large managed care data repository that covers major US population centers. The patients were 12 to 64 years old, with ≥12 months of pre- and postindex enrollment and ≥1 pharmacy claim(s) for BFC or FSC initiated during June 1, 2007, and September 30, 2010; the first prescription fill date was defined as the index date. Patients with other respiratory diseases and/or cancer were excluded. Exacerbation was defined as asthma-related hospitalization, emergency department visit, and/or oral corticosteroid prescription fill. Cohorts were matched by using propensity scores.

RESULTS: A total of 3043 patients per cohort were matched and balanced. During the 12 months following the initiation the BFC cohort had lower adjusted exacerbations per person year versus the FSC cohort (0.85 vs 0.93; RR 0.92, 95% CI [0.85-0.99]), lower oral corticosteroid fill rates, and fewer asthma-related emergency department visits but comparable asthma-related hospitalization.

CONCLUSIONS: Asthma exacerbation was lower for BFC versus FSC initiators due to lower rates of oral corticosteroid use and asthma-related emergency department visits, which indicate better treatment effectiveness of those patients initiated with BFC compared with FSC. **(J Allergy Clin Immunol Pract 2014;2:719-26)**

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Abbreviations used
BFC- Budesonide–formoterol fumarate dihydrate combination
DCI- Deyo-Charlson index
ED- Emergency department
FSC- Fluticasone propionate–salmeterol combination
GERD- Gastroesophageal reflux disease
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-adrenergic agonist
LTRA- Leukotriene receptor antagonist
OCS- Oral corticosteroid
OR- Odds ratio
PDC- Proportion of days covered
RR- Rate ratio
SABA- Short-acting β_2-adrenergic-agonist

Key words: *Asthma; Comparative effectiveness; Retrospective cohort study; Inhaled corticosteroids; Long-acting β_2-adrenergic agonist; short-acting β_2-adrenergic-agonists; Budesonide-formoterol combination; Fluticasone-salmeterol combination*

Asthma, a common respiratory condition that results from inflammation in both large and small airways,[1,2] directly impacts an estimated 24.6 million people in the United States.[3] Total health care costs directly attributable to asthma care in the United States were estimated at $37.2 billion (in 2007).[4] Medical Expenditure Panel Survey data for 2002 to 2007 showed that asthma imposed an incremental society-wide cost of $56 billion (adjusted to 2009 US$).[5] Treatment goals include achieving adequate control and reducing the risk of exacerbations and serious impairment.[6] Long-term controller medications, such as inhaled corticosteroids (ICS), are recommended by the current Expert Panel Report-3 for patients with persistent asthma.[7] For patients ages ≥12 years, the guidelines for the diagnosis and management of asthma indicate that the addition of a long-acting β_2-adrenergic agonist (LABA) be given equal weight to the option of increasing the ICS alone for patients inadequately controlled on ICS alone and for those patients with high levels of impairment and elevated risks of asthma exacerbation.[7] Currently, 3 ICS-LABA combination therapies are approved for use in the United States: budesonide–formoterol fumarate dihydrate (BFC),[8] fluticasone propionate–salmeterol combinations (FSC) therapy,[9] and mometasone–formoterol fumarate dihydrate.[10]

Clinical trials that assess BFC and FSC showed mixed results in the United States.[11] Lasserson et al[11] reviewed 5 randomized studies (5537 adults) in the Cochrane Airways Group register that compared fixed-dose FSC and BFC of adults and children diagnosed with asthma. Treatment durations were a minimum of 12 weeks; most of the studies assessed treatment for a 6-month period. Study populations had prior treatment with inhaled steroids (fluticasone/salmeterol or orbudesonide/formoterol) and had moderate or mild airway obstruction. Because of the imprecision of the estimated effects of asthma exacerbations, definitive conclusions about the superiority of either agent remain indeterminate.[11] With the growing recognition of the impact of asthma management on health care resources and costs, payers espouse the urgent need for real-world effectiveness data on asthma therapies beyond clinical efficacy and lung function.[12,13] In particular, data on the effect of controller therapies on avoidable asthma exacerbation and health care resource utilization are important.

Two population-based retrospective studies, in Canada[14] and in Germany,[13] evaluated comparative effectiveness of BFC versus FSC in asthma management. By using a matched cohort design, the Canadian study showed that, compared with patients on FSC, patients who received BFC were significantly less likely to require asthma-related emergency department (ED) visits or hospitalizations and oral corticosteroid (OCS) fills, and required less short-acting β_2-adrenergic-agonists (SABA) per week.[14] The German study demonstrated that patients with chronic asthma who initiated BFC therapy had a greater probability of treatment success with fewer severe asthma exacerbations and fewer OCS prescription fills.[13] However, the device (dry powder inhaler) and a commonly used indication (use for maintenance and reliever therapy) for BFC approved in these countries are not approved in the United States. To our knowledge, no studies to date have compared the 2 agents by using the US device (a pressurized metered dose inhaler) and with the US approved indication. The objective of the current study was to evaluate the real-world effectiveness of the ICS-LABA combination by comparing asthma exacerbation rates and health care resource utilization over a 1-year period after initiation of BFC and FSC with devices and indications approved in the United States.

METHODS

Data source and study design

This retrospective cohort study (NCT01623544) used integrated medical and pharmacy claims data to describe and compare differences in key outcomes among patients with asthma who initiated BFC versus FSC treatments between June 1, 2007, and September 30, 2010. The index date was defined as the date of the first pharmacy claim for either study medication. The patients were assigned to BFC or FSC cohorts based on their first prescription fill. Study data were acquired from the HealthCore Integrated Research Database (HealthCore Inc., Wilmington, Del), a diverse longitudinal administrative claims repository that contains data from commercial health plans in the northeast, midwest, south, and west regions of the United States. Researchers only had access to de-identified patient data, and patient anonymity and confidentiality were safeguarded in compliance with the Health Insurance Portability and Accountability Act. Institutional review board approval was not required for this observational study.

Study population

Patients were considered to have a claims-based asthma diagnosis if they had 1 inpatient visit with a primary diagnosis code for asthma or 1 ED visit with an asthma diagnosis or with 2 or more medical claims (any visit combination) with an asthma diagnosis in the 12 months before the index date. Generic Product Identifier Codes (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) were used to identify patients who received BFC or FSC combination therapy. International Classification of Diseases, Ninth Revision Clinical Modification codes (493.0x, 493.1x, or 493.9x) were used to identify asthma.

Inclusion criteria. Patients were required to be between 12 and 64 years of age on the index date and to have ≥1 BFC or FSC prescription fill during the intake period. A second fill for the same ICS-LABA combination in the 12 months after the index prescription (postindex period) was required for inclusion in the study. For inclusion, patients had to be naive (no