Dual-Controller Asthma Therapy: Rationale and Clinical Benefits

MODULE B

The 1997 National Heart, Lung, and Blood Institute (NHLBI) Expert Panel guidelines on asthma management recommend a 4-step approach to asthma therapy based on the level of asthma severity: mild intermittent asthma, mild persistent asthma, moderate persistent asthma, or severe persistent asthma. For any patient with persistent asthma (steps 2, 3, or 4), inhaled corticosteroids are the cornerstone of care because of their robust efficacy and potent anti-inflammatory effects. This slide set reviews the newest clinical data regarding asthma management at steps 3 and 4, when combination therapy (that includes inhaled corticosteroids) is nearly always warranted.

Reference
The use of dual-controller therapy—that is, the concurrent administration of two controller medications with complementary mechanisms of action—is one of the treatment strategies recommended in the 1997 National Heart, Lung, and Blood Institute (NHLBI) guidelines for patients with persistent asthma. Dual-controller therapy is one of two broad treatment strategies for patients whose asthma is inadequately controlled with inhaled corticosteroids, which are long-term controller medications that improve asthma symptoms, normalize lung function, and help to mitigate damage to the airways by virtue of their anti-inflammatory mechanism of action. In patients whose asthma is inadequately controlled with inhaled corticosteroids, the NHLBI guidelines suggest either increasing the dose of inhaled corticosteroids (ie, remaining on monotherapy) or adding another long-term controller therapy (ie, initiating dual-controller therapy).

**Reference**

Comparing the Therapeutic Options

- Dual-controller therapy versus increasing inhaled corticosteroid dose
- Dual-controller therapy versus monotherapy with a leukotriene modifier
- Comparisons among dual-controller regimens

A substantial body of data, which postdates the 1997 NHLBI guidelines, demonstrates that dual-controller therapy confers better efficacy than monotherapy (ie, than either increasing the dose of inhaled corticosteroids or using a leukotriene modifier alone) for initial maintenance therapy as well as for asthma inadequately controlled on inhaled corticosteroids alone. Moreover, the data suggest that certain combination regimens used in dual-controller therapy are more effective than others. This slide set reviews these data.

- First, studies comparing the efficacy of dual-controller therapy with that of increasing the dose of the inhaled corticosteroid are considered.
- Then, studies comparing the efficacy of dual-controller therapy with that of monotherapy with a leukotriene modifier are discussed.
- Finally, studies comparing different dual-controller regimens (ie, an inhaled corticosteroid plus a long-acting β2-agonist versus an inhaled corticosteroid plus a leukotriene modifier) are reviewed.
Why should dual-controller therapy be more effective than monotherapy with inhaled corticosteroids?

It is now well established that asthma arises from two main pathophysiologic components: (1) dysfunction of the airway smooth muscles, which leads to bronchoconstriction, bronchial hyperreactivity, and smooth muscle hypertrophy and hyperplasia; and (2) inflammation of the airways, which leads to activation and accumulation of inflammatory cells; edema; damage to the airway epithelium; and thickening of the airway basement membrane.¹

Medications used with inhaled corticosteroids in dual-controller regimens include long-acting β₂-agonists and leukotriene modifiers. Neither of these classes of medication has a mechanism of action that overlaps completely with that of the inhaled corticosteroids with which they are combined in dual-controller regimens. The complementary mechanisms of components of dual-controller regimens are hypothesized to lead to enhanced control of asthma relative to that achievable with single–mechanism-of-action therapies. With some dual-controller regimens—as with those involving a long-acting bronchodilator and an inhaled corticosteroid—both the bronchoconstrictive and the inflammatory components of asthma are targeted.

