Dual components of optimal asthma therapy: scientific and clinical rationale for the use of long-acting β-agonists with inhaled corticosteroids

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The authors describe the scientific rationale for using an inhaled corticosteroid with an inhaled long-acting β2-agonist. They discuss the clinical trials demonstrating that using an inhaled corticosteroid with an inhaled long-acting β2-agonist provides greater overall asthma control compared with increasing the dose of inhaled corticosteroid. In addition, they review the clinical trials comparing the addition of a leukotriene modifier to an inhaled corticosteroid versus using an inhaled corticosteroid with an inhaled long-acting β2-agonist. Discussion also includes descriptions of trials showing reduced exacerbations of asthma when using an inhaled corticosteroid with an inhaled long-acting β2-agonist. Finally, the authors provide evidence for the ability to detect deteriorating asthma when using an inhaled corticosteroid with an inhaled long-acting β2-agonist, and they provide a comparison of salmeterol and formoterol, two long-acting β2-agonists.

Asthma affects approximately 17 million Americans, and its prevalence and morbidity are increasing.1 Hospitalizations and emergency care visits for asthma, though largely preventable, are on the rise.2 In 1995 alone, asthma was the number one reason for school absences in the United States, with more than 10 million missed school days. In addition, the goals of asthma management as defined by the National Institutes of Health Expert Panel Review in 19973 are not being achieved for many patients.4 Unfortunately, regardless of disease severity, patients have a tendency to underestimate their level of asthma control, and many patients with asthma live with significant symptoms and restrictions. At the present time, optimal asthma control often requires a complex multidrug regimen that is difficult for patients to follow.5 This review will discuss the scientific and clinical rationale for treating the dual components of asthma with an inhaled corticosteroid (ICS) and a long-acting β2-agonist (LABA).

Goals of asthma therapy

The goals of asthma management include symptom control, elimination of nighttime awakenings due to asthma, confidence to be physically active, elimination of the need for emergency care, elimination of absence from work or school, and limited need for quick-relief medication.3 Many patients with asthma suffer needlessly because of suboptimal control of their symptoms. The recent “Asthma in America” survey4 of 2509 patients with asthma and more than 700 healthcare providers revealed the following:

- Forty-one percent of patients with asthma required urgent care for their asthma in the past year.
- Thirty percent of patients with asthma were awakened by breathing problems at least once a week.
- Forty-eight percent of patients with asthma said that they had limitations in their ability to participate in sports or recreational activities because of their asthma.

- Forty-one percent of patients who reported symptoms that met National Institutes of Health (NIH) criteria for moderate persistent asthma, 61% still considered their asthma to be “well controlled” or “completely controlled.”
- Twenty percent of patients who reported symptoms that met NIH criteria for severe persistent asthma, 32% still considered their asthma to be “well controlled” or “completely controlled.”

For optimal management, patients with persistent asthma require daily controller therapy.3 According to the NIH guidelines, ICSs are the most effective anti-inflammatory medications available.3 Inhaled corticosteroids have been shown to reduce symptoms, reduce risk of hospitalizations for asthma, reduce deaths from asthma, improve lung function, and improve or prevent several of the
Inhaled corticosteroids have been shown to be the most effective anti-inflammatory medications currently available for long-term control of persistent asthma. Several ICSs are currently available to treat the acute and chronic inflammation of asthma, including fluticasone propionate (FP), beclomethasone dipropionate, triamcinolone, flunisolide, and budesonide.

Interdependence of bronchoconstriction and inflammation

The response of the airways to inhaled allergens illustrates the independence of the two components of asthma. For example, the early-phase response after exposure to an allergen can be completely prevented by treatment with a β2-agonist, but this class of drug has no effect on the late-phase response of asthma. Conversely, a single dose of an ICS has no effect on the early-phase response to an inhaled allergen, but it does prevent the late-phase response. However, the interdependence of inflammation and effects on airway smooth muscles can be just as important. Airway inflammation and the release of inflammatory mediators by inflammatory cells can significantly contribute to bronchial hyperresponsiveness, and thus to bronchoconstriction. Likewise, airway smooth muscle has been shown to release inflammatory mediators, which contribute to inflammation in the airways.

