

Inhaled corticosteroids plus salmeterol or montelukast: Effects on resource utilization and costs

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Background: Experimental clinical studies have demonstrated that the addition of salmeterol to inhaled corticosteroids (ICSs) is superior to the addition of montelukast to ICSs. Observational research from real-world clinical practice is needed to confirm these results.

Objective: The present study was designed to assess, in clinical practice, the comparative impact on health care utilization and cost of 2 dual-controller therapies, ICS + salmeterol and ICS + montelukast.

Methods: This study involved the use of a 24-month pre/post retrospective design in patients continuously enrolled in any of 14 United HealthCare plans. Outcomes assessed were post-index pharmacy costs, rates of emergency department visits and hospitalizations, numbers of filled prescriptions for short-acting β -agonists (SABAs), total asthma costs, and total health care costs.

Results: Subjects in the ICS + salmeterol group had 35% fewer post-index SABA claims than subjects in the montelukast add-on group ($P \leq .05$). Subjects using ICS + montelukast were 2.5 times more likely to have an asthma-related hospitalization than subjects using ICS + salmeterol ($P \leq .065$). Total adjusted asthma costs were 63% higher for the patients receiving ICS + montelukast than for the patients receiving ICS + salmeterol ($P \leq .0001$). In addition, total health care costs were 25% lower in the ICS + salmeterol group. ($P \leq .0004$). Additional reductions in hospitalization and emergency department visits were observed when the patients on FP + salmeterol were studied separately.

Conclusion: In comparison with the use of montelukast and ICS, the use of salmeterol and ICS was associated with a significant reduction in SABA use, decreased hospital event rates, and significantly lower total asthma care costs. (*J Allergy Clin Immunol* 2002;109:433-9.)

Key words: Dual-controller therapy, asthma, inhaled corticosteroids, leukotriene modifiers, montelukast, fluticasone, salmeterol, pharmacoeconomic evaluation

Abbreviations used

ED:	Emergency department
FP:	Fluticasone propionate
ICD-9:	International Classification of Diseases (9th revision)
ICS:	Inhaled corticosteroid
LTM:	Leukotriene modifier
NIH:	National Institutes of Health
OR:	Odds ratio
RCT:	Randomized clinical trial
SABA:	Short-acting β -agonist

The National Institutes of Health (NIH) Expert Panel Report 2 on the diagnosis and management of asthma outlines 5 general goals of asthma therapy and provides a therapeutic algorithm designed to achieve these goals.¹ A primary guideline goal is the prevention of symptoms and exacerbations associated with asthma. Despite these efforts, data from the Centers for Disease Control and Prevention indicate that (1) there remains a high incidence of asthma-related hospitalizations (nearly 500,000 per year) and emergency department (ED) visits (almost 2,000,000 a year) and (2) there has been no discernable reduction in annual asthma mortality.² Studies have further demonstrated that the goals of reducing the incidence of sleep disturbance and asthma-related limitations in exercise have not been met.³

The NIH guidelines recommend the use of inhaled corticosteroids (ICSs) as the primary controller therapy for patients aged ≥ 12 years who have mild persistent asthma. For patients with moderate persistent asthma, the guidelines suggest several options—principally, higher dosages of ICSs and the use of an ICS and a long-acting β -agonist or a sustained-release theophylline preparation. Since the publication of the guidelines, several leukotriene modifiers (LTMs) have been introduced and used for both primary and add-on controller therapy. However, a role for LTMs as add-on therapy for the treatment of asthma has not yet achieved consensus.

Basic scientific research has identified mechanisms for the complementary action of ICSs and long-acting β -agonists.⁴ Nine clinical studies involving nearly 4000 patients have demonstrated that greater clinical efficacy is achieved when salmeterol is added to an ICS than when the ICS dose is doubled.⁵ In addition, 2 recent randomized clinical trials (RCTs) have demonstrated that the addition of salmeterol to an ICS provided superior asthma control and improved lung function in comparison with the addition of montelukast to an ICS.^{6,7}

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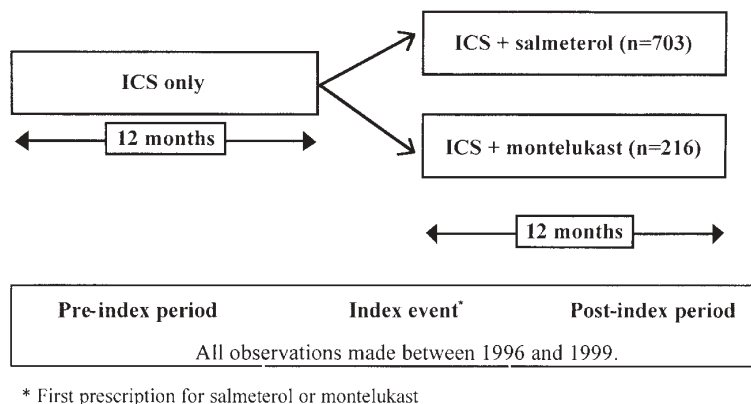


FIG 1. Schematic of study design.

