

# Combination Therapy with Inhaled Long-Acting $\beta_2$ -Agonists and Inhaled Corticosteroids: A Paradigm Shift in Asthma Management

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Long-acting inhaled  $\beta_2$ -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  $\beta_2$ -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  $\beta_2$ -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  $\beta_2$ -agonist in the treatment of asthma relative to other treatment regimens.

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Asthma, a chronic airway disease, affects approximately 17.3 million people in the United States.<sup>1</sup> It is associated with significant morbidity and mortality. Approximately 5000 deaths are attributed to asthma each year.<sup>2</sup> Asthma

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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.<sup>3–5</sup>

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.<sup>6</sup> However, asthma generally is underdiagnosed in the primary care setting.<sup>7</sup> Underdiagnosis of asthma by general practitioners may be a result of physicians' lack of awareness of the morbidity experienced by these patients.<sup>8</sup> 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 bronchoconstriction. Thus, pharmacotherapy for

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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.<sup>9, 10</sup> 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.<sup>11–19</sup> 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.<sup>20–22</sup> 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).<sup>23–28</sup> Similarly, the long-acting  $\beta_2$ -agonist bronchodilators have been shown to improve pulmonary function and reverse bronchoconstriction better than the short-acting  $\beta_2$ -agonists (e.g., albuterol), theophylline, and

the leukotriene modifiers.<sup>29–34</sup> Both the inhaled corticosteroids and the long-acting  $\beta_2$ -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 (cyclooxygenase 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.<sup>35</sup> 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  $\beta_2$ -agonists bind to the  $\beta_2$ -adrenoceptor, thereby stimulating the production of cyclic adenosine 3',5'-monophosphate and

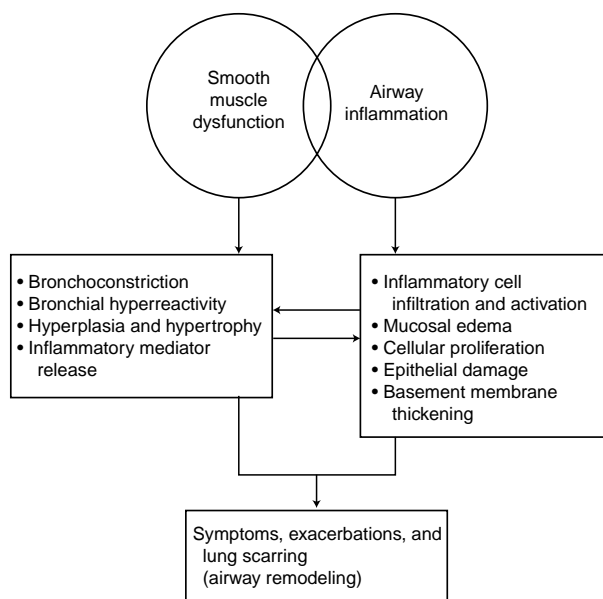


Figure 1. The dual components of asthma.

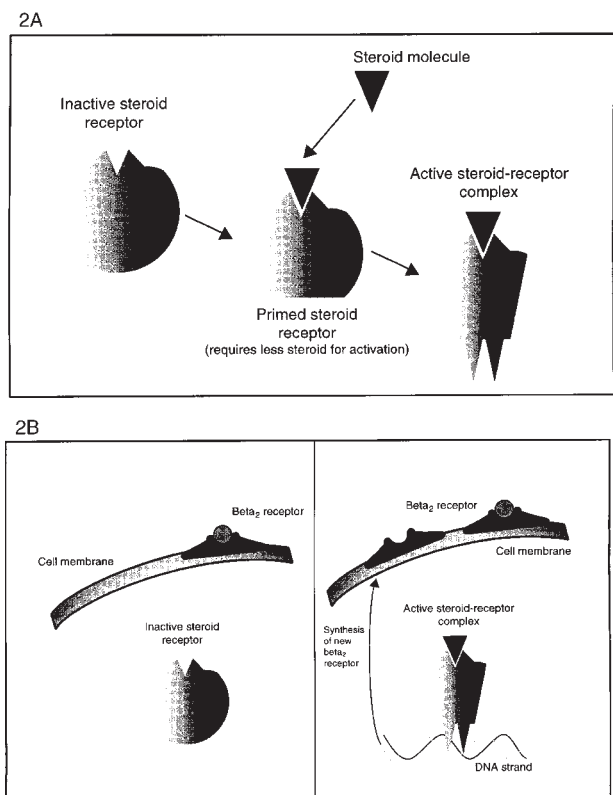


Figure 2. In vitro evidence suggests that  $\beta_2$ -agonists may prime inactive corticosteroid receptors (2A) and that corticosteroids may increase the number of  $\beta_2$ -receptors and their sensitivity to  $\beta_2$ -agonists (2B). Primed receptors are activated more easily by corticosteroids, 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  $\beta_2$ -agonist is more effective than a higher dosage of an inhaled corticosteroid alone.

causing relaxation of bronchial smooth muscle and inhibition of the release of proinflammatory mediators (in vitro) from mast cells.<sup>36</sup>

When used concurrently, these two classes of drugs have complementary effects on each other (Figure 2).<sup>37-43</sup> Inhaled corticosteroids have been shown to upregulate  $\beta_2$ -receptor expression. In human lung, corticosteroids increased  $\beta_2$ -adrenergic receptor transcription.<sup>38</sup> Corticosteroids also induce  $\beta_2$ -receptor messenger RNA transcription and improve  $\beta_2$ -receptor function in human airway epithelial and glandular cells (in vivo and in vitro).<sup>40</sup> Likewise, long-acting  $\beta_2$ -agonists enhance the effects of corticosteroids, a process that may occur through priming of the glucocorticoid receptor for activation.<sup>41</sup> In support of this concept, the long-acting  $\beta_2$ -agonist, salmeterol, enhances steroid-induced inhibition of cell proliferation and inflammatory mediator release, and it enhances steroid-induced eosinophil apoptosis.<sup>39, 42</sup> Recently, the authors of one study<sup>43</sup> reported a synergistic increase in the inhibitory effects of inhaled corticosteroids on tumor necrosis factor- $\alpha$ -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  $\beta_2$ -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  $\beta_2$ -agonists and vice versa.<sup>36</sup>

