ABSTRACT

The differences between clinical trials and clinical practice often create difficulty for generalizing results of controlled studies to normal clinical use. Observational studies, which assess the effects of medication as they are used outside the confines of a clinical trial, help to bridge the gap between clinical trials and clinical practice. This article reviews the results of observational studies assessing the effects of dual-controller regimens, including a long-acting \( \beta_2 \) agonist and those including a leukotriene modifier, on outcomes in asthma. These observational studies complement the clinical trials data by providing an indication of how the dual-controller regimens perform in typical clinical practice.


Four of 10 patients with asthma suffer moderate persistent or severe persistent symptoms and, according to National Heart, Lung, and Blood Institute (NHLBI) guidelines, are appropriate candidates for dual-controller therapy, or combinations of 2 or more pharmacotherapies with complementary mechanisms of action.\(^1\) The NHLBI guidelines recommend that inhaled corticosteroids, which are potent anti-inflammatory agents, be the cornerstone of dual-controller regimens because of the significance of inflammation in the pathophysiology of asthma. Classes of pharmacotherapy added to inhaled corticosteroids in dual-controller regimens include long-acting \( \beta_2 \) agonists, theophyllines (which are used infrequently), and the leukotriene modifiers, a relatively new class of pharmacotherapy for asthma.

Because of extensive clinical research into the relative merits of the various asthma treatment options, many data are available to assist health care providers in choosing among dual-controller regimens. Much of the evidence from randomized, controlled clinical trials demonstrates that dual-controller regimens composed of a long-acting \( \beta_2 \) agonist and an inhaled corticosteroid are more effective at improving lung function and asthma symptoms than are dual-controller regimens composed of a leukotriene modifier and an inhaled corticosteroid (see the article by Suissa,\(^2\) this issue).\(^3,4\) Clinical trials data, however, do not provide a comprehensive assessment of the effects of pharmacotherapy. By virtue of strict patient selection criteria and procedural controls, clinical trials can infer causality between a manipulation (in this case, administration of a dual-controller regimen) and an effect (changes in asthma symptoms or lung function). However, controlled clinical trials are not always directly applicable to clinical practice. In clinical practice, many more heterogeneous patient populations are treated than are enrolled in clinical trials, and patients are not always treated as consistently or monitored as effectively as they are in clinical trials.

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These differences between clinical trials and clinical practice sometimes render it difficult to generalize results of controlled studies to normal clinical use. Observational studies, which assess the effects of medication as they are used outside the confines of a clinical trial, help to bridge the gap between clinical trials and clinical practice. This article reviews the results of observational studies assessing the effects of dual-controller regimens, including a long-acting β2 agonist and those including a leukotriene modifier, on outcomes in asthma. These observational studies complement the clinical trials data by providing an indication of how the dual-controller regimens perform in typical clinical practice.

Observational Studies on Dual-Controller Regimens

The effects of dual-controller regimens containing a long-acting β2 agonist and those containing a leukotriene modifier have been compared in several observational studies conducted throughout the United States. These studies are reviewed below. In many cases in these studies, baseline differences among groups of patients receiving various treatment combinations were observed. For example, groups may have differed in average age or in prestudy frequency of use of oral corticosteroids. When appropriate, these baseline differences were controlled in statistical analyses of treatment groups through the use of multivariate models.

Study 1

Health care costs and health care utilization were compared in a 2-year, retrospective study among patients who were using various dual-controller regimens for asthma and who were enrolled in 1 of 14 affiliated United HealthCare plans from January 1, 1996, through September 30, 1999. Patients diagnosed with asthma who had received a prescription for the long-acting β2 agonist salmeterol or the leukotriene modifier montelukast and who had filled prescriptions for inhaled corticosteroids during both the year before and the year after receiving a prescription for salmeterol or montelukast were studied. Patients were divided into 3 groups depending on their prescription use during the year after the initial salmeterol or montelukast prescription:

(1) Fluticasone propionate + salmeterol group composed of patients who had filled at least 1 prescription for the inhaled corticosteroid fluticasone propionate and at least 1 prescription for salmeterol (n = 261);
(2) Inhaled corticosteroid + salmeterol group, composed of patients who had filled at least 1 pre-

![Figure 1. Percentage of Patients with at Least 1 Asthma-Related Hospitalization or Emergency Department Visit per Year as a Function of Dual-Controller Regimen](image)

ICS = inhaled corticosteroid; LTM = leukotriene modifier.
Data from references 5 and 6.
scription for an inhaled corticosteroid excluding fluticasone propionate and at least 1 prescription for salmeterol (n = 363); or

(3) Inhaled corticosteroid + montelukast group, composed of patients who had filled at least 1 prescription for an inhaled corticosteroid and at least 1 prescription for montelukast (n = 216).

The results show that in analyses adjusting for differences in baseline characteristics among the 3 groups, asthma-related hospitalizations were significantly less frequent (1.1%) in the group receiving fluticasone propionate + salmeterol compared with the group receiving an inhaled corticosteroid + montelukast (4.6%; Figure 1). A similar, but not statistically significant, pattern of results was observed for emergency department visits during the year after the initial prescription of salmeterol or montelukast (Figure 1).

