

# Alternative agents for anti-inflammatory treatment of asthma

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Recent guidelines for the management of asthma have emphasized the role of inflammation in persistent asthma. Medications with anti-inflammatory properties are recommended as the primary long-term-control medications. Of the available choices of long-term-control medications, inhaled corticosteroids are the preferred medication. A literature review of the available studies supports this recommendation of inhaled corticosteroids as the preferred agents for long-term control. Other long-term-control medications—specifically nedocromil, theophylline, and leukotriene modifiers, but not cromolyn—can supplement the beneficial effect of inhaled corticosteroids on pulmonary function and symptom control. Long-acting  $\beta_2$ -adrenergic agonists can also provide an additive clinical benefit to inhaled corticosteroids on symptom control and pulmonary function, but they do not provide additional anti-inflammatory effect. Extended long-term studies of each of the long-term-control medications with anti-inflammatory actions are needed to assess their specific effect on airway remodeling and on the natural history of asthma.

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**Key words:** Glucocorticoids, cromolyn, nedocromil, theophylline, leukotriene, zileuton, zafirlukast, montelukast, beclomethasone, budesonide

In February 1997 the National Institutes of Health released the National Heart, Lung, and Blood Institute *Expert Panel Report 2 (EPR-2): Guidelines for the Diagnosis and Management of Asthma*.<sup>1</sup> Based on the original Expert Panel Report published in 1991,<sup>2</sup> the new Guidelines have incorporated the enlarged scientific base of published articles on asthma from the preceding 6 years. The original Expert Panel had introduced inflammation as 1 of the 3 etiologic components of asthma, in addition to reversible airflow obstruction and bronchial hyperresponsiveness. The EPR-2 Guidelines, by comparison, reflect the increasing evidence supporting the primary role of inflammation in asthma. Thus in EPR-2, asthma is defined as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells.”<sup>1</sup> Furthermore, the EPR-2 Guidelines relate this inflammatory process to the clinical manifestations of asthma: “In susceptible

## Abbreviations used

|        |                                                                                      |
|--------|--------------------------------------------------------------------------------------|
| BAL:   | Bronchoalveolar lavage                                                               |
| BALF:  | Bronchoalveolar lavage fluid                                                         |
| BDP:   | Beclomethasone dipropionate                                                          |
| BHR:   | Bronchial hyperresponsiveness                                                        |
| BID:   | Twice daily                                                                          |
| EPR-2: | Expert Panel Report-2 of the National Asthma Education and Prevention Program (1997) |
| ICS:   | Inhaled corticosteroid(s)                                                            |
| LT:    | Leukotriene                                                                          |
| PEF:   | Peak expiratory flow                                                                 |
| QID:   | Four times daily                                                                     |
| TID:   | Three times daily                                                                    |

individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.”<sup>1</sup>

In recognition of the crucial role of inflammation in asthma, EPR-2 recommends that all patients with persistent asthma (ie, those whose asthma is associated with symptoms more than twice weekly, who have persisting airflow obstruction when free of symptoms, or who manifest increased diurnal variability of their peak expiratory flow [PEF]) receive “long-term-control medications” with anti-inflammatory properties.<sup>1</sup> Anti-inflammatory medications are defined as “those that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (eg, eosinophils, mast cells, activated lymphocytes, macrophages, and cytokines; or eosinophilic cationic protein and tryptase; or extravascular leakage of albumin, fibrinogen, or other vascular proteins) and thus decrease the intensity of airway hyperresponsiveness.”<sup>1</sup> The long-term-control medications, as specified in EPR-2, are listed in Table I.

The goals of asthma therapy that are targeted by use of long-term-control medications with anti-inflammatory actions are listed in Table II. These goals include not only the control of symptoms and avoidance of drug-related side effects but also the avoidance of airway remodeling, a potential long-term complication of asthma. Airway wall remodeling is associated with progressive deterioration in lung function and development of fixed airflow obstruction, although the etiology and incidence rate of this complication in patients with asthma are not yet well established.

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**TABLE I.** Long-term-control medications

- Corticosteroids
- Cromolyn sodium/Nedocromil sodium
- Long-acting  $\beta_2$ -agonists
- Methylxanthines
- Leukotriene pathway modifiers

From the National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda (MD): NIH/National Heart, Lung, and Blood Institute; April 1997. Publication No. 97-4051.

