Dual-Controller Regimens I: Data From Randomized, Controlled Clinical Trials

MODULE B
Objective

To review the data from randomized, controlled clinical trials of a new dual-controller regimen comprising the inhaled corticosteroid fluticasone propionate and the long-acting $\beta_2$-agonist salmeterol in the treatment of asthma

Dual-controller therapy, or combinations of two or more pharmacotherapies with complementary mechanisms of action, is recommended by the National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines for patients who suffer moderate persistent or severe persistent asthma. In dual-controller therapy, an inhaled corticosteroid is combined with one of several classes of medication including a long-acting $\beta_2$-agonist, a leukotriene modifier, or (less commonly) theophylline. Dual-controller regimens have been extensively researched in randomized, controlled clinical trials and, increasingly, in observational studies.

In choosing among dual-controller regimens, health care providers should consider information from both controlled clinical trials and observational studies because the two sources provide complementary information. Controlled clinical trials, which employ strict patient selection criteria and methodologic controls, allow causal inferences to be made about the effects of a manipulation (in this case, the effects of a dual-controller regimen on clinical status of a patient).

The randomized, controlled clinical trial is best suited to measure the efficacy of a medicine—ie, the ability of the medicine to improve health under carefully controlled conditions—while the observational study is best suited for evaluating the effectiveness of a medicine—ie, the extent to which the medicine improves health in a clinical practice setting. This slide set reviews data from randomized, controlled clinical trials on a new dual-controller therapy (ie, the combination of the inhaled corticosteroid fluticasone propionate and the long-acting $\beta_2$-agonist salmeterol administered in a single delivery system) for asthma. The body of evidence from randomized, controlled clinical trials regarding the efficacy of the dual-controller therapy illustrates the value of systematic, well-controlled evaluation of a medication.

Reference

The effects of the fluticasone propionate-salmeterol combination have been evaluated in a systematic program of randomized, controlled clinical trials involving more than 1200 patients with persistent asthma. These studies, examples of which are described herein, demonstrate the fluticasone propionate-salmeterol combination to be more effective than (1) placebo, (2) either medication administered alone, and (3) other dual-controller regimens.

**Fluticasone Propionate-Salmeterol Combination Versus Fluticasone Propionate Alone, Salmeterol Alone, and Placebo**

Kavuru et al compared the efficacy of fluticasone propionate-salmeterol (100 mcg-50 mcg bid) with that of fluticasone propionate alone (100 mcg bid), salmeterol alone (50 mcg bid), or placebo in a 12-week, randomized, double-blind, parallel-group clinical trial conducted in 356 patients with asthma. Patients were enrolled if they were not adequately controlled on their current asthma therapy, and they were stratified at baseline according to their asthma therapy: 70% of patients were using low-dose inhaled corticosteroids at study entry, and 30% were using salmeterol alone at study entry. The primary end point in this study was pulmonary function as measured by morning predose forced expiratory volume in 1 second (FEV₁).

Reference

The results demonstrate that improvements in pulmonary function as measured by morning predose FEV₁ were significantly greater with the fluticasone propionate-salmeterol combination than with either medication administered alone.¹ At the last study visit, patients receiving the fluticasone propionate-salmeterol combination showed a 25% improvement in morning predose FEV₁ compared with 15%, 5%, and 1% improvements with fluticasone propionate alone, salmeterol alone, and placebo, respectively.

Reference

The percentage of patients withdrawn from the study because of worsening asthma was lower with the fluticasone propionate-salmeterol combination (3%) compared with fluticasone propionate alone (11%), salmeterol alone (35%), or placebo (49%).

A similar pattern of results was observed for secondary measures of efficacy including morning and evening peak expiratory flow rate (PEF), percentage of days with no use of rescue albuterol, percentage of days with no symptoms, and percentage of nights with no awakenings.

Reference
These data were corroborated and extended by the results of a 12-week, randomized, double-blind, parallel-group clinical trial study assessing the effects of a 250-mcg bid dose of fluticasone propionate combined with 50 mcg bid salmeterol compared with fluticasone propionate alone (250 mcg bid), salmeterol alone (50 mcg bid), or placebo among 349 patients with asthma.\(^1\) Patients had mean baseline FEV\(_1\) percentages ranging from 66% to 69% of predicted values and were not optimally controlled on inhaled corticosteroid therapy. The primary end point in this study was pulmonary function as measured by morning predose FEV\(_1\).

Reference

The results show that improvements in pulmonary function as measured by morning predose FEV$_1$ were significantly greater with the fluticasone propionate-salmeterol combination compared with the other treatments. At the last study visit, patients receiving the fluticasone propionate-salmeterol combination showed a 23% improvement in morning predose FEV$_1$ compared with 13%, 4%, and -5% changes in the groups receiving fluticasone propionate alone, salmeterol alone, or placebo.