## 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  $\beta_2$ -agonists might result in tolerance or mask an increase in airway inflammation, thus leading to an increase in exacerbations or more severe exacerbations.<sup>44</sup>

The results of several studies indicate that the addition of a long-acting  $\beta_2$ -agonist to an inhaled corticosteroid in patients with symptoms does

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

One group of authors<sup>45</sup> 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  $\mu\text{g}/\text{day}$ . 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<sup>12</sup>) 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  $\beta_2$ -agonist formoterol 12  $\mu\text{g}$  twice/day to either low-dosage (200  $\mu\text{g}/\text{day}$ ) or high-dosage (800  $\mu\text{g}/\text{day}$ ) budesonide in 852 patients with asthma who were previously symptomatic but had been stabilized over 4 weeks while receiving budesonide 1600  $\mu\text{g}/\text{day}$ .<sup>46</sup> 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  $\beta_2$ -agonist might mask the symptoms of an impending exacerbation, another group of authors<sup>49</sup> 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 formoterol use.

**Table 1. Studies Describing Treatment with a Long-Acting  $\beta_2$ -Agonist and an Inhaled Corticosteroid**

Study Design	Previous Treatment	Age Range (yrs)	Drug Regimen (no. of pts)	Treatment Duration	Results
<b>Add long-acting <math>\beta_2</math>-agonists vs leukotriene modifiers</b>					
R, DB, PG <sup>32</sup>	ICS in 80% of patients	12–73	SL 42 $\mu$ g MDI (144) ZL 20 mg b.i.d. (145)	4 wks	SL > ZL, $p \leq 0.001$ ; AM PEF: 29.6 vs 13.0 L/min; symptom-free days: 22.4% vs 8.8%; FEV <sub>1</sub> : NS
R, DB, PG <sup>33</sup>	ICS	15–83	SL 50 $\mu$ g 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 <sub>1</sub> : NS
R, DB, PG <sup>34</sup>	ICS	15–83	FP 100 $\mu$ g + SL 50 $\mu$ g powder b.i.d. (222) FP 100 $\mu$ g + ML 10 mg q.d. (225)	12 wks	FP + SL > FP + ML, $p \leq 0.032$ ; AM PEF: 24.9 vs 13.0 L/min; FEV <sub>1</sub> : 0.34 vs 0.20 L; % days without albuterol: 26.3% vs 19.1%
Retrospective analysis of 2 R, DB, PG studies <sup>69</sup>	ICS	$\geq 12$	SL 42 $\mu$ g 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 <sub>1</sub> : NS
<b>Add salmeterol vs <math>\uparrow</math> dosage inhaled corticosteroids</b>					
Meta-analysis of 9 R, DB, PG trials <sup>45</sup>	ICS 200–1600 $\mu$ g/day	$\geq 12$	$\uparrow$ dosage of ICS 400–2000 $\mu$ g/day SL 42 or 50 $\mu$ g b.i.d. (3685 total)	12–26 wks	SL > $\uparrow$ dosage of ICS, $p \leq 0.02$ ; AM PEF difference: 27.7 L/min; FEV <sub>1</sub> difference: 0.08 L; % symptom-free days: 15%; exacerbation difference: 2.73%
R, DB, PG <sup>46</sup>	ICS	18–70	BD 100 $\mu$ g b.i.d. (213) BD 100 $\mu$ g + FM 12 $\mu$ g b.i.d. (210) BD 400 $\mu$ g b.i.d. (214) BD 400 $\mu$ g + FM 12 $\mu$ g b.i.d. (215)	12 mo	BD + FM > higher-dosage BD, $p \leq 0.01$ ; $\downarrow$ severe exacerbation: 63% vs 49%; daytime symptom score: 0.33 vs 0.53
Retrospective analysis of 425 severe exacerbations <sup>49</sup>	ICS	18–70	BD 100 $\mu$ g b.i.d. (213) BD 100 $\mu$ g + FM 12 $\mu$ g b.i.d. (210) BD 400 $\mu$ g b.i.d. (214) BD 400 $\mu$ g + FM 12 $\mu$ g 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
<b>Combined vs individual agents</b>					
R, DB, PG <sup>47</sup>	ICS	12–69	SL 50 $\mu$ g + FP 250 $\mu$ g combination powder b.i.d. (84) SL 50 $\mu$ g b.i.d. (88) FP 250 $\mu$ g b.i.d. (84) Placebo (93)	12 wks	Combination > SL, FP, or placebo, $p \leq 0.036$ ; change in FEV <sub>1</sub> : 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 <sup>48</sup>	ICS or SL only	12–70	SL 50 $\mu$ g + FP 100 $\mu$ g combination powder b.i.d. (92) SL 50 $\mu$ g b.i.d. (92) FP 100 $\mu$ g b.i.d. (90) Placebo (82)	12 wks	Combination > SL, FP, or placebo, $p \leq 0.025$ ; change in FEV <sub>1</sub> : 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  $\beta_2$ -Agonist and an Inhaled Corticosteroid (continued)**