Of the medications listed in Table I, the EPR-2 Guidelines state a clear preference for the use of inhaled corticosteroids (ICS) as the long-term-control agent of choice for initial treatment of persistent asthma. More specifically, they state that "corticosteroids are the most potent and consistently effective long-term-control medication for asthma."<sup>1</sup> In regard to the other long-term-control medications, EPR-2 states that the clinical response to cromolyn and nedocromil is less predictable than that to ICS. Methylxanthines appear to be mildly anti-inflammatory and may be considered as a nonpreferred alternative to ICS when cost and adherence to inhaled treatment are important considerations. In addition, on the basis of data available at the time the EPR-2 was written, leukotriene pathway modifiers may be considered as alternatives to low-dose ICS for patients with mild persistent asthma, but further studies will be required to establish a more specific role and positioning for this class of drugs in asthma therapy. In reviewing the available data on the long-acting  $\beta_2$ -agonists, the EPR-2 concluded that these drugs should be used only in conjunction with anti-inflammatory medications and that they are not the preferred primary long-term-control medication.

This review addresses the relative effectiveness of ICS compared with the other EPR-2-designated long-term-control medications, in particular their ability to meet the goals of asthma therapy identified in Table II. Evidence for the anti-inflammatory action of each class of drugs is reviewed. The classes of drugs are also compared in their ability to control the direct and indirect markers of asthmatic inflammation. Finally, the nonsteroidal drugs are evaluated in their role as anti-inflammatory agents when combined with ICS.

## EVIDENCE FOR ANTI-INFLAMMATORY ACTIONS OF THE LONG-TERM-CONTROL MEDICATIONS

### Cromolyn sodium

It is well recognized that cromolyn sodium has an excellent safety profile. Furthermore, it may be used in children as young as age 2 years and can be easily administered to young children through a nebulizer. The majority of the studies demonstrating clinical efficacy of cromolyn were performed with the Spinhaler inhalation powder delivery system (Fisons Corp, Rochester, NY), a formulation that is no longer available since the intro-

duction of the pressurized metered-dose inhaler. Because of the limitations in application of bronchoalveolar lavage (BAL) and biopsy studies at the time of the introduction of cromolyn, the available *in vivo* studies on anti-inflammatory effects are very limited. The early studies assessed effects on allergen challenge as measured by pulmonary function parameters, an admittedly indirect measure of anti-inflammatory effect.

Several studies have supported clinical efficacy of cromolyn when compared with placebo as demonstrated by improvement in PEF, FEV<sub>1</sub>, reduction in rescue bronchodilator use, and reduced symptom scores.<sup>3-5</sup>

Löwhagen and Rak<sup>6</sup> demonstrated a slight protective effect compared with placebo in the increase in bronchial hyperresponsiveness (BHR) that developed during the allergy season when cromolyn (20 mg four times daily [QID]) was given by Spinhaler. The difference in BHR was approximately 1 doubling dose at 2 weeks into the pollen season. The difference in symptoms was marginal.

Biopsy studies in patients with asthma treated with cromolyn therapy are limited in number. Hoshino and Nakamura<sup>7</sup> obtained biopsy specimens of bronchial mucosa from 9 adult patients with mild-to-moderate atopic asthma (mean FEV<sub>1</sub>, 65%) before and after 12 weeks of open-label (ie, no placebo) treatment with inhaled cromolyn, 2 mg QID, administered through pressurized metered-dose inhaler. The investigators reported that cromolyn reduced the numbers of eosinophils, mast cells, T lymphocytes, and macrophages and significantly inhibited the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial-leukocyte adhesion molecule-1. Cell infiltration was generally reduced by 50% to 75%. There were no significant changes noted in the neutrophil counts.

Studies to specifically measure the anti-inflammatory effects of cromolyn are very limited. Findings of some clinical trials, however, have suggested that cromolyn may exert anti-inflammatory effect, based on observed improvements in pulmonary function, symptom control, and inhibition of early- and late-phase pulmonary response, as well as an increase in BHR after allergen challenge.<sup>3-8</sup>

### Nedocromil sodium

Nedocromil sodium is indicated for the treatment of mild-to-moderate asthma and may be used in children as young as 6 years of age. Similar to cromolyn, several studies have supported the clinical efficacy of nedocromil versus placebo, as demonstrated by improvement in PEF, FEV<sub>1</sub>, a reduction in rescue bronchodilator use, and reduced symptom scores.<sup>9-13</sup> However, questions have been raised about the comparable effects of cromolyn and nedocromil.