Reference

The percentage of patients withdrawn from the study because of worsening asthma was lower with the fluticasone propionate-salmeterol combination (4%) compared with fluticasone propionate alone (22%), salmeterol alone (38%), or placebo (62%).

Reference
Study 3

- 12-week, randomized, double-blind, parallel-group study in 447 patients with asthma
- Fluticasone propionate-salmeterol combination 100 mcg/50 mcg bid) better than fluticasone propionate 100 mcg bid and montelukast 10 mg qd
  - Morning PEF (24.9 L/min vs 13.0 L/min)
  - Evening PEF (19 L/min vs 10 L/min)
  - Morning predose FEV₁ (0.34 L vs 0.20 L)


Fluticasone Propionate-Salmeterol Combination Versus Fluticasone Propionate-Montelukast Combination or Montelukast Alone

The fluticasone propionate-salmeterol combination has also been compared with the leukotriene modifier montelukast administered either in combination with fluticasone propionate¹ or alone.² In the first study, a 12-week, randomized, double-blind, parallel-group study conducted in 447 patients with asthma, the combination of fluticasone propionate and salmeterol (100 mcg/50 mcg bid) was significantly more effective than the combination of fluticasone propionate 100 mcg bid and montelukast 10 mg qd at improving, compared with baseline,

- Morning PEF over weeks 1 through 12 (24.9 L/min vs 13.0 L/min; *P*<.05);
- Evening PEF over weeks 1 through 12 (19 L/min vs 10 L/min; *P*<.001); and
- Morning predose FEV₁ (0.34 L vs 0.20 L; *P*<.001).¹

Consistent with these data, results of a randomized, double-blind, 12-week study conducted in 423 patients with asthma demonstrate that combination therapy with fluticasone propionate and salmeterol (100 mcg/50 mcg bid) resulted in significantly greater improvement than administration of montelukast (10 mg qd) alone in several parameters including morning predose FEV₁, morning and evening PEF, and percentages of symptom-free days, rescue medication-free days, and nights with no awakenings.² The authors suggested that using combination therapy to target the two main pathophysiologic components of asthma (ie, inflammation and bronchoconstriction) is more effective for maintenance treatment than is treatment with a single-mediator agent such as montelukast.

References


Several studies have shown that the fluticasone propionate-salmeterol combination is more effective in controlling lung function and asthma symptoms than an inhaled corticosteroid alone administered at a 2-fold higher dose than the fluticasone propionate in the combination.\textsuperscript{1-3} The results of these studies were recently supplemented by findings of a randomized, double-blind, parallel-group study comparing the efficacy of the fluticasone propionate-salmeterol combination (100 mcg/50 mcg) with that of the inhaled corticosteroid budesonide administered at a 4-fold higher dose (ie, 400 mcg) than the fluticasone propionate in the combination.\textsuperscript{4} Patients (N=349) received either the fluticasone propionate-salmeterol combination (100 mcg/50 mcg bid) or budesonide (400 mcg bid) for 12 weeks. At the end of treatment, patients in the combination-therapy group compared with the budesonide group showed significantly greater improvement in both morning PEF (difference of 11 L/min) and evening PEF (difference of 11 L/min). The onset of significant improvement in PEF with the combination vs budesonide was evident beginning within the first 7 days of initiation of therapy. The authors suggested that the ability to control asthma with a 4-fold lower microgram corticosteroid dose with the combination regimen may help to improve safety of asthma treatment by minimizing exposure to the systemic effects of inhaled corticosteroids.

References
Conclusions

- A systematic program of randomized, controlled clinical trials can be used to build an evidence base regarding the efficacy profile of a medication.

- The data show that the fluticasone propionate-salmeterol combination is more effective than placebo, either medicine administered alone, and other combination-therapy and monotherapy regimens in improving lung function and reducing respiratory symptoms in asthma.

- The cross-study consistency of these data and their corroboration by results of observational studies render the findings compelling.

Considered in aggregate, these data exemplify how a systematic program of randomized, controlled clinical trials can be used to build a strong evidence base regarding the efficacy profile of a medication. The data show that the fluticasone propionate-salmeterol combination is more effective than placebo, either medicine administered alone, and other combination-therapy and monotherapy regimens in improving lung function and reducing respiratory symptoms in asthma. The cross-study consistency of the data lends credence to the findings. Considered in the context of data from observational studies showing the “real-world” utility of combination therapy involving fluticasone propionate and salmeterol, the results of these randomized, controlled clinical trials become compelling.