Combination Therapy with Inhaled Long-Acting β_2-Agonists and Inhaled Corticosteroids: A Paradigm Shift in Asthma Management

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Long-acting inhaled β_2-agonists and inhaled corticosteroids are classes of drugs with different mechanisms of action that are commonly used to provide effective long-term control of persistent asthma. Scientific and clinical data support the complementary mechanisms of action of the inhaled corticosteroids and the long-acting β_2-agonists in achieving a superior level of asthma control. In addition, evidence supports significant reductions in exacerbations and effective control of airway inflammation with an inhaled corticosteroid and a long-acting β_2-agonist versus higher dosages of inhaled corticosteroids or combinations of other therapeutic agents with an inhaled corticosteroid. Finally, there are distinct economic advantages to combining an inhaled corticosteroid and a long-acting β_2-agonist in the treatment of asthma relative to other treatment regimens.
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OUTLINE

Asthma, a chronic airway disease, affects approximately 17.3 million people in the United States.[1] It is associated with significant morbidity and mortality. Approximately 5000 deaths are attributed to asthma each year.[2] Asthma accounts for an estimated total health care cost of $11 billion each year and an annual loss of more than 3 million work days and 10 million school days.[3–5]

Adult-onset asthma frequently is encountered in primary care and has been reported to occur in over 10%, and potentially as high as 17%, of the primary care patient population.[6] However, asthma generally is underdiagnosed in the primary care setting.[7] Underdiagnosis of asthma by general practitioners may be a result of physicians' lack of awareness of the morbidity experienced by these patients.[8] Given the morbidity and mortality associated with asthma and its prevalence in the primary care community, clinicians must prescribe therapy that is effective and directed to the major pathophysiologic alterations associated with this disease.

Asthma is a disease of two components: inflammation and bronchoconstriction (Figure 1). It is a complex disease involving many airway cells and mediators. To our knowledge, no single treatment regimen exists to effectively treat both the underlying inflammation and the

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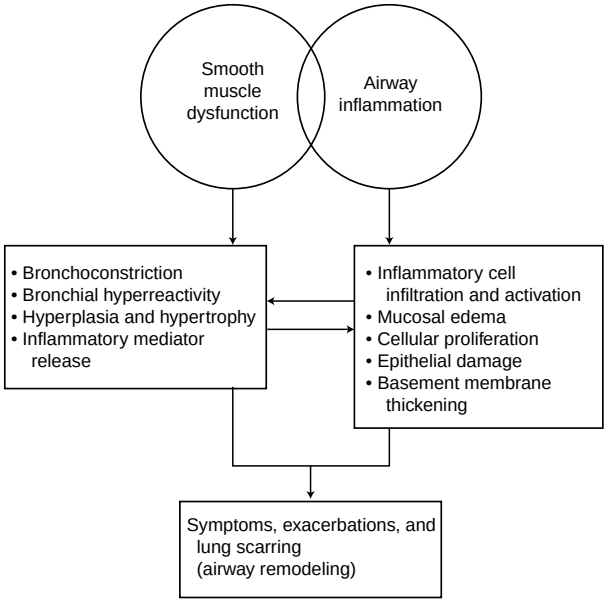
asthma has focused on treating both components of the disease individually. Consequently, the drugs administered most frequently to treat asthma are those that promote bronchodilatation and those that reduce inflammation.

As the complexity of a drug regimen increases, poor adherence to a treatment plan is likely to occur.[9, 10] The impact of poor adherence to treatment is poor control of the underlying inflammation and bronchoconstriction, which, on a long-term basis, could contribute to the development of severe asthma exacerbations and possibly to irreversible damage to the lungs—a process known as airway remodeling.[11–19] Even widespread educational programs and promotion of national treatment guidelines have not overcome problems associated with suboptimal adherence to treatment regimens, which often include more than one controller agent.[20–22] Clearly, new approaches to the long-term treatment of asthma are needed.