In an *in vitro* study, Leung et al<sup>14</sup> examined the effect of nedocromil and cromolyn on inhibition of anti-IgE-induced histamine release from human lung mast cells obtained by BAL and dispersed lung fragments. Nedocromil had more activity than cromolyn in a dose-

**TABLE II.** Goals of asthma therapy

- Prevent chronic and troublesome symptoms (eg, coughing or breathlessness at night, in the early morning, or after exercise)
- Maintain (near) normal pulmonary function
- Maintain normal activity levels (including exercise)
- Prevent recurrent exacerbations of asthma and minimize need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no drug-related adverse effects from medication

Modified from the National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda (MD): NIH/National Heart, Lung, and Blood Institute; April 1997. Publication No. 97-4051.

response analysis by 1 order of magnitude. The effect of nedocromil on mast cells in bronchoalveolar lavage fluid (BALF) was greater than that on mast cells from dispersed lung fragments. The clinical relevance of this evaluation is difficult to extrapolate, however, because it was an *in vitro* analysis with constant drug concentrations, conditions unlike those expected *in vivo*.

Similar to cromolyn, the specific studies to measure the anti-inflammatory effects of nedocromil are very limited. However, clinical studies of nedocromil—especially those indicating improvements in pulmonary function, symptom control, and inhibition of early- and late-phase pulmonary response, as well as increased BHR after an allergen challenge in the presence of nedocromil—have suggested an anti-inflammatory effect of this drug comparable to that of cromolyn.

### Theophylline

The reported anti-inflammatory actions of theophylline have been reviewed by Barnes and Pauwels.<sup>15</sup> Based on *in vitro* and *in vivo* studies in experimental animal models and in human beings, these authors cited evidence that theophylline, even at relatively low blood levels of 5 to 10  $\mu\text{g/mL}$ , inhibits the late bronchial response to allergen inhalation, inhibits release of certain pro-inflammatory cytokines, inhibits the action of some cells involved in the airway inflammation of asthma, and reduces microvascular leakage and airway hyperresponsiveness.

In studies of theophylline in human beings, the bronchial inflammatory response to allergen inhalation has been demonstrated.<sup>16</sup> For example, in a study of 19 patients with atopic asthma, 12 of whom were treated for 6 weeks with theophylline (placebo,  $n = 11$ ), Sullivan et al<sup>17</sup> reported that bronchial biopsy specimens taken 24 hours after allergen challenge revealed a significant reduction in total and activated eosinophils in the airway mucosa of the patients who received theophylline compared with those who received placebo; however, no significant changes were noted in the number of lymphocyte subsets or mast cells in either treatment group. In the study by Ward et al,<sup>16</sup> alterations in the lymphocyte subsets in the peripheral blood, observed in patients receiving placebo after allergen challenge, were absent in those treated with theophylline. Theophylline did not prevent the increase in BHR 24 hours after allergen challenge.<sup>16</sup> Theophylline administered for 10 weeks also failed to improve BHR in 12 subjects, whereas there was significant improvement in histamine sensitivity in the 24 subjects who received beclomethasone dipropionate (BDP), 800  $\mu\text{g/d}$ , for the same duration.<sup>18</sup>

When theophylline was discontinued in a group of 27 asthmatic patients treated with long-term theophylline who were also receiving high-dose ICS and who had a mean theophylline blood level of 8.6  $\mu\text{g/mL}$ , there was an increase in symptoms and a deterioration in pulmonary function.<sup>19</sup> Eight of the patients underwent bronchial biopsy before and after discontinuation of theophylline. After theophylline had been stopped, the number of both CD4+ and CD8+ T lymphocytes in the bronchial wall increased, as did the number of activated eosinophils.<sup>19</sup> When, on the other hand, theophylline was added to the ICS regimen in another group of patients, bronchial biopsy specimens revealed that the addition of theophylline reduced the number of CD8+ T lymphocytes, as well as the number of cells containing the pro-inflammatory cytokines IL-4 and IL-5.<sup>20</sup> Clinically, the addition of theophylline with a mean blood level of 10.9  $\mu\text{g/mL}$  was accompanied by improved PEF and decreased nocturnal asthma.<sup>20</sup>

Thus evidence for an anti-inflammatory action both in the setting of allergen challenge and in chronic asthma has been presented for theophylline. The failure to block allergen-induced BHR or to modify existing airway hyperresponsiveness suggests that this anti-inflammatory action is less than that achieved with low-to-moderate doses of ICS.