Study Design	Previous Treatment	Age Range (yrs)	Drug Regimen (no. of pts)	Treatment Duration	Results
<b>Effect of salmeterol on inflammation</b>					
R, DB, PG, biopsy <sup>50</sup>	ICS	42 (mean)	FP 200 $\mu$ g b.i.d. (19) FP 500 $\mu$ g b.i.d. (19) FP 200 $\mu$ g + SL 50 $\mu$ g b.i.d. (18)	12 wks	FP + SL caused a $\downarrow$ in submucosal mast cells vs FP 200 $\mu$ g ( $p < 0.05$ ); no worsening of airway inflammation with addition of SL
R, DB, PG, biopsy, bronchoalveolar lavage <sup>51</sup>	ICS	20–70	SL 50 $\mu$ g powder b.i.d. (13) FP 100 $\mu$ g powder b.i.d. (16) Placebo (16)	12 wks	No deterioration in airway inflammation; $\downarrow$ in EGI-positive (activated) eosinophils from 18.3 to 7.6 cells/mm with SL + ICS ( $p = 0.01$ )
<b>Concurrent vs individual and higher-dosage inhaled corticosteroids</b>					
R, DB, PG <sup>70</sup>	Short-acting $\beta$ -agonists only	12–61	SL 42 $\mu$ g + FP 88 $\mu$ g b.i.d. (25) SL 42 $\mu$ g + FP 220 $\mu$ g b.i.d. (21) FP 220 $\mu$ g b.i.d. (23) FP 88 $\mu$ g b.i.d. (23) SL 42 $\mu$ g b.i.d. (21) Placebo (23)	4 wks	FP + SL > FP, SL, or placebo, $p < 0.05$ ; change in FEV <sub>1</sub> : 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
<b>Add salmeterol vs <math>\uparrow</math> dosage budesonide, triamcinolone acetonide, or fluticasone propionate</b>					
R, DB, PG <sup>71</sup>	ICS	36 (mean)	SL 50 $\mu$ g + FP 100 $\mu$ g b.i.d. (176) BD 400 $\mu$ g b.i.d. (173)	12 wks	FP + SL > BD, $p \leq 0.022$ ; AM PEF: 426 vs 415 L/min; PM PEF: 435 vs 424 L/min; asthma symptoms: NS
R, DB, PG <sup>72</sup>	ICS	14–80	SL 50 $\mu$ g + FP 250 $\mu$ g b.i.d. (180) BD 800 $\mu$ g b.i.d. (173)	24 wks	FP + SL > BD, $p < 0.05$ ; FEV <sub>1</sub> : 2.53 vs 2.44 L; AM PEF: 406 vs 380 L/min; % symptom-free days increase: 60% vs 34%
R, DB, PG <sup>73</sup>	ICS	12–79	FP 88 $\mu$ g + SL 42 $\mu$ g b.i.d. (167) FP 220 $\mu$ g b.i.d. (180) TAA 600 $\mu$ g b.i.d. (680 total)	12 wks	FP + SL > FP and TAA, $p < 0.05$ ; change in FEV <sub>1</sub> : 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)
<b>Combined vs concurrent therapy</b>					
R, DB, PG <sup>74</sup>	ICS	12–79	SL 50 $\mu$ g + FP 500 $\mu$ g combination powder b.i.d. (167) SL 50 $\mu$ g + FP 500 $\mu$ g concurrent inhalers b.i.d. (171) FP 500 $\mu$ g 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 <sup>75</sup>	ICS	13–75	SL 50 $\mu$ g + FP 250 $\mu$ g combination powder b.i.d. (180) SL 50 $\mu$ g + FP 250 $\mu$ g concurrent powder inhalers b.i.d. (191)	28 wks	Clinical equivalence with combination and concurrent treatment; AM PEF: 43 and 36 L/min



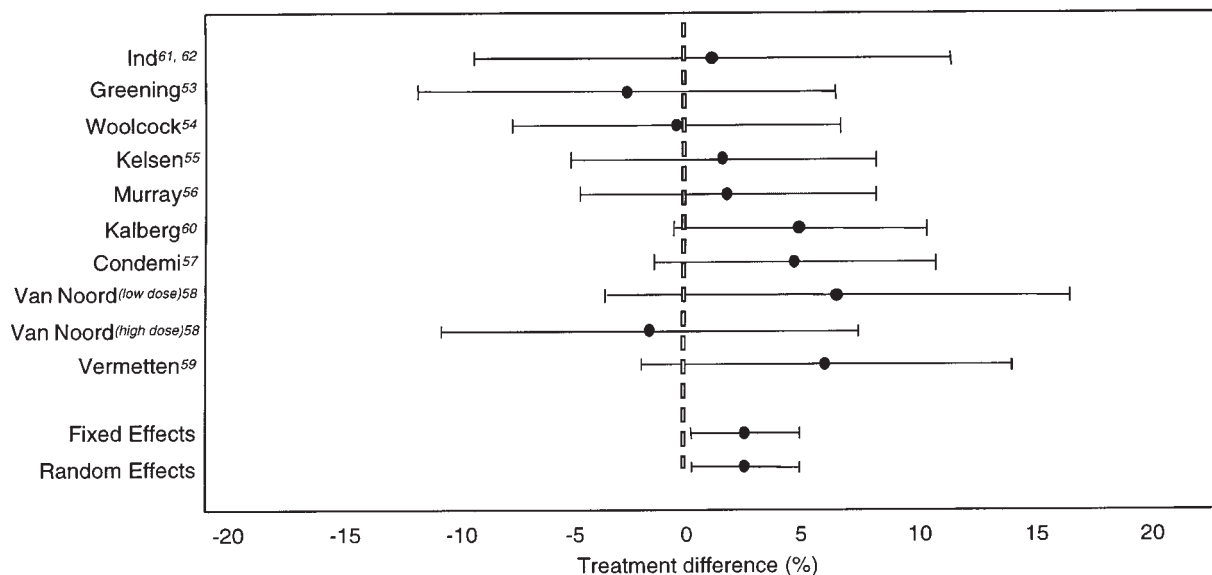
**Table 1. Studies Describing Treatment with a Long-Acting  $\beta_2$ -Agonist and an Inhaled Corticosteroid (continued)**