A study by Fish et al⁶ examined patients on ICS who added, in a randomized, blinded fashion, either inhaled salmeterol or oral montelukast (10 mg). Patients treated with the addition of salmeterol had significantly greater improvement in terms of symptom-free days, use of rescue albuterol, and morning peak expiratory flow rate. In a second study, Nelson et al⁷ investigated patients still symptomatic despite the use of inhaled fluticasone propionate (FP) 100 µg twice daily. Patients were randomized to the addition of either salmeterol or montelukast 10 mg in addition to their FP. In a confirmation of the results of Fish et al, it was noted that the patients treated with the addition of salmeterol had significantly greater improvement in FEV₁ and peak expiratory flow rate, a greater number of rescue-free days, and improved symptom scores in comparison with patients receiving the addition of montelukast. Furthermore, the rate of asthma exacerbations was 69% lower in those patients treated with the combination of fluticasone and salmeterol than in those patients treated with the combination of fluticasone and montelukast.

Although the results of the RCTs have demonstrated the superior efficacy of ICS plus salmeterol in comparison with ICS plus montelukast, these RCTs were conducted under controlled, experimental conditions in selective patient samples. The primary objective of the clinical trial design is to maximize internal validity, which is the ability of a study to establish a cause-and-effect relationship between intervention and outcome. Maximizing external validity—the generalizability of study results to the population of interest—is secondary. It is beneficial, therefore, to assess whether the superior outcomes observed in the experimental setting translate into improved outcomes in the observational “real-world” setting. Accordingly, to compare outcomes in the real-world setting, the present investigation used retrospective administrative claims data from United HealthCare, a large managed care organization, to compare the health care utilization and costs associated with the use of dual-controller therapies in subjects with asthma. It was hypothesized that the superior outcomes observed in RCTs among patients receiving ICS plus salmeterol relative to patients receiving ICS plus montelukast would translate

into observable savings in asthma-related resource utilization and costs in real-world clinical practice.

METHODS

Design and sample

This study was designed primarily to assess the comparative impact on health care utilization and cost of 2 common dual-controller therapies: (1) ICSs used concurrently with salmeterol (ICS + salmeterol) and (2) ICSs used concurrently with montelukast (ICS + montelukast). In a follow-up analysis, patients receiving FP + salmeterol were compared separately, because clinical and economic studies appear to differentiate FP from the other members of its therapeutic class in terms of outcomes and costs.⁸⁻¹⁰ Fig 1 displays a schematic of the primary research design. The study involved the use of a 24-month pre/post retrospective design to compare asthma-related service utilization and costs among patients continuously enrolled in any of 14 United HealthCare plans. Ingenix Pharmaceutical Services conducted all of the analyses. (United HealthCare and Ingenix Pharmaceutical Services are both subsidiaries of United Health Group.)

Patients aged 4 to 65 years, each with a primary medical claim for asthma (International Classification of Diseases [9th revision] [ICD-9] code 493.XX) and currently receiving ICSs, were eligible for inclusion. The index event was defined as the first claim for salmeterol or montelukast in the period January 1, 1997, through September 30, 1998, establishing the 12-month pre-index and 12-month post-index periods. Patients were also required to have at least 1 filled ICS prescription in both the pre- and post-index periods. This research design follows the stepwise approach to the pharmacologic management of asthma recommended by the NIH guidelines, and it intentionally mirrors the basic study protocols of the aforementioned RCTs.^{6,7} To prevent contamination effects, patients treated with montelukast or salmeterol could not receive the other index drug or an alternative LTM in either the pre-index or the post-index period. Patients in the FP + salmeterol subanalysis could not receive a post-index ICS other than FP. Patients with a diagnosis of cystic fibrosis were excluded.