### Long-acting $\beta_2$ -agonists

Although the long-acting inhaled  $\beta_2$ -agonists have properties *in vitro* that suggest they could have useful anti-inflammatory properties,<sup>21</sup> this class of long-term-control medication has not been demonstrated to have any significant anti-inflammatory action in patients with asthma. In a study by Gardiner et al,<sup>22</sup> a group of asthmatic patients receiving low-to-moderate-dose ICS underwent bronchoscopy with BAL.<sup>22</sup> There was evidence of increased epithelial cells and increased eosinophils in the lavage fluid. Inhaled salmeterol was then added for 8 weeks. Repeat bronchoscopy at the end of this period revealed no change in the number of eosinophils, the percentage of CD4+ and CD8+ T lymphocytes, or the percentage of T lymphocytes expressing the HLA-DR activation marker.<sup>22</sup>

Methacholine challenge and bronchoscopy with BAL were performed at 4:00 AM in a group of patients with nocturnal asthma before and after 5 weeks of salmeterol therapy (100  $\mu\text{g}$  twice daily [BID]).<sup>23</sup> Although it significantly decreased nocturnal awakening, salmeterol produced no change in either BHR or in the indices of air-

TABLE III. Comparison of cromolyn sodium with ICS

| Parameter                             | ICS                                                   | Duration and significance                    | Comparator                                                                    |
|---------------------------------------|-------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------|
| FEV <sub>1</sub>                      |                                                       |                                              |                                                                               |
| Svendsen et al (1987) <sup>38</sup>   | BDP 400 µg/d<br>+0.6 L                                | 8 wk<br><i>P</i> < .01                       | Cromolyn 8 mg/d MDI<br>+0.18 L                                                |
| Kraemer et al (1987) <sup>39</sup>    | BDP 300 or 600 µg/d<br>48% increase                   | 2 mo<br><i>P</i> < .01                       | Cromolyn 60 mg/d via nebulizer<br>5%-15% increase                             |
| Price and Weller (1995) <sup>41</sup> | FP 100 µg/d<br>79.1%*-to 87.8% predicted value        | 8 wk<br>NS                                   | Cromolyn 80 mg/d via Spinhaler<br>77.8%*-82.4% predicted value                |
| PEF                                   |                                                       |                                              |                                                                               |
| Svendsen et al (1987) <sup>38</sup>   | BDP 400 µg/d<br>+100 L/min                            | 8 wk<br><i>P</i> < .01                       | Cromolyn 8 mg/d MDI<br>+30 L/min                                              |
| Price and Weller (1995) <sup>41</sup> | FP 100 µg/d<br>93%*-107% predicted value<br>(morning) | 8 wk<br>7.5% difference,<br><i>P</i> = .0001 | Cromolyn 80 mg/d via Spinhaler<br>89%*-95% predicted value                    |
| BHR                                   |                                                       |                                              |                                                                               |
| Svendsen et al (1987) <sup>38</sup>   | BDP 400 µg/d<br>+0.2 ln PC <sub>20</sub>              | 8 wk<br><i>P</i> = .001                      | Cromolyn 8 mg/d MDI<br>+0.2 ln PC <sub>20</sub> then -0.2 ln PC <sub>20</sub> |
| Shapiro et al (1991) <sup>40</sup>    | Triamcinolone 600 µg/d<br>no change                   | 12 wk<br>NS                                  | Cromolyn 60 mg/d via nebulizer<br>no change                                   |
| Kraemer et al (1987) <sup>39</sup>    | BDP 300 or 600 µg/d<br>5.9-fold improvement           | 2 mo                                         | Cromolyn 20 mg via nebulizer TID<br>1.9-fold improvement                      |
| Symptoms                              |                                                       |                                              |                                                                               |
| Price and Weller (1995) <sup>41</sup> | FP 100 µg/d<br>15%*- to 84%                           | 8 wk<br>symptom-free days,<br><i>P</i> < .05 | Cromolyn 80 mg/d via Spinhaler<br>15%*-62%                                    |
| β <sub>2</sub> -Agonist use           |                                                       |                                              |                                                                               |
| Price and Weller (1995) <sup>41</sup> | FP 100 µg/d<br>1.97* to 0.49 doses/d                  | 8 wk<br>daytime relief medication,<br>NS     | Cromolyn 80 mg/d via Spinhaler<br>1.91* to 0.64 doses/d                       |