Total asthma-related costs of health care as well as total asthma-related pharmacy costs (a subset of total health care costs) were significantly lower during the year after the initial prescription of salmeterol or montelukast among patients receiving either fluticasone propionate or another inhaled corticosteroid + salmeterol compared with patients receiving an inhaled corticosteroid + montelukast (Figure 2). Although all groups experienced an increase in pharmacy and total health care costs with the addition of a medication to their inhaled corticosteroid regimen, the increases (when the costs for the year prior to the initial salmeterol or montelukast prescription were compared with those for the year after) were approximately 7 times lower with the combination of fluticasone propionate and salmeterol than they were with the combination of an inhaled corticosteroid and montelukast. In aggregate, these data show that the addition of a long-acting β₂ agonist to an inhaled corticosteroid regimen is associated with lower health care costs and less health care utilization than is the addition of a leukotriene modifier to an inhaled corticosteroid regimen.

**STUDY 2**

A similar pattern of results was obtained in a second 2-phase study. The first phase, conducted in 4 geographically diverse health maintenance organizations covering approximately 4.4 million patients, was a pilot project using claims data from January 1998 through April 1999. The second phase, conducted in 2 health maintenance organizations covering approximately 3.5 million patients, was a more comprehensive, 2-year follow-up using data from January 1996 through December 1999. For both phases, claims data were used to identify patients ages 12 years and older who were treated with the following combinations:

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**Figure 2. Total Asthma-Related Costs and Pharmacy Costs Associated with Dual-Controller Regimens for Asthma**

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ICS=inhaled corticosteroid; LTM = leukotriene modifier.

Data from references 5 and 6.
• Fluticasone propionate + salmeterol (n = 967 Phase I; n = 121 Phase II);
• Inhaled corticosteroid (excluding fluticasone propionate) + salmeterol (n = 2511 Phase I; n = 844 Phase II); or
• Inhaled corticosteroid + leukotriene modifier (n = 826 Phase I; n = 360 Phase II).

The results show that in both phases the combination of fluticasone propionate or another inhaled corticosteroid + salmeterol was associated with significantly lower total asthma-related costs than was the combination of an inhaled corticosteroid and a leukotriene modifier (Figure 3). Similarly, the combination of pharmacy and outpatient costs (components of total asthma-related costs) were significantly lower during both phases in patients receiving fluticasone propionate or another inhaled corticosteroid + salmeterol than in patients receiving the combination of an inhaled corticosteroid and a leukotriene modifier. Emergency department costs and inpatient costs did not differ significantly among the treatment conditions.

**Studies 3 and 4**

In corroboration of these data, results of Study 3, conducted in a large New England insurance company, demonstrate that mean monthly total asthma-related costs were approximately 20% lower among patients receiving the combination of an inhaled corticosteroid + salmeterol (n = 259) compared with those receiving the combination of an inhaled corticosteroid + a leukotriene modifier (n = 106). Mean monthly total asthma-related costs were $101 for the inhaled corticosteroid + salmeterol group compared with $128 for the inhaled corticosteroid + leukotriene modifier group.

Finally, in Study 4, conducted in a large pharmacy benefits management company, the addition of salmeterol to an inhaled corticosteroid regimen was associated with 11% less increase in asthma-related health care costs than was the addition of a leukotriene modifier to an inhaled corticosteroid regimen. Asthma-related health care costs during the 6 months after the addition of salmeterol or a leukotriene antagonist were $684 and $767 per enrollee, respectively.

**Conclusions**

Considered together, the results of these retrospective, observational studies show that dual-controller regimens composed of an inhaled corticosteroid and a long-acting β₂ agonist are associated with lower health care costs and less frequent use of health care resources than are dual-controller regimens composed of an inhaled corticosteroid and a leukotriene modifier. Because of the limitations inherent in observational study designs, these data in themselves are not defini-
tive evidence of the superiority of the inhaled corticosteroid/long-acting $\beta_2$ agonist combination. However, considered in the context of data from randomized, controlled clinical trials enrolling more than 2000 patients with asthma, the results of these observational studies become more compelling. The clinical trials data consistently demonstrate a significant benefit of the inhaled corticosteroid/long-acting $\beta_2$ agonist combination over the leukotriene modifier-containing combination on lung function and asthma symptoms. That the data from the “real-world” setting of these observational studies corroborate the clinical trials data lends practical credence to the clinical trials findings. Evidence from both the controlled clinical trials setting and from clinical practice converges to demonstrate the value of the inhaled corticosteroid/long-acting $\beta_2$ agonist combination.

The reason that the inhaled corticosteroid/long-acting $\beta_2$ agonist combination appears to be more effective in clinical trials and observational studies than do inhaled corticosteroid/leukotriene modifier combinations remains to be elucidated. Possibly, the differential effectiveness results from the divergent mechanisms of action of long-acting $\beta_2$ agonists, which relax respiratory smooth muscle to produce long-lasting bronchodilation to complement the anti-inflammatory effects of corticosteroids, and leukotriene modifiers, which, like corticosteroids, whereas leukotriene modifiers possess more modest anti-inflammatory properties and bronchodilating properties appear not to augment those actions afforded by the inhaled corticosteroids plus long-acting $\beta_2$ agonists combinations.

REFERENCES