

The risk of hospitalization in patients with asthma switched from an inhaled corticosteroid to a leukotriene receptor antagonist

David A. Stempel, MD,^a Lionel Pinto, MS,^b and Richard H. Stanford, PharmD^c

Seattle, Wash, Woodland Hills, Calif, and Research Triangle Park, NC

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Asthma-related hospitalization rates were compared over a 2-year period between a cohort of patients with asthma who switched from an inhaled corticosteroid in year 1 to a leukotriene modifier in year 2 (n = 285) and a matched cohort continuously treated with an inhaled corticosteroid (n = 570). During year 1, patients were well maintained, with a hospitalization rate of 1.1% to 1.4%. During year 2, 2.5% of the patients switched to a leukotriene modifier had one or more asthma-related hospitalizations compared with 0.6% of the patients continuously receiving an inhaled corticosteroid. Patients treated with a leukotriene modifier were at 7 times greater risk for an asthma-related hospitalization compared with patients who continued to receive an inhaled corticosteroid (risk-adjusted odds ratio, 7.1; 95% CI, 2.79-17.95). These data are consistent with the results of well-controlled clinical trials showing that leukotriene modifiers may be associated with deterioration of asthma control relative to inhaled corticosteroids. Considered in aggregate, the data support the conclusion that leukotriene modifiers should not be substituted for inhaled corticosteroids as a single-controller therapy for asthma. (*J Allergy Clin Immunol* 2002;110:39-41.)

Key words: Fluticasone propionate, retrospective analysis, leukotriene modifier, leukotriene receptor antagonist, inhaled corticosteroid, asthma, claims data, asthma costs, single-controller therapy

The 1997 National Asthma Education Panel guidelines identify the prevention of asthma exacerbations and hospitalizations as a primary goal of asthma care.¹ Approximately half a million patients in the United States are hospitalized each year because of asthma,² and

hospitalizations account for nearly 30% of the direct medical costs of this disease.³ Patients with asthma exacerbations leading to hospitalization have impaired well-being and functional ability and lose time from work and other daily activities. In addition, inhaled corticosteroids are the only treatment for asthma that has consistently been shown to reduce the morbidity and mortality of the disease.⁴

Clinical trials of single-controller therapy show that patients treated with inhaled corticosteroids experience greater improvement in lung function, better asthma control, and, often, fewer asthma exacerbations than patients treated with the more recently introduced leukotriene modifiers.⁵⁻⁷ Furthermore, in a randomized, double-blind clinical trial,⁸ patients switched from beclomethasone dipropionate to a leukotriene modifier compared with those maintained on beclomethasone dipropionate experienced clinical deterioration, as measured by worsening asthma control and decline in lung function. The latter has been shown to be a strong predictor of risk of asthma exacerbations.⁹ This study of patients with asthma enrolled in 3 major US health plans was conducted to determine whether the finding of decreased exacerbations with inhaled corticosteroids compared with leukotriene modifiers could be validated in a claims analysis of hospitalization rates.

METHODS

The study was a pre-post retrospective analysis using medical and pharmacy claims of patients ages 4 to 64 years with a medical claim for asthma who were continuously enrolled for at least 24 months in one of 3 geographically diverse US health plans that covered approximately 4 million members. The frequency of hospitalizations over a 1-year period was compared between a cohort of patients switching from an inhaled corticosteroid to a leukotriene modifier (leukotriene modifier cohort) and a cohort of patients continuously using inhaled corticosteroids (inhaled corticosteroid cohort).

Both cohorts were required to have at least one prescription claim for an inhaled corticosteroid and no claims for a leukotriene modifier during the first year of the study (year 1). The index prescription claim for the leukotriene modifier cohort was the first prescription for a leukotriene modifier (in year 2). Patients in the leukotriene modifier cohort were defined as those receiving at least 2 consecutive leukotriene modifier claims (index plus one more) within 90 days of each other, without an intervening controller

From ^athe University of Washington, Seattle; ^bHealth Benchmarks, Inc, Woodland Hills; and ^cGlaxoSmithKline, Research Triangle Park.

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Reprint requests: David A. Stempel, MD, 9121 NE 16th St, Bellevue, WA 98004.

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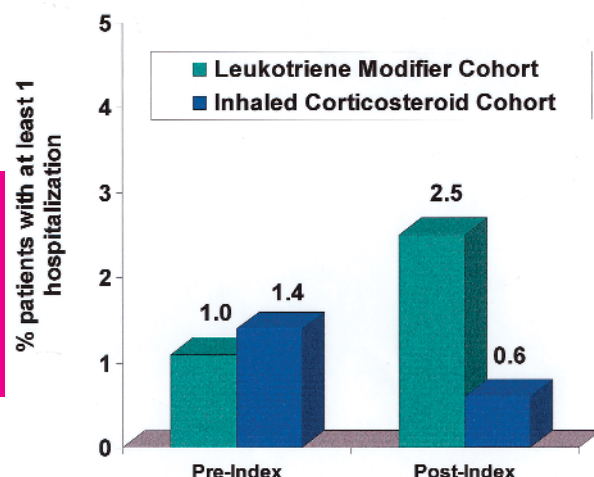


FIG 1. Percentage of patients with at least one hospitalization during the year before and the year after the index event.