Outcomes

All paid claims accrued in the 24-month observation period were aggregated by patient to create cost and utilization outcomes. Costs were derived from actual paid amounts, including patient copayments. Asthma-related utilization and costs were identified through use of individual provider claims with a primary or secondary ICD-9 code for asthma (493.XX), facility claims with a primary ICD-9 code for asthma, and pharmaceutical claims coded as “Bron-

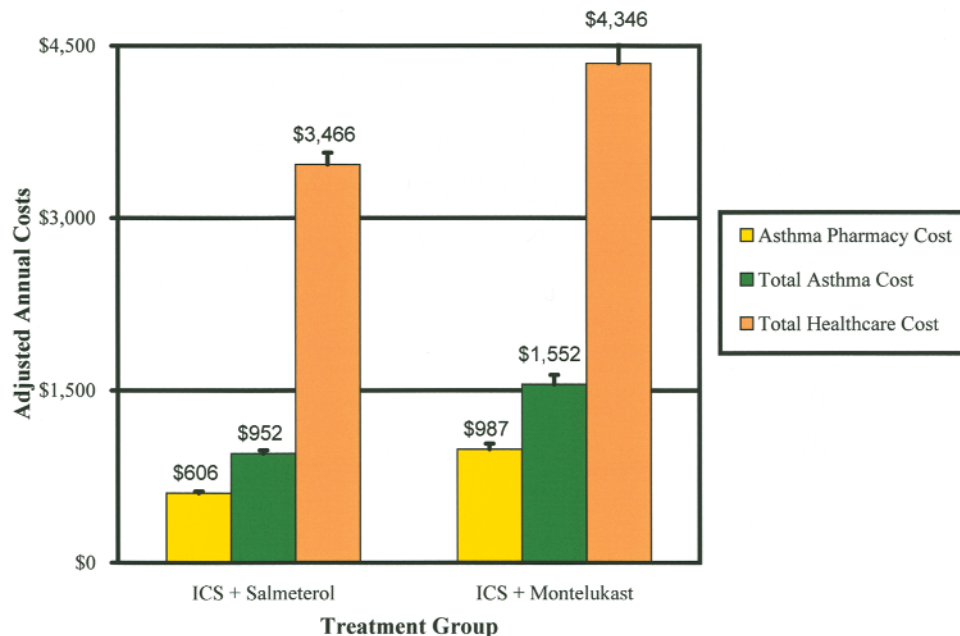


FIG 2. Annual asthma-related pharmacy, total asthma-related, and total health care costs per member by treatment group. Shown are least squares means of annual per-patient costs adjusted for age, sex, provider specialty, respiratory comorbidity, health plan, pre-index pharmacy utilization, and pre-index health care utilization and costs. SEs are included on each bar. Costs in the ICS + montelukast group were significantly higher than those in the ICS + salmeterol group ($P < .001$ for all pairwise comparisons).

chodilators and Related Drugs.” Outcomes were post-index pharmacy costs, rates of ED visits and hospitalizations, numbers of filled prescriptions for short-acting β_2 -agonists (SABAs), and total asthma and total health care costs.

Statistical analysis

Post-index intercohort differences in costs were assessed for statistical significance through use of ordinary least squares regression. For binary outcomes such as the presence or absence of a post-index ED visit, analyses included logistic regression and related methods for limited dependent variables. Ordinary least squares and logistic regression appropriately controlled for potential compositional differences among the groups that might otherwise have influenced the group comparisons. Covariates included demographics (age, sex), prescriber specialty (of the index pharmacy claim), indication of chronic obstructive lung disease or other respiratory comorbidity, pre-index use of SABAs and oral corticosteroids, pre-index asthma care cost, pre-index ED and inpatient events, and the specific United HealthCare health plan in which the patient was enrolled. The pre-index SABA use, cost, and utilization covariates acted as surrogate markers or proxies for asthma severity and overall patient health status variables that are not routinely collected in administrative claims databases. All significance tests were 2-tailed.

The regression analyses were preceded by univariable and bivariable descriptive statistics to assess the distributional properties of the study variables and the functional forms of the relationships between the independent and dependent variables. Analyses included univariable summary statistics, histograms, and frequency tables. Residuals from bivariable and multivariable regressions were assessed for violations of the assumptions of normality, linearity, homoscedasticity, and multicollinearity.^{11,12} Because of the large positive skew of the cost outcomes, these data were transformed through use of the natural log function. Potential interactions between independent variables were investigated; in several models,

the interaction of age and sex was included, inasmuch as sex differences in health service use were mediated by age. To facilitate interpretation and use of the data, comparisons among the cohorts were expressed whenever possible through use of adjusted means (ie, least squares means) or adjusted odds ratios (ORs). To facilitate interpretation, logged cost data were transformed to actual units (dollars) through use of common exponentiation formulas.¹³ The exponentiation of the adjusted means on the logarithmic scale yielded adjusted geometric means costs on the original cost scale.