Study Design	Previous Treatment	Age Range (yrs)	Drug Regimen (no. of pts)	Treatment Duration	Results
R, DB, PG <sup>76</sup>	ICS	12–78	SL 50 $\mu$ g + FP 100 $\mu$ g combination powder b.i.d. (121) SL 50 $\mu$ g + FP 100 $\mu$ g concurrent powder inhalers (123)	12 wks	Clinical equivalence with combination and concurrent treatment; AM PEF: 42 and 33 L/min
R, DB, PG <sup>77</sup>	ICS	4–11	SL 50 $\mu$ g + FP 100 $\mu$ g combination powder b.i.d. (125) SL 50 $\mu$ g + FP 100 $\mu$ g concurrent powder inhalers b.i.d. (132)	12 wks	Clinical equivalence with combination and concurrent treatment; AM PEF: 33 and 28 L/min

R = randomized; DB = double-blind; PG = parallel group; ICS = inhaled corticosteroid; SL = salmeterol; MDI = metered-dose inhaler; ZL = zafirlukast; AM = morning; PEF = peak expiratory flow; FEV<sub>1</sub> = forced expiratory volume in 1 second; NS = not significant; ML = montelukast; FP = fluticasone propionate; BD = budesonide; FM = formoterol; PM = evening; TAA = triamcinolone acetonide.

In another study,<sup>48</sup> the authors showed that in 356 patients previously treated with low dosages of an inhaled corticosteroid or salmeterol, none of the patients treated for 12 weeks with the combination product (fluticasone propionate 100  $\mu$ g and salmeterol 50  $\mu$ g twice/day) were withdrawn from the study owing to clinical exacerbations compared with withdrawal rates of 16%, 6%, and 4% in patients treated with salmeterol, placebo, or fluticasone propionate alone, respectively. Another group<sup>47</sup> reported similar results in 349 patients previously treated with medium dosages of an inhaled corticosteroid.

In that 12-week study, fewer patients (2%) treated with the combination product (fluticasone propionate 250  $\mu$ g and salmeterol 50  $\mu$ g twice/day) were withdrawn from the study because of clinical exacerbations compared with patients treated with placebo (17%), salmeterol (12%), or fluticasone propionate (7%) alone. These results do not indicate that control of airway inflammation, as assessed by exacerbation rates, is compromised by the addition of a long-acting  $\beta_2$ -agonist to the inhaled corticosteroid. In contrast, these data indicate that exacerbations are greatly reduced with combination treatment



**Figure 3.** Difference in proportion of patients with one or more exacerbations (with 95% confidence intervals). Positive differences indicate treatment benefit with addition of salmeterol. (Adapted from reference 45 with permission.)

using two classes of drugs that have different modes of action, indicating a beneficial effect on overall asthma control.

### *Control of Airway Inflammation*

Results of two bronchial biopsy and bronchoalveolar lavage studies indicate that the addition of a long-acting  $\beta_2$ -agonist to inhalation corticosteroid therapy is at least as effective as higher dosages of an inhaled corticosteroid in controlling airway inflammation.<sup>50, 51</sup> In the first study,<sup>50</sup> the effect of 12 weeks of treatment with fluticasone propionate 400  $\mu\text{g}/\text{day}$ , with (18 patients) or without (19 patients) salmeterol 50  $\mu\text{g}$  twice/day, and fluticasone propionate 1000  $\mu\text{g}/\text{day}$  (19 patients) on airway inflammation was evaluated in 56 patients who were symptomatic despite therapy with an inhaled corticosteroid. Bronchial biopsy results showed that compared with baseline and fluticasone propionate 400  $\mu\text{g}/\text{day}$  alone, the combination significantly reduced the number of airway mast cells. There was also a significant reduction from baseline in CD4<sup>+</sup> cells in the combination group that was not seen with either dosage of fluticasone propionate alone.

The second study<sup>51</sup> evaluated the effect of 12 weeks of supplementary treatment with placebo, salmeterol 50  $\mu\text{g}$  twice/day, or fluticasone propionate 100  $\mu\text{g}$  twice/day on airway inflammation in 45 patients with asthma who were symptomatic on low dosages of an inhaled corticosteroid. As in the first study,<sup>50</sup> the results of the second study<sup>51</sup> showed that airway inflammation, as assessed by EGI-positive (activated) eosinophils in bronchial biopsy specimens, was at least as effectively controlled in patients treated with a low dosage of an inhaled corticosteroid and salmeterol compared with higher dosages of an inhaled corticosteroid alone. Thus, combination therapy with a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid may provide a level of control of airway inflammation that is as effective as that of higher dosages of an inhaled corticosteroid.