MDI, Metered-dose inhaler; FP, fluticasone propionate; NS, not statistically significant.

\*Baseline value.

way inflammation.<sup>23</sup> Further support for the absence of anti-inflammatory action of salmeterol was shown in a study by Yates et al,<sup>24</sup> which demonstrated the lack of effect on exhaled nitric oxide in patients receiving ICS or in patients using only inhaled β<sub>2</sub>-agonists.

### Leukotriene pathway modifiers

The cysteinyl leukotrienes are potent mediators released from mast cells and eosinophils that contract airway smooth muscle, increase vascular permeability, and increase mucus secretion. Leukotrienes also attract and activate inflammatory cells in the airways of patients with asthma.

The leukotriene pathway from arachidonic acid begins with the action of the enzyme 5-lipoxygenase, which converts arachidonic acid to an unstable intermediate leukotriene (LT) A<sub>4</sub>. LTA<sub>4</sub>, in turn, may be converted by LTA<sub>4</sub> hydrolase to LTB<sub>4</sub>, a potent chemoattractant, or by LTC<sub>4</sub> synthase to the cysteinyl leukotriene LTC<sub>4</sub>, which is further converted by dipeptidases to LTD<sub>4</sub> and LTE<sub>4</sub>.<sup>25</sup> The importance of LTB<sub>4</sub> in asthma is undefined, because it is primarily a chemoattractant for neutrophils.<sup>26</sup> The cysteinyl leukotrienes, on the other hand, have actions clearly relevant to the pathophysiology of asthma including bronchial smooth muscle contraction, increased vascular permeability, and mucus secretion.<sup>26</sup> The cysteinyl

leukotrienes have been found in increased levels in the bronchoalveolar fluid and in the urine of patients with asthma.<sup>26</sup>

Bronchial inhalation challenges with both LTE<sub>4</sub><sup>27</sup> and LTD<sub>4</sub><sup>28</sup> have resulted in an increase, within 4 hours, in the number of eosinophils in induced sputum<sup>28</sup> and in bronchial biopsy specimens.<sup>27</sup> Administration of several LTD<sub>4</sub> antagonists has decreased bronchoconstriction after allergen inhalation challenge. The early<sup>29-31</sup> and the late<sup>29-31</sup> airflow obstruction after allergen challenge and the secondary increase in nonspecific BHR<sup>31,32</sup> have all been reported to decrease. Segmental bronchial allergen challenges have also been conducted. BAL 24 hours after allergen challenge has demonstrated a decreased eosinophilic influx after treatment with the 5-lipoxygenase inhibitor zileuton.<sup>33</sup> By comparison, BAL 48 hours after segmental challenge demonstrated diminished numbers of basophils and lymphocytes in asthmatic subjects receiving zafirlukast.<sup>34</sup>

Nocturnal asthma is associated with a significant increase in LTB<sub>4</sub> in the BALF and increased urinary excretion of LTE<sub>4</sub>.<sup>35</sup> When patients began receiving zileuton, both LTB<sub>4</sub> in BALF and urinary LTE<sub>4</sub> were decreased, as was the percentage of eosinophils in the BALF. Subjects in a 13-week study of zileuton versus placebo underwent dry cold air challenges before treat-