RESULTS

Baseline comparisons

There were 919 patients who met the established selection criteria. The study population consisted of 703 patients in the ICS + salmeterol group and 216 patients in the ICS + montelukast group. Baseline comparisons showed that subjects in the ICS + montelukast group were younger, were less likely to be female (consistent with the age of the population), and had higher pre-index asthma management costs than the study subjects in the ICS + salmeterol groups (Table I). The pre-index ED rate was the same for the 2 groups (13.9%). Pre-index hospitalization rates were 4.2% for the ICS + montelukast group and 4.6% for the ICS + salmeterol group. These modest pre-index differences were appropriately controlled for in the multivariate models. Pre-index utilization of SABAs was similar in the 2 treatment groups. The baseline characteristics of the FP + salmeterol subgroup were similar to those for the ICS + salmeterol cohort with respect to age, sex, and hospitalization rates; however, at 17.2% the baseline ED rates were higher.

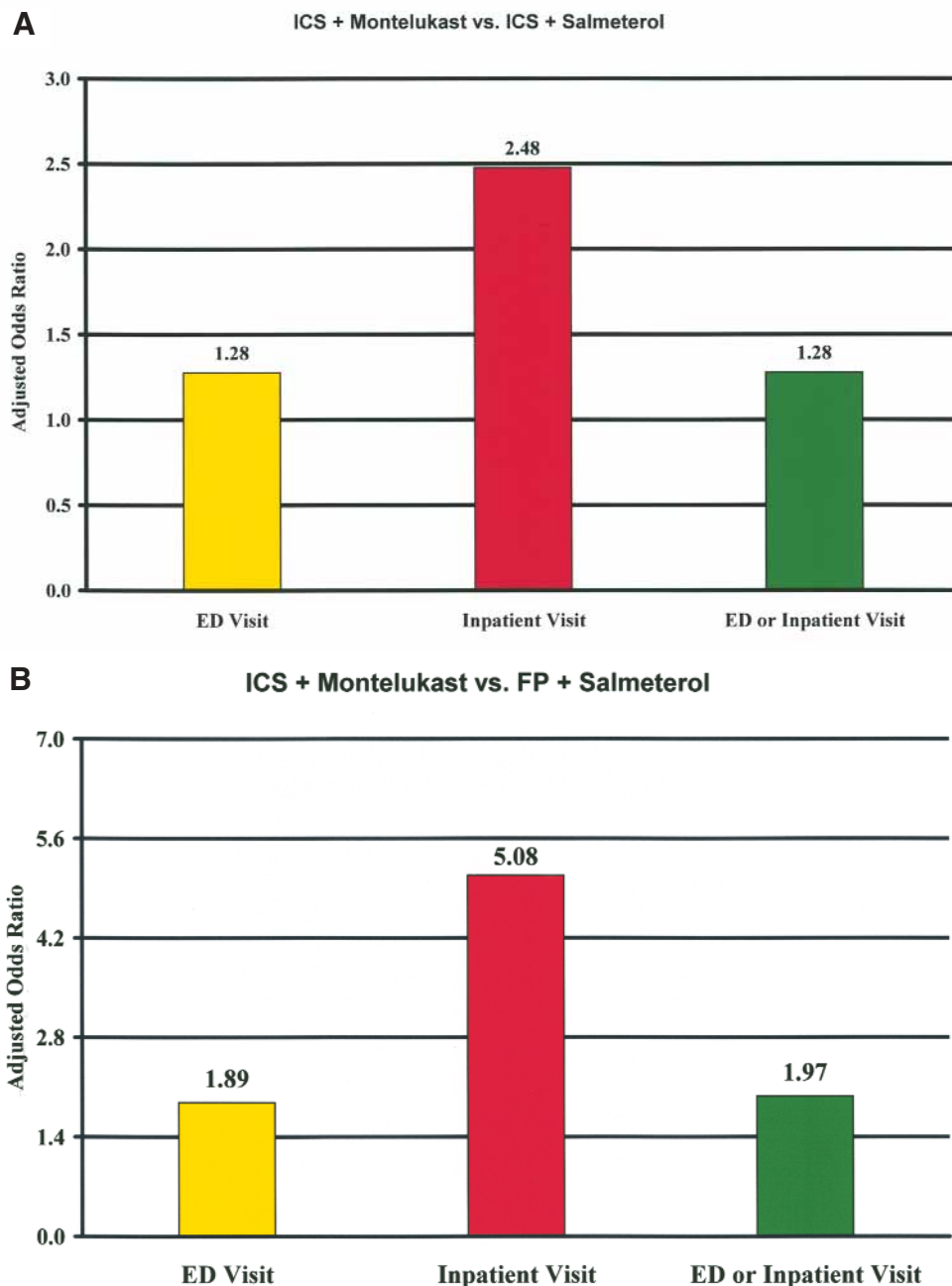


FIG 3. A, Adjusted ORs for an asthma-related ED visit or hospitalization by treatment group: ICS + montelukast vs ICS + salmeterol. **B,** Adjusted ORs for an asthma-related ED visit or hospitalization by treatment group: ICS + montelukast vs FP + salmeterol. Shown are ORs of the risk of having an asthma-related ED visit or hospitalization, adjusted for age, sex, provider specialty, respiratory comorbidity, health plan, pre-index pharmacy utilization, and pre-index health care utilization. The dependent variable assessed whether or not the patient had ≥ 1 asthma-related ED visit or hospitalization in the 1-year follow-up. The *P* values for the ORs for ICS + montelukast vs ICS + salmeterol were .3724, .0652, and .3564 for the ED visit, inpatient visit, and ED/inpatient analyses, respectively. The *P* values for the ORs for ICS + montelukast vs FP + salmeterol were .0656, .0299, and .0421 for the ED visit, inpatient visit, and ED/inpatient analyses, respectively.