### *Effect on Airway Remodeling*

Asthma is a chronic inflammatory process of the airways. By definition, any inflammatory process would involve repair and restoration of normal tissue structure and function, which could include replacement of injured tissue by connective tissue and its eventual maturation into scar tissue. In asthma, these processes and

development of scar tissue in the airways may result in altered structure and function often referred to as remodeling of the airways (Figure 1). These structural and functional changes can include thickening of the airway wall as a result of an increase in airway smooth muscle mass, increased vascularity, increases in mucous glands resulting in excessive mucus production, thickening of the reticular basement membrane, and increased collagen deposition.<sup>52</sup>

Because inflammation is an early feature of asthma and is present even in patients with very mild or intermittent asthma, early initiation of an antiinflammatory treatment regimen may be necessary for the prevention of airway remodeling.<sup>11</sup> Several studies have suggested that early intervention with an inhaled corticosteroid may prevent airway remodeling that results from inflammation.<sup>15, 17, 18</sup> However, the effects of antiinflammatory drugs on the processes involved in airway remodeling are not completely understood and require further study.<sup>52, 53</sup>

### *Adding a Long-Acting $\beta_2$ -Agonist versus Other Regimens*

Clinicians frequently question what actions should be taken for a patient who is symptomatic while receiving inhaled corticosteroids: increase the dosage of the inhaled corticosteroid, add theophylline, add a leukotriene modifier, or add a long-acting  $\beta_2$ -agonist. The following published data from clinical trials that specifically evaluated the long-acting  $\beta_2$ -agonist therapy compared with other therapies suggest that the addition of a long-acting  $\beta_2$ -agonist bronchodilator provides greater improvement in lung function and asthma symptom control than do the other therapeutic options.

### *Increased Dosage of an Inhaled Corticosteroid*

A large and consistent body of published data from randomized, controlled clinical trials support the findings of statistically significant increases in efficacy with the addition of a long-acting  $\beta_2$ -agonist compared with increasing the dosage of an inhaled corticosteroid in patients who are symptomatic on the corticosteroid.<sup>45, 46, 54-63</sup> These findings are true for all efficacy parameters studied (need for rescue albuterol, forced expiratory volume in 1 second [FEV<sub>1</sub>], PEF, symptoms, exacerbations) and are not dependent on the inhaled corticosteroid or inhaled long-acting  $\beta_2$ -agonist administered.

One group of authors<sup>45</sup> performed a meta-

analysis based on nine parallel group trials of 12 weeks or greater duration with 3685 patients (aged 12 years or older) who were symptomatic while receiving inhalation corticosteroid therapy. Patients in the studies were randomly assigned to treatment with salmeterol or an increased dosage (at least doubling) of their inhaled corticosteroid. The addition of salmeterol resulted in improved lung function and increased number of days and nights without symptoms or need for rescue treatment. More important, fewer patients experienced exacerbations with salmeterol compared with a higher dosage of an inhaled corticosteroid. These studies support the premise that asthma is a two-component disease and the treatment of both components is necessary for optimal control in most patients.

### *Theophylline*

Several clinical trials compared the efficacy of a long-acting  $\beta_2$ -agonist and theophylline in adult and adolescent patients, most of whom were previously treated with an inhaled corticosteroid. The results of these studies show that salmeterol 42  $\mu\text{g}$  twice/day was significantly more effective than theophylline in improving morning PEF, FEV<sub>1</sub>, and asthma symptoms and reducing nighttime awakenings and need for rescue albuterol after treatment for 2–12 weeks.<sup>64, 65</sup> The authors of another study<sup>66</sup> reported significant improvements with salmeterol inhalation powder 50  $\mu\text{g}$  twice/day in the median percentage of nights with no asthma symptoms and no need for rescue albuterol compared with dosage titration of slow-release theophylline; although, no significant differences were noted between treatment groups in PEF, symptoms, or need for rescue albuterol during the day.

### *Leukotriene Modifiers*

Leukotriene modifiers are a relatively new class of drugs used to treat asthma. Three leukotriene modifiers—zafirlukast (Accolate; AstraZeneca Pharmaceuticals, Wilmington, DE), zileuton (Zyflo; Abbott Laboratories, Abbott Park, IL), and montelukast (Singulair; Merck & Co., Inc, Whitehouse Station, NJ)—are commercially available in the U.S. Leukotrienes are one of the many mediators implicated in asthma. They cause bronchoconstriction, mucus secretion, inflammatory cell infiltration, and increased microvascular permeability. By blocking the effects of leukotrienes or inhibiting their production, these drugs may decrease asthma

symptoms and improve lung function. The current National Institutes of Health guidelines state that leukotriene modifiers may be considered an alternative to low-dosage inhaled corticosteroids for patients with mild persistent asthma. Although the results of a few studies show that the addition of a leukotriene modifier to an inhalation corticosteroid regimen may provide some clinical benefit,<sup>67, 68</sup> leukotriene modifiers were shown to be less effective than inhaled corticosteroids in head-to-head studies, and, to our knowledge, no lung biopsy data exist to support significant antiinflammatory effects.<sup>26–28</sup> Thus, their role as a controller in persistent asthma remains undefined.<sup>12</sup>

### *Zafirlukast*

Two reports in the literature compared the efficacy of salmeterol 42  $\mu\text{g}$  twice/day with that of zafirlukast 20 mg twice/day in symptomatic patients with asthma aged 12 years or older, most of whom were previously treated with an inhaled corticosteroid.<sup>32, 69</sup> The first was a 4-week study with 299 patients in which the authors reported that salmeterol significantly improved morning and evening PEF, daytime asthma symptoms, nighttime asthma symptoms, percentage of symptom-free days, and percentage of days and nights with no need for rescue albuterol compared with zafirlukast.<sup>32</sup>

In the other report, which included data from two studies (including the study just mentioned), a retrospective analysis in 429 patients previously treated with an inhaled corticosteroid revealed significantly greater improvements in morning PEF, percentage of symptom-free days, asthma symptom scores, and percentage of days with no need for rescue albuterol, as well as a significant reduction in the need for rescue albuterol, compared with zafirlukast.<sup>69</sup>

These data indicate that the addition of a long-acting  $\beta_2$ -agonist in patients symptomatic while receiving an inhaled corticosteroid provides significantly greater improvements in lung function and asthma symptom control than does the addition of a leukotriene modifier.

### *Montelukast*

The authors of one study<sup>33</sup> reported on the efficacy of salmeterol inhalation powder 50  $\mu\text{g}$  twice/day compared with oral montelukast 10 mg once/day in a 12-week study with 948 patients aged 15 years or older who were symptomatic despite daily inhalation of a corticosteroid.