Scientific Rationale

Inhaled corticosteroids are more potent and effective in controlling airway inflammation than any of the other available long-term controllers (e.g., nedocromil, cromolyn, leukotriene modifiers).[23–28] Similarly, the long-acting β_2-agonist bronchodilators have been shown to improve pulmonary function and reverse bronchoconstriction better than the short-acting β_2-agonists (e.g., albuterol), theophylline, and the leukotriene modifiers.[29–34] Both the inhaled corticosteroids and the long-acting β_2-agonists are quite effective in the treatment of persistent asthma; however, these two classes of drugs have different mechanisms of action.

Corticosteroids prevent the formation of both prostaglandins (cyclooxgenase pathway) and leukotrienes (5-lipoxygenase pathway) from arachadonic acid. Inhaled corticosteroids also inhibit multiple airway inflammatory cells that may be involved in the asthma response.[35] Corticosteroids modulate the action of numerous inter- and intracellular mediators and influence the transcription of target genes that regulate the production of cytokines, receptors, and enzymes. The long-acting β_2-agonists bind to the β_2-adrenoceptor, thereby stimulating the production of cyclic adenosine 3′,5′-monophosphate and



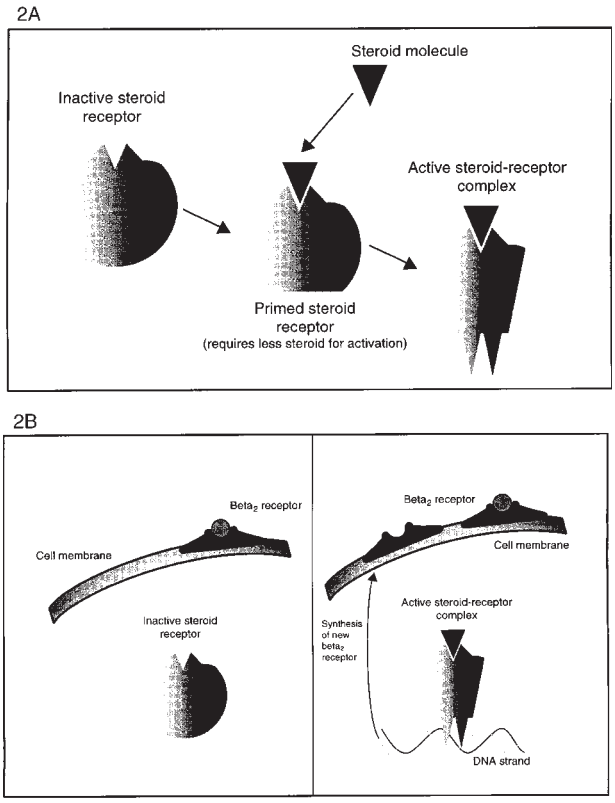


Figure 2. In vitro evidence suggests that β_2-agonists may prime inactive corticosteroid receptors (2A) and that corticosteroids may increase the number of β_2-receptors and their sensitivity to β_2-agonists (2B). Primed receptors are activated more easily by corticosteroids, and less steroid is required to convert the primed receptor to an active receptor. This priming effect could explain why a lower dosage of an inhaled corticosteroid plus a long-acting β_2-agonist is more effective than a higher dosage of an inhaled

causing relaxation of bronchial smooth muscle and inhibition of the release of proinflammatory mediators (in vitro) from mast cells.[36]

When used concurrently, these two classes of drugs have complementary effects on each other (Figure 2).[37–43] Inhaled corticosteroids have been shown to upregulate β_2-receptor expression. In human lung, corticosteroids increased β_2-adrenergic receptor transcription.[38] Corticosteroids also induce β_2-receptor messenger RNA transcription and improve β_2-receptor function in human airway epithelial and glandular cells (in vivo and in vitro).[40] Likewise, long-acting β_2-agonists enhance the effects of corticosteroids, a process that may occur through priming of the glucocorticoid receptor for activation.[41] In support of this concept, the long-acting β_2-agonist, salmeterol, enhances steroid-induced inhibition of cell proliferation and inflammatory mediator release, and it enhances steroid-induced eosinophil apoptosis.[39, 42] Recently, the authors of one study[43] reported a synergistic increase in the inhibitory effects of inhaled corticosteroids on tumor necrosis factor-α–stimulated interleukin-8 release by salmeterol in cultured human airway smooth muscle cells.