Dual-component pharmacology

Healthcare providers are faced with many challenges in helping their patients obtain optimal asthma control. Confidence in the ability of a patient to follow a given treatment regimen is of paramount importance to the healthcare provider. Because both bronchoconstriction and inflammation play a role in the pathogenesis of asthma, treatment regimens that address both components would provide the most efficacious treatment for patients with persistent asthma. Concurrent treatment with both an inhaled LABA and an ICS is recommended in treatment guidelines.
for those patients with persistent asthma whose asthma is not controlled with a single controller medication. However, dosing with both an inhaled LABA and an ICS has necessitated the use of two separate inhalers and is cumbersome for many patients. When prescribing asthma medications, dosing frequency, complexity of the drug regimen, ability of the patient to use the inhaler correctly, and potential medication side effects must be considered. To address the need for a more convenient dosage form and, it is hoped, one that would enhance patient compliance, combination products have recently been developed. The combination of salmeterol (SAL), a LABA, and FP, an ICS, in one inhaler has been recently approved in the United States for the treatment of asthma. The combination of budesonide and formoterol is available in some countries, but not in the United States.

As noted previously, ICSs have a broad range of anti-inflammatory activities in asthma. However, they also have effects that complement those of inhaled LABAs. For example, corticosteroids may reduce or prevent bronchial hyperresponsiveness, and therefore bronchoconstriction, by inhibiting the release of cytokines and other inflammatory mediators from inflammatory cells. In addition, corticosteroids may allow β2-agonists to be more effective by increasing the number of available β2-receptors and their sensitivity to β2-agonists.

A growing body of in vitro evidence suggests that in addition to their primary bronchodilatory effects, inhaled LABAs may also enhance the effects of ICSs. Specifically, β2-agonists may prime inactive glucocorticoid receptors for activation by a ligand-independent pathway. Primed receptors would be more easily activated by corticosteroids (Figure 1 depicts the proposed mechanism). This priming effect of LABAs could explain why using a lower dose of an ICS with an inhaled LABA is more effective than a much higher dose of an inhaled corticosteroid alone, as seen in multiple, randomized, double-blinded studies that are reviewed in the following text.

The effects of dual-component therapy with an inhaled LABA and an ICS on mediators of airway inflammation in vivo have recently been evaluated. Two recent studies used bronchial biopsies to investigate the complementary effects of ICSs and LABAs on the control of airway inflammation. Li and associates assessed the effect of SAL when used with a low dose of an ICS on airway inflammation in patients with symptomatic asthma enrolled in a randomized, double-blind, parallel-group, placebo-controlled trial. Subjects were already receiving an ICS and had either SAL, 50 μg twice daily (n = 13); FP, 100 μg twice daily (n = 16); or placebo twice daily (n = 16) added to their current ICS therapy for 12 weeks. Paired bronchial biopsies were evaluable in 40 of the patients. The biopsies demonstrated that airway inflammation was at least as effec-
tively controlled when SAL was used with low-dose ICSs compared with higher doses of ICSs alone. Greater reductions in symptom scores and daily rescue use of albuterol were noted when SAL was used with ICSs compared with increasing the dose of ICS dose alone (P < .05).

A study by Sue-Chu and colleagues31 provides further support for the complementary effects of ICS and LABAs on controlling airway inflammation in patients with asthma. Fifty-six patients who were symptomatic despite ICS therapy were assigned at random to receive FP, 200 μg twice daily (n = 19); FP, 500 μg twice daily (n = 19); or FP, 200 μg twice daily with SAL, 50 μg twice daily (n = 18) for 12 weeks. Bronchial biopsies and methacholine challenges were done at baseline and after 12 weeks of treatment. In this study, the numbers of eosinophils were low in all groups at baseline and did not change significantly with treatment. However, the numbers of mast cells were reduced with FP, 200 μg, plus SAL, 50 μg, but not with FP alone at either the 200-μg or 500-μg dosages. Likewise, using SAL, 50 μg, with FP, 200 μg, was accompanied by decreases in CD3-, CD4-, and CD25-positive lymphocytes that were similar to or greater than those seen with higher doses of FP alone.31