Patients treated with salmeterol had significantly greater improvements in morning and evening PEF, percentage of symptom-free days, percentage of rescue-free days, and overall daytime symptoms, compared with those taking montelukast.

In another study,<sup>34</sup> the authors compared the efficacy and safety of 12 weeks of treatment with the combination product fluticasone propionate 100 µg and salmeterol 50 µg administered twice/day versus montelukast 10 mg once/day as add-on therapy (i.e., fluticasone propionate plus salmeterol vs fluticasone propionate plus montelukast) in adults and adolescents with asthma suboptimally controlled with inhalation corticosteroid therapy. Treatment with the combination product resulted in significantly greater improvements in morning and evening PEF, FEV<sub>1</sub>, and shortness of breath and a reduction in the need for rescue albuterol and exacerbations compared with fluticasone propionate plus montelukast.

### **Inhaled Corticosteroid with a Long-Acting $\beta_2$ -Agonist**

#### **Efficacy**

Several studies compared the efficacy of the concurrent administration of a long-acting  $\beta_2$ -agonist with an inhaled corticosteroid (or both classes of drugs in a single product) with that of placebo, the individual agents alone, budesonide, triamcinolone acetonide, or montelukast.<sup>34, 47, 48, 70-73</sup> These studies demonstrated that the combination of salmeterol and fluticasone propionate (at low and medium dosages) significantly improved pulmonary function and asthma symptom control and reduced the need for rescue albuterol compared with placebo, the individual agents alone, budesonide, triamcinolone acetonide, or montelukast in patients with asthma previously treated with or without an inhaled corticosteroid.

#### **Placebo**

In one 4-week study,<sup>70</sup> the authors reported the superior efficacy of concurrent treatment with salmeterol 42 µg and fluticasone propionate at both the 88- and 220-µg doses administered through a metered-dose inhaler (MDI) compared with placebo in improving FEV<sub>1</sub> and asthma symptom control and reducing the need for rescue albuterol in 136 adults and adolescents previously treated with short-acting  $\beta_2$ -agonists

alone. The authors of two 12-week studies<sup>47, 48</sup> reported similar results to those of the 4-week study with the combination product (salmeterol 50 µg with fluticasone propionate either 100 µg or 250 µg) administered as an inhaled powder in adults and adolescents (705 patients) previously treated with either salmeterol<sup>48</sup> or an inhaled corticosteroid.<sup>47, 48</sup> Patients treated with the combination product were significantly less likely to withdraw from either of these studies due to worsening of asthma compared with those receiving placebo.

#### **Individual Agents Alone**

Several studies compared the efficacy of concurrent use of a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid (or a combination product) with the individual agents alone.<sup>46-48, 70, 74</sup> In patients previously treated with low to high dosages of an inhaled corticosteroid<sup>46-48, 74</sup> or long- or short-acting  $\beta_2$ -agonists alone,<sup>47, 70</sup> treatment with salmeterol plus low to medium dosages of an inhaled corticosteroid (used either concurrently or in a combination product) significantly improved FEV<sub>1</sub> or PEF and/or asthma symptom control compared with inhaled corticosteroids<sup>46-48, 70</sup> or long-acting  $\beta_2$ -agonists alone.<sup>47, 48</sup>

#### **No Previous Treatment with Inhaled Corticosteroids**

In a small, double-blind, double-dummy pilot study of 136 patients (21-25 patients in each treatment arm) with asthma not previously treated with inhaled corticosteroids, concurrent treatment with salmeterol and fluticasone propionate either 88 or 220 µg twice/day for 4 weeks significantly improved predose FEV<sub>1</sub> compared with salmeterol, fluticasone propionate 88 µg, or fluticasone propionate 220 µg alone. Concurrent treatment significantly increased morning and evening PEF, area under the 12-hour serial FEV<sub>1</sub> curve, percentage of nights with no awakenings, and percentage of days with no symptoms and reduced symptom scores compared with fluticasone alone but not with salmeterol.<sup>70</sup>

#### **Previous Treatment with Salmeterol or Low- or Medium-Dosage Inhaled Corticosteroids**

In two 12-week double-blind studies of a total of 705 patients with asthma previously treated with salmeterol or low-to-medium dosages of inhaled corticosteroids, the combination

products (fluticasone propionate 100 µg-salmeterol 50 µg and fluticasone propionate 250 µg-salmeterol 50 µg, both twice/day) significantly increased FEV<sub>1</sub>, area under the 12-hour serial FEV<sub>1</sub> curve, probability of remaining in the study (i.e., fewer withdrawals because of worsening asthma), and morning and evening PEF and significantly reduced symptom scores and need for albuterol compared with fluticasone propionate and salmeterol alone. The combination products also significantly increased the percentage of days with no symptoms compared with salmeterol or fluticasone propionate alone.<sup>47, 48</sup>

#### *Previous Treatment with High-Dosage Inhaled Corticosteroids*

In a double-blind, double-dummy 12-week study of 503 patients with asthma previously treated with high-dosage inhaled corticosteroids, the combination product (fluticasone propionate 500 µg-salmeterol 50 µg twice/day) significantly increased morning and evening PEF. In addition, the combination product increased the percentage of symptom-free and rescue-free days, and the percentage of symptom-free and rescue-free nights compared with fluticasone propionate alone.<sup>74</sup>

In a double-blind, 1-year study (the FACET study), concurrent treatment with budesonide (100 or 400 µg) and formoterol 12 µg twice/day significantly increased FEV<sub>1</sub> and morning and evening PEF and reduced both daytime and nighttime symptoms compared with budesonide alone.<sup>46</sup>