The exact role that these complementary actions play in producing the clinical benefits associated with the use of both an inhaled corticosteroid and a long-acting β_2-agonist in patients with asthma is not completely defined. However, these data do suggest that, besides their different mechanisms of action in asthma, inhaled corticosteroids may confer benefits to the effectiveness of long-acting β_2-agonists and vice versa.[36]

Clinical Rationale

Control of Inflammation

Effect on Exacerbations

Exacerbations are regarded as a practical marker for overall disease control and control of the underlying pathophysiology of asthma. Thus, exacerbation rates are an excellent indicator of whether or not a drug regimen is effective. Some investigators have suggested that long-term treatment with long-acting β_2-agonists might result in tolerance or mask an increase in airway inflammation, thus leading to an increase in exacerbations or more severe exacerbations.[44]

The results of several studies indicate that the addition of a long-acting β_2-agonist to an inhaled

not increase the frequency of exacerbations.[45–49] By contrast, the combination of these two classes of drugs more effectively reduces asthma exacerbations than do higher doses of an inhaled corticosteroid alone.[45–49] Table 1 summarizes the details of these studies, as well as the studies described in the following sections.

One group of authors[45] performed a meta-analysis on nine studies that evaluated the efficacy of adding salmeterol versus doubling the dose of inhaled corticosteroid in patients aged 12 years or older who were symptomatic while receiving an inhaled corticosteroid at a minimum dosage of 200 µg/day. The total number of exacerbations and the number of moderate and severe exacerbations were reduced significantly by adding salmeterol to a low dosage of an inhaled corticosteroid (as defined by the National Heart, Lung, and Blood Institute guidelines[12]) compared with a higher dosage of an inhaled corticosteroid alone (Figure 3).

The Formoterol and Corticosteroids Establishing Therapy (FACET) study examined the effect of adding the long-acting β_2-agonist formoterol 12 µg twice/day to either low-dosage (200 µg/day) or high-dosage (800 µg/day) budesonide in 852 patients with asthma who were previously symptomatic but had been stabilized over 4 weeks while receiving budesonide 1600 µg/day.[46] After 1 year of treatment, the rate of severe exacerbations was reduced by 63% with the combination of formoterol and the higher dosage of budesonide, by 49% with the higher dosage of budesonide alone, and by 26% with formoterol and the lower dosage of budesonide. At both the low and high dosages of budesonide, adding formoterol resulted in greater reductions in severe and mild exacerbations compared with those of inhaled corticosteroid alone.

To evaluate whether or not treatment with a long-acting β_2-agonist might mask the symptoms of an impending exacerbation, another group of authors[49] analyzed the changes in peak expiratory flow (PEF) and asthma symptoms during the 2 weeks before and after the 425 severe exacerbations that occurred during the FACET study. The exacerbations that occurred in patients taking formoterol did not differ in severity or in response to treatment compared with exacerbations in patients not taking formoterol (i.e., no statistical significance). There was no difference in the ability of patients to recognize deteriorating asthma, regardless of

Table 1. Studies Describing Treatment with a Long-Acting β_2-Agonist and an Inhaled Corticosteroid