Results of the multivariable models

Asthma-related and total health care costs. In the 1-year treatment period, the ICS + montelukast group had significantly higher pharmacy, total asthma-related, and

total health care costs than the ICS + salmeterol subjects ($P \leq .001$). When a comprehensive array of covariates was adjusted for, the subjects receiving ICS + montelukast, in comparison with the subjects receiving ICS + salmeterol, accrued annually 62.8% greater asthma-related pharmacy

TABLE I. Baseline demographics and asthma-specific health services use by treatment group

Variable	Treatment group				
	Primary analysis*			Subgroup**	
	ICS + montelukast	ICS + salmeterol	P value	FP + salmeterol	P value
N	216	703		261	
Age (y)	30.9 (19.8)	40.5 (16.3)	< 0.05	39.0 (17.1)	< 0.05
Female (%)	52.8	61.5	< 0.05	60.9	NS
Respiratory comorbidity† (%)	22.2	23.0	NS	26.1	NS
SABAs (refills)	5.6 (5.8)	5.7 (5.8)	NS	5.8 (6.5)	NS
Oral steroid use (refills)	1.5 (2.0)	1.3 (2.0)	NS	1.8 (2.2)	NS
ED visits (% ≥1)	13.9	13.9	NS	17.2	NS
Inpatient admission (% ≥1)	4.2	4.4	NS	4.6	NS
ED or inpatient visit (% ≥1)	15.3	15.9	NS	19.9	NS
Pharmacy cost (\$)	458 (437)	378 (359)	< 0.05	368 (355)	< 0.05
Total cost (\$)	1210 (1820)	1020 (1863)	NS	1038 (1300)	NS

Each value is mean (± SD) or percent. P values were derived from F or χ^2 tests of the null hypothesis of no significant difference between groups: *ICS + montelukast vs ICS + salmeterol; **ICS + montelukast vs FP + salmeterol. All service use presented is asthma-related.

SABAs, Short-acting β -agonists.

†Respiratory comorbidities were identified with International Classification of Diseases (9th revision) codes (chronic obstructive pulmonary disease and other respiratory combinations): 491.0, 491.1, 491.2, 491.20, 491.21, 491.8, 491.9, 492.0, 492.8, 493.2, 494, 496.