**TABLE IV.** Comparison of nedocromil sodium with ICS

| Parameter                           | ICS                                          | Duration and significance | Comparator                                            |
|-------------------------------------|----------------------------------------------|---------------------------|-------------------------------------------------------|
| FEV <sub>1</sub>                    |                                              |                           |                                                       |
| Svensden et al (1989) <sup>50</sup> | BDP 400 µg/d<br>+0.50 L                      | 6 wk<br>NS                | Nedocromil 8 mg/d MDI<br>+0.32 L                      |
| PEF                                 |                                              |                           |                                                       |
| Svensden et al (1989) <sup>50</sup> | BDP 400 µg/d<br>+63.1 L/min                  | 6 wk<br>NS                | Nedocromil 8 mg/d MDI<br>+44.7 L/min                  |
| BHR                                 |                                              |                           |                                                       |
| Svensden et al (1989) <sup>50</sup> | BDP 400 µg/d<br>+1.43 ln PC <sub>20</sub>    | 6 wk<br><i>P</i> < .05    | Nedocromil 8 mg/d MDI<br>+0.547 in PC <sub>20</sub>   |
| Bel et al (1990) <sup>49</sup>      | BDP 400 µg/d<br>1.23-2.97 mg/mL methacholine | 16 wk<br>NS               | Nedocromil 8 mg/d MDI<br>1.22-2.59 mg/mL methacholine |

NS, Not statistically significant; MDI, metered-dose inhaler.

ment and at 1 to 10 days after completion of the study, when zileuton should no longer have been present in detectable levels in the blood.<sup>36</sup> Subjects who had received zileuton required 50% more dry cold air to produce a positive challenge response, whereas there was no significant increase in the placebo group. Patients in a 6-month study of zileuton required 62% less oral steroid rescue medication than the group receiving placebo.<sup>37</sup>

Taken together, these studies indicate that some drugs in this class are able to decrease the inflammatory component of allergen challenge, as indicated by a reduction in the late pulmonary response (which is thought to reflect an inflammatory effect), by blunting allergen-induced increases in BHR, and by a reduction in the cellular response to allergen challenge. Evidence for an anti-inflammatory effect on the chronic inflammation of asthma comes from studies showing decreased airway eosinophilia in patients with nocturnal asthma, decreased response to dry cold air after 3 months of zileuton therapy, and a decreased number of asthma exacerbations requiring intervention with oral steroids during a 6-month period of treatment with zileuton. The leukotriene pathway modifiers represent a new class of drugs, one which is being actively studied, so further information should be forthcoming to expand the information on their anti-inflammatory potential.

#### COMPARISON OF THE EFFECT OF LONG-TERM-CONTROL MEDICATIONS ON THE CLINICAL AND INFLAMMATORY MANIFESTATIONS OF ASTHMA

The EPR-2 Guidelines state that ICS are the most potent and consistently effective of the long-term-control medications.<sup>1</sup> The following section and Table III summarize the results of available studies that compare the clinical effectiveness of the alternative long-term-control medications with ICS. It is important to note that the comparative studies evaluated the effect of the medications on lung function, a few on bronchial reactivity, and none on direct markers of inflammation. The issue of study design and intent, as well as the comparative effect

of ICS within the class of medications, is addressed in the subsequent reviews by Drs Kelly and Sorkness in this issue.

#### Cromolyn sodium

Comparative studies with cromolyn and ICS have shown differences favoring cromolyn in blocking the pulmonary response to an allergen when these medications are given before the allergen challenge.<sup>8</sup> However, clinical studies directly comparing the 2 agents over an extended treatment period support the greater efficacy of ICS over cromolyn. Table III presents data from 4 clinical trials in which cromolyn was administered in various formulations and compared with low-to-moderate doses of ICS.

For example, one study<sup>38</sup> compared cromolyn, 2 mg QID, administered through a pressurized metered-dose inhaler, with inhaled BDP, 200 µg BID, in a crossover design with a treatment duration of 8 weeks in each arm. The effect on FEV<sub>1</sub>, forced vital capacity, and BHR was greater with BDP than with cromolyn. For BHR, the cromolyn group showed initial improvement but a subsequent reduction below baseline, whereas the BDP group improved and remained improved throughout the treatment period. Patients who initially received BDP had a greater reduction in BHR than those in the cromolyn treatment arm, but this observed improvement in BHR deteriorated when the patients were crossed over to cromolyn therapy.