Finally, Kips and coworkers32 evaluated the effects of adding formoterol to low doses of budesonide compared with higher doses of budesonide alone on inflammatory markers (eosinophils and eosinophil cationic protein) in induced sputum. In this year-long study, patients received budesonide, 100 μg, with formoterol, 12 μg given twice daily (n = 29), or budesonide, 400 μg twice daily alone (n = 31). The regimen of low-dose budesonide with formoterol controlled airway inflammation (as assessed by sputum eosinophil numbers) as well as a fourfold higher dose of budesonide.32

Clinical rationale for using an inhaled corticosteroid with an inhaled long-acting β2-agonist

Use of an ICS with an inhaled LABA compared with ICS or inhaled LABA alone—Using an ICS with an inhaled LABA results in superior efficacy compared with using an ICS or inhaled LABA alone. Two studies in the literature have outlined these results.

In a multicenter, randomized, placebo-controlled, double-blind, 12-week study in 356 patients 12 years of age and older, Kavuru and associates33 compared combination therapy with FP (100 μg) and SAL (50 μg) given twice daily with the same dose of FP (100 μg) and the same dose of SAL (50 μg) given alone twice daily.33 A placebo arm was also included, and all treatments were administered through the Diskus (breath-activated multidose dry powder inhalation) device. At baseline, patients were symptomatic and had a mean forced expiratory volume in 1 second (FEV1) of 64% predicted. Primary endpoints were morning predose FEV1, FEV1 area under the curve, and withdrawals resulting from worsening asthma. Patients who were treated with the combination of FP and SAL had significantly greater protection from worsening asthma, greater improvements in predose FEV1 at endpoint, and greater improvements in asthma symptom scores, percentage of days with no asthma symptoms, and rescue use of albuterol compared with patients receiving either FP or SAL alone at the same doses. Significant reductions in asthma symptoms, use of albuterol as rescue medication, and improvements of morning and evening peak expiratory flow rate (PEF) occurred within the first day of treatment with the FP-and-SAL combination.34 The FP-and-SAL combination was well tolerated, and adverse events observed with the FP-and-SAL combination were comparable to those observed with the individual agents given alone.34

In their multicenter, randomized, placebo-controlled, double-blind, 12-week study in 349 patients 12 years of age and older, Shapiro and colleagues35 compared a combination of FP (250 μg) and SAL (50 μg) given twice daily with the same dose of FP (250 μg) and the same dose of SAL (50 μg) given alone twice daily.35 A placebo arm was also included, and all treatments were administered via the breath-activated dry powder inhaler. At baseline, patients were symptomatic on ICS therapy and had FEV1 of 66% to 69% predicted. Primary endpoints were the same as those in the Kavuru and associates33 study, and the results were also similar in that with therapy combining FP (250 μg) with SAL (50 μg), patients had greater improvements in all measures of efficacy than patients treated with FP or SAL alone. No diminution of the 12-hour bronchodilator effect of SAL was seen after the 12 weeks of therapy as demonstrated by serial 12-hour FEV1 measurements. A diverse events observed with the FP-and-SAL combination were pharmacologically predictable and did not increase in severity or frequency as compared with the agents when given alone at the same doses. Morning cortisol and ACTH stimulation tests were also assessed in a subset of patients and showed no difference between the group given combination therapy with FP (250 μg) and SAL (50 μg) or placebo.35

Fluticasone-and-salmeterol combination therapy compared with fluticasone and salmeterol given concurrently in separate dry powder inhalation devices—Several studies have demonstrated comparability of the FP-and-SAL combination therapy to concurrent administration of FP and SAL at the same doses via separate inhalers.

Bateman (combination of FP [100 μg] and SAL [50 μg]),36 Chapman (combination of FP [250 μg] and SAL [50 μg]),37 and Aubier (combination of FP [500 μg] and SAL [50 μg])38 and their respective coworkers evaluated the safety and efficacy of FP and SAL given concurrently via separate dry powder inhalation devices with the same doses of FP and SAL given as the FP-and-SAL combination product. When differences were seen between the groups receiving combination and those receiving concurrent therapy, the differences favored the FP-and-SAL combination. However, the differences were small and not statistically significant.

Use of an ICS with an inhaled LABA versus higher doses of ICS—Using an ICS with an inhaled LABA results in superior efficacy compared with doubling the dose of ICSs. Numerous clinical trials (Table)39-45 have shown superior results in morning and evening peak expiratory flow (PEF), FEV1, symptom scores, need
for rescue albuterol, and other parameters when using an ICS with an inhaled LABA versus a higher dose of ICS alone. Details of several of these studies follow.