#### *Combination Product versus Concurrent Use*

Several studies in adults and adolescents demonstrated similar improvements in FEV<sub>1</sub>, PEF, and asthma symptoms with a combination product (salmeterol 50 µg with fluticasone propionate 100, 250, or 500 µg delivered in a powder formulation through the Diskus inhaler [GlaxoSmithKline Inc., Ware, UK]) and with the concurrent administration of salmeterol and fluticasone at the same doses in separate Diskus devices.<sup>74–76</sup> These studies lasted 12–28 weeks and included patients previously treated with low, medium, or high dosages of inhaled corticosteroids. In addition, children (aged 4–11 yrs) symptomatic while receiving inhaled corticosteroids also had similar improvements in FEV<sub>1</sub>, PEF, and asthma symptoms with the combination product (fluticasone propionate 100 µg-salmeterol 50 µg) and concurrent therapy.<sup>77</sup>

#### *Budesonide*

Efficacy of the combination product (fluticasone propionate 100 µg plus salmeterol 50 µg twice/day) administered as a powder through the Diskus device was compared with that of a 4-fold higher microgram dosage of budesonide (400 µg twice/day) over 12 weeks in 349 adults and adolescents with asthma previously treated with low-dosage inhaled corticosteroids.<sup>71</sup> The combination product significantly improved morning and evening PEF by day 1 compared with budesonide.

In another study,<sup>72</sup> efficacy of the combination product (fluticasone propionate 250 µg plus salmeterol 50 µg twice/day) administered as an inhalation powder through the Diskus device was compared with that of more than a 3-fold higher microgram dosage of budesonide (800 µg twice/day) over 24 weeks in 353 adults and adolescents with asthma previously treated with medium-to-high dosages of inhaled corticosteroids. The combination product significantly improved morning and evening PEF by day 1, improved daytime symptoms, and reduced the need for rescue albuterol compared with budesonide.

#### *Triamcinolone Acetonide*

Efficacy of concurrent treatment with fluticasone propionate 88 µg and salmeterol 42 µg twice/day was compared with that of triamcinolone acetonide 600 µg twice/day (all treatments administered through MDIs) over 12 weeks in 680 adults and adolescents with asthma previously treated with low dosages of inhaled corticosteroids.<sup>73</sup> Treatment with combination therapy significantly improved FEV<sub>1</sub> by the first week, morning PEF by the second week, and evening PEF by the first week compared with triamcinolone acetonide. Combination therapy also significantly increased the percentage of rescue- and symptom-free days and reduced symptom scores, need for rescue albuterol, and nighttime awakenings compared with triamcinolone acetonide.

#### *Safety*

The combination product (fluticasone propionate plus salmeterol) was well tolerated in clinical trials and had a safety profile similar to that of the agents used concurrently at the same doses in separate devices.<sup>46–48, 70, 74</sup> The adverse-effect profile with concurrent or combination

treatment was similar with respect to frequency and type of adverse effects, electrocardiogram results, morning plasma cortisol findings, synthetic cosyntropin stimulation results, physical examination findings, and routine laboratory test results.<sup>47, 48, 70, 74-77</sup> Concurrent or combination treatment is well tolerated regardless of the formulation used (i.e., administration in either a powder or aerosol formulation).<sup>47, 48, 70, 74-77</sup> The use of a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid together did not alter the adverse-effect profile observed with either agent alone. Concurrent treatment with a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid may permit asthma control to be achieved at a lower dosage of inhaled corticosteroid, thereby reducing the likelihood of systemic adverse effects related to the corticosteroid.

### Quality of Life

The effect of therapy with a combination product containing salmeterol and fluticasone propionate in improving health-related quality of life, as measured by responses to the Asthma Quality of Life Questionnaire (AQLQ), was evaluated in two placebo-controlled clinical trials in patients with asthma previously treated with inhaled corticosteroids.<sup>78, 79</sup>

The combination product fluticasone propionate 100  $\mu\text{g}$  and salmeterol 50  $\mu\text{g}$  administered twice/day in the Diskus powder device produced significantly greater improvements in overall AQLQ score than salmeterol or fluticasone propionate alone or placebo in 356 patients with asthma. The differences in AQLQ scores between treatments were clinically meaningful<sup>80</sup> when the combination was compared with placebo (1.3 difference) or salmeterol (1.0 difference). Sleep scores were also significantly higher with the combination compared with the other treatments.<sup>78</sup>

The combination product fluticasone propionate 250  $\mu\text{g}$  and salmeterol 50  $\mu\text{g}$  administered twice/day in the Diskus powder device produced clinically meaningful improvements in overall AQLQ scores and in the four individual domains of the AQLQ in patients with asthma compared with salmeterol alone or placebo. Improvements with the combination product in total AQLQ and in three individual domains were also significantly greater than that with fluticasone propionate alone, though the differences between each regimen were only clinically meaningful for one of the domains (emotional function).<sup>79</sup>

## Clinical Issues

### Adherence to Treatment Plan

Multiple drug regimens can be confusing to patients and can lead to poor adherence to treatment schedules.<sup>9, 10</sup> The combination of a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid in a single inhalation device would simplify the management of asthma and provide treatment with two effective drugs that have complementary mechanisms of action. The need for less frequent rescue albuterol as a result of the efficacy of combination therapy may further simplify asthma treatment regimens.