TABLE II. Numbers and percentages of patients with at least 1 asthma-related ED visit or hospitalization by treatment group

Variable	Treatment group					
	Primary analysis				Subgroup	
	ICS + montelukast		ICS + salmeterol		FP + salmeterol	
N	216		703		261	
	Pre	Post	Pre	Post	Pre	Post
No. w/ED visit (%)	30 (13.9)	28 (13.0)	98 (13.9)	76 (10.8)	45 (17.2)	23 (8.8)
No. w/hospitalization (%)	9 (4.2)	10 (4.6)	31 (4.4)	12 (1.7)	12 (4.6)	3 (1.1)

costs (\$987 vs \$606) and 63.0% greater (\$600 higher) total asthma-related costs (\$1552 vs \$952; Fig 2). This difference persisted when adjusted total health care costs were studied. ICS + montelukast was associated with a 25.4%/\$880 per year ($P = .0004$) greater total expenditure for health care in comparison with the ICS + salmeterol cohort. The secondary analysis also showed similar increases in asthma pharmacy, total asthma, and total health care costs for patients using ICS + montelukast in comparison with patients using FP + salmeterol.

Asthma-related ED and hospital rates. Table II shows the unadjusted rates of asthma-related ED and hospitalization visits before and after the initiation of dual-controller therapy for patients in each treatment group. Because ED and hospital use was a relatively rare event, we estimated the odds of asthma-related ED and hospital events in the post-index period. Fig 3 illustrates the adjusted odds of asthma-related ED visits and hospitalizations after the initiation of dual-controller therapy. The risk of a hospitalization was 2.5-fold greater with ICS + montelukast than with ICS + salmeterol ($P = .0656$). In the secondary analysis, in which FP + salmeterol was compared with the cohort using montelukast, the risk increased to 5-fold ($P = .0299$). ED utilization

showed the greatest relative reduction with the addition of salmeterol, but this did not achieve statistical difference. The FP + salmeterol secondary analysis demonstrated a statistically significant 2-fold reduction in acute ED or hospitalizations for asthma in comparison with ICS + montelukast ($P = .0421$).

SABA use. The results of the regression analysis demonstrated that subjects in the ICS + salmeterol group had significantly lower post-index SABA use (3.29 canisters/year) than subjects in the ICS + montelukast group (4.45 canisters/year). This reduction was greatest in subjects in the FP + salmeterol subgroup (2.79 canisters/year). All pairwise differences achieved significance at the $P < .0001$ level. (Fig 4)

DISCUSSION

RCTs have consistently demonstrated that the addition of a long-acting bronchodilator to an ICS produces better lung function, better symptom scores, and a lower rate of utilization of SABAs than does the addition of an LTM such as montelukast or zafirlukast.^{6,7,11,14} Our results, using real-world data, are consistent with the findings observed in the RCTs. Patients treated with ICS + sal-