- In their multicenter, double-blind study, Condenzi and associates evaluated 437 patients aged 12 years and older who were symptomatic despite receiving low-dose FP therapy (88 μg twice daily) for 2 to 4 weeks. Patients were randomly assigned to receive the same FP dose plus SAL (42 μg twice daily) or have their FP dosage increased (220 μg twice daily). Patients were treated for 6 months. The group using SAL with low-dose FP had significantly greater improvement in lung function (morning PEF) and symptom control compared with the group receiving the higher dose of FP alone (P < .001). These results are consistent with the dual-component disease hypothesis of asthma, and show that to achieve optimal control, both inflammation and bronchoconstriction should be treated.

- Murray and colleagues, in a randomized, double-blind, parallel-group, multicenter study, evaluated 514 adults with persistent asthma who were symptomatic despite therapy with beclomethasone dipropionate (BDP). The patients were randomly assigned to use BDP (168 μg twice daily) with the addition of SAL (42 μg twice daily), or to increase their dosage of BDP (336 μg twice daily). The group using SAL with low-dose BDP had greater improvements in lung function (FEV₁ and morning PEF) and patient-rated symptom scores, as well as greater reductions in daytime albuterol use and greater increases in rescue-free days than did the group receiving double the dose of BDP (P < .05).

### Table

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<th>Comparator and reference</th>
<th>No. of patients</th>
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<th>Symptoms</th>
<th>Rescue use of albuterol</th>
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<td>12</td>
<td>Increased</td>
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- Use of an ICS with an inhaled LABA versus an ICS with a leukotriene modifier—Adding a leukotriene modifier to ICS versus using SAL with an ICS has been evaluated in several randomized clinical trials. These trials have demonstrated greater efficacy of using SAL with an ICS compared with either zafirlukast or montelukast as add-on therapy to ICSs in patients with persistent asthma.

- In a 16-week, randomized, double-blind, double-dummy, parallel-group, multicenter trial, Laviolette and coworkers evaluated 642 patients aged 15 years and older who had persistent asthma, 80% of whom were receiving stable doses of ICSs at entry into the study. Patients were randomly assigned to receive zafirlukast (20 mg twice daily [n = 145]) or SAL (42 μg twice daily [n = 144]) in addition to their baseline asthma therapy for 4 weeks. Improvement in morning PEF more than doubled in patients using SAL (29.6 L/min) when compared with patients receiving zafirlukast (13.0 L/min; P = .001). Patients receiving SAL also had greater improvements in all patient-rated symptom scores (P < .001), a greater number of days with no supplemental...
use of albuterol (P < .001), and a greater number of symptom-free days (P < .001) compared with patients receiving zafirlukast.

Nelson and associates\(^5\) conducted a 12-week multicenter, double-blind, double-dummy, parallel-group study in 447 patients who were symptomatic at the end of a 3-week run-in while receiving low-dose FP (100 \(\mu\)g twice daily via the dry powder inhalation device). Patients were then randomly assigned to receive combined therapy with FP (100 \(\mu\)g) and SAL (50 \(\mu\)g) twice daily or FP (100 \(\mu\)g twice daily) plus montelukast (10 mg daily). Patients treated with the combined FP and SAL had greater overall asthma control with significantly greater improvements in morning and evening PEF (\(P < .001\)), FEV\(_1\) (\(P < .001\)), rescue-free days (\(P = .032\)), and shortness of breath symptom scores (\(P = .017\)) compared with patients receiving FP plus montelukast. Of note, there were significantly fewer exacerbations of asthma in the group receiving the FP-and-SAL combination (2%) as compared with the group receiving the FP plus montelukast (6%, \(P = .031\)).

Overall asthma control with reductions in exacerbations—Studies have shown that using an ICS with an inhaled LABA reduces exacerbation rates without altering the ability to detect deteriorating asthma.