Improvements in lung function and symptom control with the combination product fluticasone and salmeterol were significant from the first day of treatment in several clinical trials.<sup>47, 48</sup> This early onset of effect would diminish the risk of suboptimal adherence to a treatment plan and would ensure that patients taking a long-acting  $\beta_2$ -agonist always would use an antiinflammatory corticosteroid concurrently and would not selectively discontinue an inhaled corticosteroid. In addition, administration of the combination product through the Diskus device, a breath-activated dry-powder delivery system that patients have found easy to use,<sup>81-84</sup> provides an alternative to the MDI for patients who are unable to use the MDI appropriately. Several studies have shown that patients prefer the Diskus device and find it easier to use than other delivery devices.<sup>82-84</sup>

### Cost-Effectiveness

Given the emphasis on containment of health care costs, the economic benefits of new drugs or treatment regimens must be demonstrated. Inhalation corticosteroid therapy is associated with a reduced risk of death from asthma, a reduced risk of asthma-related hospitalization, and a reduction in primary care and outpatient clinic visits and, therefore, may be a cost-effective treatment intervention in adults and children.<sup>20, 85-87</sup> Several studies evaluated the cost-effectiveness of treating asthma with a combination of a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid compared with an inhaled corticosteroid alone.

The authors of one study<sup>88</sup> retrospectively reviewed administrative claims data over 1 year to assess the costs associated with the addition of salmeterol in patients with asthma, most of whom were treated with an inhaled corticosteroid.



These claims data were compared with data from the 12 months preceding the first salmeterol prescription for the salmeterol group or the first respiratory drug prescription after an asthma-related claim for the control group. Patients treated with salmeterol had a 32% reduction in hospitalization rate and a 71% reduction in the length of hospitalization compared with an 8% increase in the rate of hospitalizations and a 22% decrease in the length of hospitalizations with inhaled corticosteroid alone. The cost of asthma-related prescriptions increased with the addition of salmeterol to the inhalation corticosteroid regimen. This increased cost was more than offset by a reduction in the other direct medical costs (i.e., office visits and hospitalizations). Specifically, asthma-related direct medical costs were less in patients treated with salmeterol than in control patients.

Health care use was compared in the 12 months before and after the start of concurrent inhalation fluticasone propionate and salmeterol therapy in 689 adolescent and adult patients with asthma who were identified from a general practice research database in the United Kingdom.<sup>89</sup> Concurrent therapy with fluticasone propionate and salmeterol reduced slightly asthma-related office visits (mean difference  $\pm$  standard deviation  $-0.17 \pm 3.10$ ), emergency room visits ( $-0.004 \pm 0.326$ ), and need for albuterol ( $-0.24 \pm 5.25$ ) slightly compared with baseline. Concurrent therapy significantly reduced asthma-related hospitalizations ( $p=0.0005$ ) and treatment with prednisolone ( $p=0.0001$ ) and terbutaline ( $p=0.0001$ ) compared with baseline.

Cost-effectiveness of three strengths (100, 250, and 500  $\mu\text{g}$ ) of fluticasone propionate combined with salmeterol 50  $\mu\text{g}$  in a powder product administered twice/day was compared with that of fluticasone propionate alone (100, 250, or 500  $\mu\text{g}$  twice/day, respectively) in an economic analysis using 12-week data from three randomized clinical trials in adult and adolescent patients with asthma.<sup>90</sup> Treatment effectiveness was measured in terms of successfully treated weeks, defined as a week with a mean improvement from baseline in morning PEF of 5% or greater of the PEF value predicted for the patient's age, gender, and height. The direct costs (asthma-related hospitalizations, emergency room visits, primary care contacts, and drug usage) per successfully treated week were lower for all three strengths of the combination product (\$18.31, \$23.82, and \$44.30) than for the

equivalent dosage of fluticasone propionate alone (\$20.50, \$49.08, and \$59.18) despite higher drug costs with the combination product.

The cost-effectiveness of fluticasone propionate 250  $\mu\text{g}$  combined with salmeterol 50  $\mu\text{g}$  in a powder product administered twice/day was compared with that of budesonide 800  $\mu\text{g}$  twice/day in adults and adolescents with asthma who were symptomatic despite treatment with inhaled corticosteroids 800–1200  $\mu\text{g}/\text{day}$ . Treatment effectiveness over 24 weeks was measured in terms of successfully treated weeks, defined as 5% or greater improvement in morning PEF, episode-free days (a day without the need for rescue agent, no nocturnal awakenings, or adverse events), and symptom-free days. The combination product produced significantly higher proportions of successfully treated weeks, episode-free days, and symptom-free days compared with those of budesonide. The cost/successfully treated week was lower for the combination product than for budesonide (\$24.80/wk vs \$36.40/wk), as were the costs/episode-free day (\$6.20/day vs \$9.10/day) and symptom-free day (\$5.10/day vs \$6.40/day).<sup>91</sup>

## Summary

We attempted to answer the clinician's question regarding when to begin or switch to combination therapy with a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid. Combination therapy is an appropriate intervention in symptomatic patients with persistent asthma previously treated with short-acting  $\beta_2$ -agonists alone, a leukotriene modifier alone, or an inhaled corticosteroid. Combination therapy with a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid offers distinct clinical and economic advantages compared with other multiple drug regimens for the long-term control of persistent asthma. Scientific and clinical data support complementary mechanisms of action of these two classes of drugs in achieving a superior level of asthma control and increasing quality of life compared with increasing the dosage of the inhaled corticosteroid, taking the individual agents alone, or taking another controller such as theophylline or a leukotriene modifier. The concurrent use of a long-acting  $\beta_2$ -agonist and an inhaled corticosteroid has a safety profile similar to that of the individual agents used alone at the same dosages and may permit asthma control to be achieved at a lower dosage for the corticosteroid, thereby reducing the likelihood of systemic

adverse effects related to the inhaled corticosteroid. Airway inflammation effectively is controlled by the addition of a long-acting  $\beta_2$ -agonist to an inhaled corticosteroid, and exacerbations are greatly reduced with combination treatment. The availability of this combination in a single product will likely simplify and increase patient adherence to an asthma treatment plan.

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