TABLE I. Demographic and clinical characteristics 1 year before the index event

	Leukotriene modifier cohort (n = 285)	Inhaled corticosteroid cohort (n = 570)
Mean $\pm$ SD age, y	29.36 $\pm$ 19.3	28.94 $\pm$ 20.1
Male, n (%)	134 (47)	268 (47)
Short-acting β -agonist prescriptions (mean $\pm$ SD)	4.6 $\pm$ 4.5	3.8 $\pm$ 4.1
Hypertension present, n (%)	37 (13)	57 (10)
Diabetes present, n (%)	11 (4)	21 (4)
Cardiovascular disease present, n (%)	33 (12)	55 (10)
Asthma-related hospitalization, n (%)	3 (1)	8 (1.4)

claim. The index prescription claim for the inhaled corticosteroid cohort was an inhaled corticosteroid claim during the same quarter as a corresponding index leukotriene modifier claim in the leukotriene modifier cohort. Patients in the inhaled corticosteroid cohort were defined as those receiving at least 2 consecutive inhaled corticosteroid claims (index plus one more) within 90 days of each other, without an intervening controller claim. Patients in the inhaled corticosteroid cohort were matched with those in the leukotriene modifier cohort on age, sex, and plan type and were selected to achieve a 2:1 inhaled corticosteroid/leukotriene modifier ratio for any given quarter.

This is an intent-to-treat analysis, and patients were allowed to receive other treatments for asthma after the initial 90-day period and were considered to be part of the initial index treatment. All consequences of initial treatment selection, switches, or augmentations were regarded as common and important consequences of initial treatment selection.

Multivariate logistic regression analyses were performed, as previously described,⁶ to evaluate differences between cohorts in the frequency of asthma-related hospitalizations. Covariates in the regression analyses included age; sex; age by sex; plan type; number of preindex prescriptions for inhaled corticosteroids, oral corticosteroids, β -agonists, and theophylline; preindex numbers of asthma-related hospitalizations; number of relevant comorbidities; and total asthma care costs. Risk-adjusted odds ratios for hospitalization in the leukotriene cohort compared with those in the inhaled corticosteroid cohort were estimated.

RESULTS

Demographics and clinical characteristics

The number of patients enrolled in the leukotriene modifier cohort was 285. Of 2103 patients meeting criteria for the inhaled corticosteroid cohort, 570 were randomly selected after each patient in the leukotriene cohort was matched with 2 patients meeting criteria for the inhaled corticosteroid cohort. Demographic and clinical characteristics are depicted in Table I.

Hospitalizations

During the year before the index event (year 1), the percentage of patients with one or more asthma-related hospitalizations was similar between cohorts at 1.1% (n = 3) for the leukotriene modifier cohort and 1.4% (n = 8) for the matched inhaled corticosteroid cohort. During the year after the index event (year 2), the percentage of patients with at least one asthma-related hospitalization was 2.5% (n = 7) in the leukotriene modifier cohort compared with 0.6% in the inhaled corticosteroid cohort (n = 3, Fig 1). Patients in the leukotriene modifier cohort were at 7 times greater risk for an asthma-related hospitalization compared with patients who continued to receive an inhaled corticosteroid (risk-adjusted odds ratio, 7.1; 95% CI, 2.79-17.95).

DISCUSSION

The results demonstrate that patients with asthma receiving inhaled corticosteroids had a low rate of hospitalizations during year 1. During the postindex year, patients switched from an inhaled corticosteroid to a leukotriene modifier had a 7-fold greater risk of being hospitalized because of asthma than did patients continuously using an inhaled corticosteroid. This finding corroborates the previous observation, from a retrospective claims analysis, that the inhaled corticosteroid fluticasone propionate was associated with a significantly lower risk of asthma-related hospitalization than the leukotriene modifier zafirlukast over a 1-year period among patients enrolled in 13 US health plans.¹⁰ This finding is also consistent with clinical data suggesting that switching from an inhaled corticosteroid (beclomethasone dipropionate) to a leukotriene modifier (montelukast) may cause deterioration in asthma control^{8,11} and with the observation that across 5 randomized, double-blind studies, zafirlukast administered for 4 to 12 weeks was associated with a higher frequency of exacerbations (14.3%) than either placebo (9.1%) or fluticasone propionate (2.7%) among patients older than 50 years with asthma.¹² The authors concluded that zafirlukast may cause deterioration of asthma by allowing inflammation to go unchecked.

Inhaled corticosteroids confer greater improvement in lung function than leukotriene modifiers, and better lung function appears to be a predictor of lower risk of exacerbation.⁹ These observations corroborate previous findings of consistently low rates of hospitalizations for

patients maintained on inhaled corticosteroids and higher rates for those taking leukotriene modifiers.¹⁰

Because of its observational design, the present study may be more representative of typical clinical practice. Although this analysis provides information that cannot be gained from a controlled clinical trial, the data should be interpreted in the context of their limitations, particularly selection bias arising from nonrandom assignment of patients to cohorts. Even though appropriate statistical methods were used to reduce this possibility, it is still a threat to internal validity. Unobserved variables, such as symptoms and lung function, could not be accounted for in this study design, and, potentially, those unobserved variables could be associated with the outcome as well. However, observational studies of this kind are intended to complement the efficacy data from randomized clinical trials, in which there are high degrees of internal validity but low degrees of generalizability.¹³ In addition, the outcomes of this study correspond with what has been observed from previous randomized clinical trials in which patients were switched from low-dose inhaled corticosteroids to leukotriene modifiers had decreases in asthma control and increases in exacerbations.^{8,11,12} The consistency of these data with results from these well-controlled clinical trials lends credence to the findings and supports the conclusion that leukotriene modifiers should not be substituted for inhaled corticosteroids as a single-controller therapy for asthma.

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