Inhaled corticosteroid plus SAL—Matz and colleagues\(^5\) conducted an analysis of data from the 104 patients who had exacerbations of asthma in two replicate multicenter, randomized, double-blind studies comparing SAL (42 \(\mu\)g) with FP (88 \(\mu\)g) versus higher-dose FP (220 \(\mu\)g) alone. Individually, the replicate studies were not powered to show differences in exacerbations of asthma between the two treatment groups. In their analysis, Matz and colleagues\(^5\) demonstrated that SAL combined with a low-dose of FP resulted in a lower rate and number of exacerbations compared with higher-dose FP alone. Exacerbations in the group receiving SAL totaled 47, as compared with 75 in the group receiving higher-dose FP (\(P = .017\)). Also, SAL had a greater protective effect in preventing exacerbations of asthma than a higher dose of FP as measured by time to first exacerbation. Matz and colleagues also found that the addition of SAL did not alter the ability to detect clinical or physiologic markers of deteriorating asthma. Indicators of worsening asthma were measured before and after exacerbations and included morning PEF, rescue use of albuterol, and symptom scores. The two treatment groups had similar changes in all these indicators during the 14 days preceding an exacerbation. However, after the exacerbation, greater improvements were observed with SAL compared with higher-dose FP. The morning PEF increased more rapidly in the patients on SAL compared with those on higher-dose FP. In addition, changes in rescue use of albuterol and symptom scores appeared to resolve more rapidly in the group receiving SAL plus low-dose FP, suggesting that the severity of exacerbations may also have been reduced in these patients.\(^5\)

Shrewsbury and colleagues\(^1\) systematically reviewed nine randomized, double-blind trials that compared SAL with a lower dose of ICSs versus increasing the ICS dose. Combining these trials, which individually were not powered to evaluate exacerbations of asthma, created a database of 3685 adult and adolescent patients for analysis. Fewer patients experienced any exacerbation of asthma when SAL was used with a low dose of an ICS compared with higher doses of an ICS alone (\(P = .02\)). Also, the percentage of patients who had moderate or severe exacerbations was also decreased with SAL therapy compared with increased-dose ICSs (\(P = .03\)).\(^1\)

Inhaled corticosteroid plus formoterol

In a year-long, multinational, double-blind, randomized, parallel-group study, Pauwels and associates\(^5\) evaluated the frequency of exacerbations in 852 patients on low (200 \(\mu\)g/d) and high (800 \(\mu\)g/d) doses of budesonide alone, or the same doses of budesonide with formoterol (12 \(\mu\)g twice). The addition of formoterol reduced the incidence of mild and severe exacerbations at both doses of budesonide, with the group treated with higher-dose budesonide plus formoterol having the greatest reduction.\(^5\)

Tattersfield and colleagues\(^3\) reviewed the 425 severe exacerbations from the study of Pauwels and associates\(^5\) to evaluate the clinical and physiologic markers of deteriorating asthma. Changes in asthma symptom scores as well as morning and evening PEF were used to detect deteriorating asthma control. The patients treated with formoterol plus a low dose of budesonide had similar changes in these parameters compared with the patients treated with a high dose of budesonide alone, suggesting that similarly to SAL, formoterol can enhance asthma control and reduce the dose of inhaled steroid necessary to control symptoms and inflammation.\(^3\)

Comments

Use of an ICS with an inhaled LABA provides optimal control for many patients with persistent asthma. Use of ICSs with inhaled LABAs has been shown to effectively treat the two major components of asthma, inflammation and bronchoconstriction. Exhaustive clinical research involving large numbers of patients has shown the clinical benefits of this dual-component approach as measured by lung function, daytime and nighttime symptoms, and rescue use of albuterol. Therapy with an inhaled LABA and an ICS has also been demonstrated to be more effective than higher doses of an ICS alone or the addition of a leukotriene modifier to an ICS. Use of inhaled LABAs in patients whose asthma symptoms are not adequately controlled on ICS therapy has been shown to be effective in reducing the incidence of exacerbations of asthma without altering the ability to detect deteriorating asthma.

The combination products of FP plus SAL and formoterol plus budesonide offer a new solution for patients with asthma and are simple to use for both patients and healthcare professionals.\(^4\) The combination helps to protect patients from the development of worsening asthma while providing greater improvement in lung function and asthma symptoms than the inhaled steroid alone at the same doses. The early, noticeable
benefit of the long-acting bronchodila-
tor component, the convenience of twice-
daily dosing, and the simplicity of a com-
bined inhalation device may make it easier for patients to adhere to therapy.

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