Asthma, rhinitis,
other respiratory
diseases

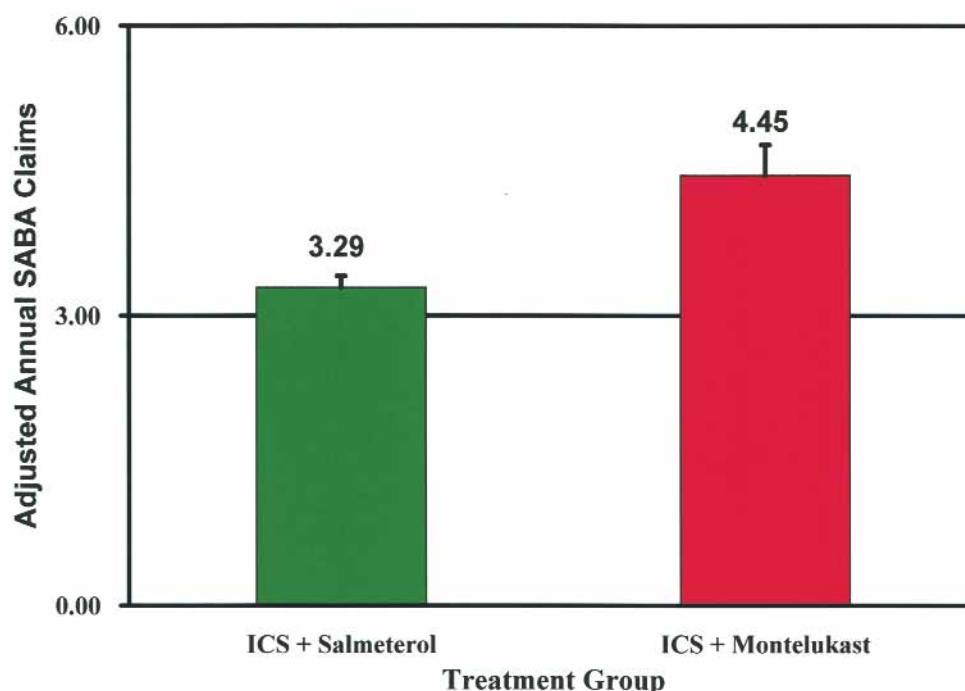


FIG 4. Adjusted SABA canister refills by treatment group. Shown are least squares mean refills adjusted for age, sex, provider specialty, respiratory comorbidity, health plan, pre-index pharmacy utilization, and pre-index health care utilization. Pairwise comparison was significantly different ($P < .0001$).

meterol incurred significantly lower asthma pharmacy costs, which included not only the acquisition costs of the study drugs themselves but also the costs of other asthma medications, such as SABAs and oral prednisone. The multivariable models showed that patients receiving ICS + salmeterol incurred both lower pharmacy costs and lower total asthma costs than patients treated with ICS + montelukast. In fact, patients receiving ICS + montelukast incurred over 60% more in pharmacy and total asthma costs than patients receiving ICS + salmeterol. Not only were there meaningful savings in total asthma costs; the use of ICS + salmeterol was associated with an average savings of \$880 per patient per year in total health care costs, this savings being of both statistical and economic significance.

Perhaps most compelling, however, is the decrease in asthma exacerbations (as measured by decreased risk of an asthma-related hospitalization) observed among patients treated with ICS + salmeterol in comparison with patients treated with ICS + montelukast. Pre- to post-index, there was a 61% reduction in the number of patients hospitalized for asthma in the ICS + salmeterol group and no change pre-to-post in the ICS + montelukast cohort. In the multivariable model, the FP + salmeterol group, despite a somewhat higher incidence of hospital and ED use in the pre-index period, also had a significant reduction in these 2 clinical events. These results are consistent with the findings in the RCTs, which also demonstrated lower exacerbations with the addition of salmeterol to ICS than with ICS + montelukast.^{5,7} To assess whether differences in physician management accounted for these reductions in exacerbations,

we also included physician specialty (ie, allergist, pulmonologist, pediatrician or general practice/internist) as a covariate. The results were, in fact, consistent across models, indicating that the differences in the risk of ED/hospitalization observed were independent of the type of physician caring for the patient. Moreover, patients treated with ICS + salmeterol required significantly fewer filled prescriptions for SABAs, a surrogate marker for increased symptom control. Taken together, these findings show that the addition of salmeterol to an ICS not only reduced hospital use (2.5-fold reduction in relative risk) and less reliance on SABAs but also did so at significantly lower incremental costs than the combination of ICS + montelukast.

Our results confirm those reported elsewhere. Two recent single-controller claims studies have demonstrated that FP use, in comparison with the use of either zafirlukast or montelukast, was associated with improved utilization outcomes and lower total costs of asthma care.^{15,16} These observational studies were consistent with the RCT data demonstrating the superiority of FP in comparison with either zafirlukast or montelukast in first-line asthma therapy^{17,18} as well as with the results of earlier studies demonstrating decreased risk of hospitalization and asthma mortality among patients treated with ICS.¹⁹⁻²¹ A dual-controller study in the Foundation Health System found lower pharmacy and total costs in patients receiving FP + salmeterol than in patients receiving ICS + LTM; furthermore, SABA usage was lower.²² The present study is consistent with these analyses in that the addition of salmeterol was a cost-effective treatment option for patients failing to gain control of their asthma on ICS alone.

Studies using retrospective claims analysis have several notable limitations. In general, adequately controlling for such potential confounders as asthma severity is a challenge, because measures of severity are not routinely collected in administrative claims databases. To compensate, surrogate markers of patient severity are used, such as pre-therapy ED visits, hospitalizations, and use of SABAs. This limitation is mitigated in that our results are consistent with the results of numerous RCTs demonstrating greater effect on clinical parameters with the addition of salmeterol. Moreover, retrospective claims studies might have greater generalizability because they include more heterogeneous samples and tend to observe patients over longer periods of time. Thus, consistent results from both RCTs and retrospective claims studies might produce the most robust conclusions because of their complementary areas of strength. Asthma-related utilization and costs were identified through use of ICD-9 codes in the claims. Disease-specific utilization and costs might vary depending on the discretion of the provider or facility. Another limitation of this study is the lack of data on indirect costs, such as absenteeism and out-of-pocket expenditures. Therefore, the costs reported in this article might be substantially underestimated, given that indirect costs constitute a significant portion of total asthma-related health care expenditures.²³