Reference
Dual-Controller Therapy Compared With Increasing Inhaled Corticosteroid Dose

- Randomized, double-blind, parallel-group, multicenter trial
- 437 patients with an FEV$_1$ of 40% to 80% of predicted
- Randomized to receive either a combination of salmeterol (42 mcg bid) and fluticasone propionate (88 mcg bid) or high-dose fluticasone propionate alone (220 mcg bid) for 24 weeks

Several studies have compared the efficacy of dual-controller regimens including a long-acting β$_2$-agonist or a leukotriene modifier plus an inhaled corticosteroid with that of increasing the dose of an inhaled corticosteroid in patients whose asthma is poorly controlled on inhaled corticosteroids alone. Uniformly across studies, the addition of a long-acting β$_2$-agonist to inhaled regimens of the corticosteroids beclomethasone dipropionate,$^1$-$^3$ fluticasone propionate,$^4$-$^5$ or budesonide$^6$ yields better control of lung function as measured by forced expiratory volume in 1 second (FEV$_1$) or peak expiratory flow rate (PEF) as well as better control of respiratory symptoms than does increasing the dose of inhaled corticosteroids.

For example, one randomized, double-blind, parallel-group, multicenter trial enrolled 437 patients (FEV$_1$ 40% to 80% of predicted) who had used fluticasone propionate 88 mcg bid for at least 2 weeks for control of asthma. These patients were randomized to receive either a combination regimen of the long-acting β$_2$-agonist salmeterol (42 mcg bid) and the inhaled corticosteroid fluticasone propionate (88 mcg bid) or high-dose fluticasone propionate alone (220 mcg bid) for 24 weeks.$^4$

References

Results: Dual-Controller Therapy Compared With Increasing Inhaled Corticosteroid Dose

MEAN CHANGE FROM BASELINE
OVER THE 24-WEEK TREATMENT PERIOD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fluticasone + Salmeterol</th>
<th>High-Dose Fluticasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM PEF</td>
<td>46.5 L/min*</td>
<td>23.8 L/min</td>
</tr>
<tr>
<td>PM PEF</td>
<td>38.2 L/min*</td>
<td>21.2 L/min</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.43 L/min*</td>
<td>0.33 L/min</td>
</tr>
<tr>
<td>Total symptoms</td>
<td>-0.43*</td>
<td>-0.26</td>
</tr>
<tr>
<td>% nights no waking</td>
<td>14.9%*</td>
<td>10.1%</td>
</tr>
<tr>
<td>Mean daily albuterol</td>
<td>-2.51 puffs*</td>
<td>-1.55 puffs</td>
</tr>
</tbody>
</table>

*P<0.05 versus higher-dose fluticasone propionate.

Note: Symptoms were scored on a 5-point scale (0 = no symptoms; 4 = symptoms causing severe discomfort).

The results show that although lung function and symptoms improved compared with baseline in both treatment groups, the group receiving the salmeterol-fluticasone propionate combination exhibited greater improvement than did the high-dose fluticasone propionate group in morning and evening PEF; FEV<sub>1</sub>; symptoms including wheezing, shortness of breath, and chest tightness; frequency of night awakenings; and supplemental albuterol use. The superiority of the combination regimen to the high-dose corticosteroid regimen at improving lung function was evident by the end of the first treatment week for PEF and by the end of the second treatment week for FEV<sub>1</sub>.

Reference

Dual-controller therapy has also been shown to confer better control of asthma than monotherapy with leukotriene modifiers. The effects of dual-controller therapy with a combination product containing the inhaled corticosteroid fluticasone propionate and the long-acting β₂-agonist salmeterol have been compared with those of monotherapy with a leukotriene modifier in two studies that yielded comparable results.

For example, in the first study—a randomized, double-blind, parallel-group, multicenter trial—423 patients remaining symptomatic on short-acting β₂-agonist were randomized to treatment with the fluticasone/salmeterol combination product (100 mcg/50 mcg twice daily) or the leukotriene modifier montelukast (10 mg once daily) for 12 weeks.

**Reference**

ADVAIR™ Diskus® Clinical Monograph. The GlaxoSmithKline Group of Companies; April 2001.
The results show that mean morning predose FEV₁ increased by 23% from baseline in patients treated with fluticasone propionate/salmeterol compared with 11% in patients treated with montelukast (*P<0.05). Secondary end points including mean changes in PEF and symptom scores also favored the fluticasone/salmeterol combination over montelukast.

Similar results were reported in a second 12-week study comparing the fluticasone/salmeterol combination product (100 mcg/50 mcg twice daily) with montelukast (10 mg once daily) for 12 weeks in 432 patients.