Study Design	Previous Treatment	Age Range (yrs)	Drug Regimen (no. of pts)	Treatment Duration	Results
Add long-acting β_2-agonists vs leukotriene modifiers					
R, DB, PG[32]	ICS in 80% of patients	12–73	SL 42 µg MDI (144) ZL 20 mg b.i.d. (145)	4 wks	SL > ZL, p≤0.001; AM PEF: 29.6 vs 13.0 L/min; symptom-free days: 22.4% vs 8.8%; FEV_1: NS
R, DB, PG[33]	ICS	15–83	SL 50 µg powder b.i.d. (476) ML 10 mg q.d. (472)	12 wks	SL > ML, p<0.001; AM PEF: 35.0 vs 21.7 L/min; symptom-free days: 24% vs 16%; FEV_1: NS
R, DB, PG[34]	ICS	15–83	FP 100 µg + SL 50 µg powder b.i.d. (222) FP 100 µg + ML 10 mg q.d. (225)	12 wks	FP + SL > FP + ML, p≤0.032; AM PEF: 24.9 vs 13.0 L/min; FEV_1: 0.34 vs 0.20 L; % days without albuterol: 26.3% vs 19.1%
Retrospective analysis of 2 R, DB, PG studies[69]	ICS	≥ 12	SL 42 µg b.i.d. ZL 20 mg b.i.d. (429 total)	4 wks	ICS + SL > ICS + ZL, p<0.001; AM PEF: 28.8 vs 13.0 L/min; symptom-free days: 20% vs 9%; FEV_1: NS
Add salmeterol vs ↑ dosage inhaled corticosteroids					
Meta-analysis of 9 R, DB, PG trials[45]	ICS 200–1600 µg/day	≥ 12	↑ dosage of ICS 400–2000 µg/day SL 42 or 50 µg b.i.d. (3685 total)	12–26 wks	SL > ↑ dosage of ICS, p≤0.02; AM PEF difference: 27.7 L/min; FEV_1 difference: 0.08 L; % symptom-free days: 15%; exacerbation difference: 2.73%
R, DB, PG[46]	ICS	18–70	BD 100 µg b.i.d. (213) BD 100 µg + FM 12 µg b.i.d. (210) BD 400 µg b.i.d. (214) BD 400 µg + FM 12 µg b.i.d. (215)	12 mo	BD + FM > higher-dosage BD, p≤0.01; ↓ severe exacerbation: 63% vs 49%; daytime symptom score: 0.33 vs 0.53
Retrospective analysis of 425 severe exacerbations[49]	ICS	18–70	BD 100 µg b.i.d. (213) BD 100 µg + FM 12 µg b.i.d. (210) BD 400 µg b.i.d. (214) BD 400 µg + FM 12 µg b.i.d. (215)	12 mo	Pattern of change in PEF, symptoms, and rescue drugs were similar in all groups, indicating no negative effect of formoterol on severity and duration of exacerbations
Combined vs individual agents					
R, DB, PG[47]	ICS	12–69	SL 50 µg + FP 250 µg combination powder b.i.d. (84) SL 50 µg b.i.d. (88) FP 250 µg b.i.d. (84) Placebo (93)	12 wks	Combination > SL, FP, or placebo, p≤0.036; change in FEV_1: 0.48 L vs 0.05, 0.25, -0.11 L; change in AM PEF: 53.5 L/min vs -11.6, 15.2, -14 L/min; % symptom-free days: 33.8% vs 2.1%, 15.4%, -7.9%
R, DB, PG[48]	ICS or SL only	12–70	SL 50 µg + FP 100 µg combination powder b.i.d. (92) SL 50 µg b.i.d. (92) FP 100 µg b.i.d. (90) Placebo (82)	12 wks	Combination > SL, FP, or placebo, p≤0.025; change in FEV_1: 0.51 L vs 0.11, 0.28, 0.01 L; change in AM PEF: 52.5 L/min vs -1.7, 17.3, -23.7 L/min; % symptom-free days: 22.6% vs 8.0%, 7.2%, -3.8%