Conclusion

Compared to the use of ICS + montelukast, the use of ICS + salmeterol was associated with a reduced risk of asthma exacerbation and treatment failure, as measured by rescue medication use and asthma-related hospital use. These differences were of greater magnitude when patients receiving FP + salmeterol were specifically compared with patients receiving ICS + montelukast. These improved outcomes were achieved within the context of significant savings in asthma and total health care management costs. The results of this observational study are consistent with the results of existing RCTs that support ICS + salmeterol as the preferred combination treatment for patients not achieving the NIH goals for asthma with monotherapy. When findings from both observational and experimental research methodologies are considered jointly,²⁴ the results are highly conclusive: the combination of ICS + salmeterol offers efficient and clinically superior disease control for asthmatic individuals requiring dual controller therapy in comparison with the combination of ICS + montelukast.

REFERENCES

1. National Asthma Education Program. Expert Panel Report 2. Guidelines for the diagnosis and treatment of asthma. NIH publication 4051. Bethesda (MD): National Institutes of Health; 1997.
2. Centers for Disease Control and Prevention. Forecasted state-specific estimates of self-reported asthma prevalence—United States, 1998. *MMWR Morb Mortal Wkly Rep* 1998;47:1002-25.
3. Asthma in America: executive summary. Glaxo Wellcome; December 1998.
4. Eickelberg O, Roth M, Lox R, Bruce V, Rudiger J, Johnson M, et al. Ligand-independent activation of the glucocorticoid receptor by β_2 -adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. *J Biol Chem* 1999;274:1005-10.
5. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000;320:1368-73.
6. Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients on concomitant inhaled corticosteroid therapy. *Chest* 2000;120:423-30.
7. Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroids plus montelukast. *J Allergy Clin Immunol* 2000;106:1088-95.
8. Raphael GD, Lanier RQ, Baker J, Edwards L, Rickard K, Lincourt WW. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. *J Allergy Clin Immunol* 1999;103:796-803.
9. Condemi JJ, Chervinsky P, Goldstein MF, Ford LB, Berger WE, Ayars GH, et al. Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. *J Allergy Clin Immunol* 1997;100:467-74.
10. Stempel DA, McLaughlin T, Griffis DL, Stanford RH. Cost analysis of the use of inhaled corticosteroids in the treatment of asthma: a 1-year follow-up. *Respir Med* 2001;95:992-8.
11. Greene WH. *Econometric analysis*. 3rd ed. Upper Saddle River (NJ): Prentice-Hall; 1997. p. 552.
12. Belsley DA, Kuy E, Welsch RE. *Regression diagnostics: identifying influential data and sources of collinearity*. New York: John Wiley & Sons; 1981.
13. Duan N. Smearing estimate: a parametric retransformation method. *J Am Stat Assoc* 1983;78:605-10.
14. Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999;103:1075-80.
15. Stempel DA, Meyer JW, Stanford RH, Yancey SW. One-year claims analysis comparing inhaled fluticasone propionate with zafirlukast for the treatment of asthma. *J Allergy Clin Immunol* 2001;107:94-8.
16. Stempel DA, Mauskopf J, McLaughlin T, Yazdani C, Stanford RH. Comparison of asthma costs in patients starting fluticasone propionate compared to patients starting montelukast. *Respir Med* 2001;3:227-34.
17. Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol* 2000;105:1123-9.
18. Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol* 2001;107:461-8.
19. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887-91.
20. Goldman M, Rahmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991-1995: is it related to increased use of inhaled corticosteroids. *J Allergy Clin Immunol* 2000;105:71-4.
21. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
22. O'Connor R, O'Donnell JC, Pinto LA, Wang SW, Wiener DJ, Castillo PA, et al. Two-year retrospective economic evaluation of three dual-controller therapies used in the treatment of asthma. *Chest*. In press.
23. National Institutes of Health: National Heart, Lung and Blood Institute. Data fact sheet, asthma statistics. Available at: <http://www.nhlbi.nih.gov/health/prof/lung/asthma/asthstat.pdf>. Accessed December 3, 2000.
24. Radford MJ, Foody JM. How do observational studies expand the evidence base for therapy? *JAMA* 2001;286:1228-9.