The more robust efficacy of this dual-controller regimen may be attributable to the dual mechanism of action of the combination, which combats both the inflammatory and bronchoconstrictive components of asthma.

**Reference**

ADVAIR™ Diskus® Clinical Monograph. The GlaxoSmithKline Group of Companies; April 2001.
Comparisons Among Dual-Controller Regimens

- Two identical randomized, double-blind, parallel-group studies
- 948 patients with an FEV1 of 68% to 69% of predicted
- Randomized to receive either salmeterol (50 mcg twice daily) or oral montelukast (10 mg once daily) in addition to stable inhaled corticosteroid regimen for 12 weeks

Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001;120:423-430.

Based on the different mechanisms of action of long-acting β2-agonists and leukotriene modifiers, dual-controller regimens composed of inhaled corticosteroid long-acting bronchodilator combinations might be expected to be more effective than dual-controller regimens composed of inhaled corticosteroids and leukotriene modifiers. Whereas the former dual-controller regimen has activity against both major pathophysiologic components of asthma (ie, inflammation and smooth muscle dysfunction), the latter dual-controller regimen is primarily anti-inflammatory. In fact, clinical studies suggest that the combination of an inhaled corticosteroid and a long-acting β2-agonist is more effective than the combination of an inhaled corticosteroid with a leukotriene modifier.

For example, Fish et al reported the results of two identical, randomized, double-blind, double-dummy, parallel-group studies of 948 patients with persistent asthma whose symptoms were inadequately controlled with inhaled corticosteroids alone. Either the long-acting β2-agonist salmeterol (50 mcg twice daily by inhalation) or the leukotriene modifier montelukast (10 mg once daily by mouth) was added to stable doses of patients’ inhaled corticosteroids (ie, beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, or triamcinolone acetonide) for a 12-week treatment period.

Reference
Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001;120:423-430.
The results demonstrate that the addition of salmeterol compared with the addition of montelukast to the inhaled corticosteroid regimen was associated with significantly greater improvement from baseline in lung function as measured by morning PEF (35.0 vs 21.7 L/min, \( P<.001 \)) and evening PEF (27.8 vs 19.0 L/min, \( P = 0.002 \)). Furthermore, dual-controller therapy with salmeterol plus an inhaled corticosteroid compared with dual-controller therapy with montelukast plus an inhaled corticosteroid:

- Improved total symptom scores for shortness of breath and chest tightness;
- Increased the number of symptom-free days and days with no requirement for rescue medications;
- Decreased supplemental albuterol use; and
- Reduced the number of nighttime awakenings per week.\(^1\)

A similar pattern of results was reported in a randomized, double-blind clinical trial comparing the efficacy and tolerability of fluticasone propionate (100 mcg) plus salmeterol (50 mcg) twice daily with that of fluticasone propionate (100 mcg) twice daily plus oral montelukast (10 mg) once daily in 447 patients with asthma who remained symptomatic on the inhaled corticosteroid alone.\(^2\)

**References**

1. Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001;120:423-430.
Conclusions

- Data support NHLBI recommendations for dual-controller therapy with an inhaled corticosteroid plus a long-acting $\beta_2$-agonist in patients with moderate persistent or severe persistent asthma.

- Combination of an inhaled corticosteroid plus a long-acting $\beta_2$-agonist is more effective than:
  - Increasing the dose of an inhaled corticosteroid;
  - Monotherapy with a leukotriene modifier; or
  - Dual-controller therapy involving an inhaled corticosteroid and a leukotriene modifier.

Considered together, these data support NHLBI recommendations for dual-controller therapy with an inhaled corticosteroid and a long-acting $\beta_2$-agonist in patients with moderate persistent or severe persistent asthma. The results show that the combination of an inhaled corticosteroid and a long-acting $\beta_2$-agonist is more effective at improving lung function and asthma symptoms than is (1) increasing the dose of an inhaled corticosteroid; (2) monotherapy with a leukotriene modifier; or (3) dual-controller therapy involving an inhaled corticosteroid and a leukotriene modifier.