Table 1. Studies Describing Treatment with a Long-Acting β_2-Agonist and an Inhaled Corticosteroid (continued)

Study Design	Previous Treatment	Age Range (yrs)	Drug Regimen (no. of pts)	Treatment Duration	Results
Effect of salmeterol on inflammation					
R, DB, PG, biopsy[50]	ICS	42 (mean)	FP 200 µg b.i.d. (19) FP 500 µg b.i.d. (19) FP 200 µg + SL 50 µg b.i.d. (18)	12 wks	FP + SL caused a ↓ in submucosal mast cells vs FP 200 µg ($p<0.05$); no worsening of airway inflammation with addition of SL
R, DB, PG, biopsy, bronchoalveolar lavage[51]	ICS	20–70	SL 50 µg powder b.i.d. (13) FP 100 µg powder b.i.d. (16) Placebo (16)	12 wks	No deterioration in airway inflammation; ↓ in EGI-positive (activated) eosinophils from 18.3 to 7.6 cells/mm with SL + ICS ($p=0.01$)
Concurrent vs individual and higher-dosage inhaled corticosteroids					
R, DB, PG[70]	Short-acting β-agonists only	12–61	SL 42 µg + FP 88 µg b.i.d. (25) SL 42 µg + FP 220 µg b.i.d. (21) FP 220 µg b.i.d. (23) FP 88 µg b.i.d. (23) SL 42 µg b.i.d. (21) Placebo (23)	4 wks	FP + SL > FP, SL, or placebo, $p<0.05$; change in FEV_1: 0.73 and 0.59 L vs 0.30, 0.27, 0.29, 0.09 L; change in AM PEF: 32 and 57 L/min vs 25, 10, 41, -1.0 L/min; % symptom-free days: FP + SL > FP and placebo groups only
Add salmeterol vs ↑ dosage budesonide, triamcinolone acetonide, or fluticasone propionate					
R, DB, PG[71]	ICS	36 (mean)	SL 50 µg + FP 100 µg b.i.d. (176) BD 400 µg b.i.d. (173)	12 wks	FP + SL > BD, $p\leq0.022$; AM PEF: 426 vs 415 L/min; PM PEF: 435 vs 424 L/min; asthma symptoms: NS
R, DB, PG[72]	ICS	14–80	SL 50 µg + FP 250 µg b.i.d. (180) BD 800 µg b.i.d. (173)	24 wks	FP + SL > BD, $p<0.05$; FEV_1: 2.53 vs 2.44 L; AM PEF: 406 vs 380 L/min; % symptom-free days increase: 60% vs 34%
R, DB, PG[73]	ICS	12–79	FP 88 µg + SL 42 µg b.i.d. FP 220 µg b.i.d. TAA 600 µg b.i.d. (680 total)	12 wks	FP + SL > FP and TAA, $p<0.05$; change in FEV_1: 0.58 L vs 0.48 and 0.34 L; change in AM PEF: 58 L/min vs 47 and 18 L/min ($p<0.05$ for TAA only); % symptom-free days: 29.2% vs 22.6% and 11.9%($p<0.05$ for TAA only)
Combined vs concurrent therapy					
R, DB, PG[74]	ICS	12–79	SL 50 µg + FP 500 µg combination powder b.i.d. (167) SL 50 µg + FP 500 µg concurrent inhalers b.i.d. (171) FP 500 µg b.i.d. (165)	28 wks	Clinical equivalence with combination and concurrent treatment; increase in AM PEF: 12% and 10%; combination > FP, $p<0.001$; change in AM PEF: 29 vs 9 L/min
R, DB, PG[75]	ICS	13–75	SL 50 µg + FP 250 µg combination powder b.i.d. (180) SL 50 µg + FP 250 µg concurrent powder inhalers b.i.d. (191)	28 wks	Clinical equivalence with combination and concurrent treatment; AM PEF: 43 and 36 L/min

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