Another study by Kraemer et al<sup>39</sup> compared BDP administered through Rotacaps (Glaxo Wellcome Inc, Research Triangle Park, NC) (100 µg caps in subjects younger than 12 years and 200 µg caps in subjects older than 12 years) with cromolyn, 20 mg, administered by nebulizer or comparable placebo three times daily (TID) for 2 months. Interestingly, all treatments were administered with albuterol. FEV<sub>1</sub> increased by 48% in the BDP group and by only 5% to 15% in the cromolyn group; in addition, the change in BHR was approximately 3-fold higher with BDP compared with cromolyn or placebo.

Shapiro et al<sup>40</sup> studied asthmatic children and compared the efficacy of triamcinolone acetonide (2 inhalations, 100 µg/inhalation) or cromolyn (20 mg in nebuliz-

**TABLE V.** Comparison of theophylline with ICS

| Parameter                         | ICS                                                                                      | Duration and significance                               | Comparator                                                                   |
|-----------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------|
| FEV <sub>1</sub>                  |                                                                                          |                                                         |                                                                              |
| Reed et al (1997) <sup>52</sup>   | BDP 336 µg/d<br>81.7%-to 83.5% predicted value                                           | 1 wk<br>NS                                              | SR Theophylline<br>81.5%-83.9% predicted value                               |
| Galant et al (1996) <sup>53</sup> | FP 100 & 200 µg/d                                                                        | FP > theophylline,<br><i>P</i> > .004                   | Theophylline                                                                 |
| PEF                               |                                                                                          |                                                         |                                                                              |
| Reed et al (1998) <sup>52</sup>   | BDP 336 µg/d<br>AM: 92%-96% predicted value<br>PM: 97%-100% predicted value              | 12 mo<br>NS                                             | SR Theophylline<br>AM: 94-96% predicted value<br>PM: 97-100% predicted value |
| Galant et al (1996) <sup>53</sup> | FP 100 & 200 µg/d                                                                        | FP > theophylline,<br><i>P</i> > .004                   | Theophylline                                                                 |
| BHR                               |                                                                                          |                                                         |                                                                              |
| Reed et al (1998) <sup>52</sup>   | BDP 336 µg/d<br>½ doubling dilution higher                                               | 12 mo<br>6 wk: <i>P</i> < .05<br>12 mo: <i>P</i> < .001 | SR Theophylline<br>no change                                                 |
| Symptoms                          |                                                                                          |                                                         |                                                                              |
| Reed et al (1998) <sup>52</sup>   | BDP 336 µg/d                                                                             | 12 mo<br>at 6 mo <i>P</i> = .002<br>favoring BDP        | SR Theophylline                                                              |
| β <sub>2</sub> -Agonist use       |                                                                                          |                                                         |                                                                              |
| Reed et al (1998) <sup>52</sup>   | BDP 336 µg/d                                                                             | 12 mo favoring BDP<br>at 6 mo<br><i>P</i> = .038        | SR Theophylline                                                              |
| Other                             |                                                                                          |                                                         |                                                                              |
| Reed et al (1998) <sup>52</sup>   | BDP 336 µg/d<br>hospital & ED: 1.2%-4.1%<br>no systemic steroids<br>80%                  | 12 mo<br>NS<br><i>P</i> = .009                          | SR Theophylline<br>hospital & ED: 1.3%-4.7%<br>no systemic steroids<br>71%   |
| Galant et al (1996) <sup>53</sup> | FP 100 & 200 µg/d<br>Not meeting asthma-stability criteria<br>100 µg: 14%<br>200 µg: 21% | <i>P</i> = .008                                         | Theophylline<br>not meeting asthma-stability criteria<br>39%                 |

SR, Sustained-release; NS, not statistically significant; FP, fluticasone propionate; ED, emergency department treatment.

er solution) with albuterol 2 inhalations TID. In this study the effect on symptoms, pulmonary function, and BHR was comparable for the 2 treatments.

In another pediatric trial, Price and Weller<sup>41</sup> compared the effects of 50 µg of fluticasone propionate BID to cromolyn, 20 mg QID, over an 8-week study period in 225 asthmatic children aged 4 to 12 years (FEV<sub>1</sub>, approximately 78% predicted value). Outcome measures improved in both groups, with a significant difference in favor of fluticasone for mean morning and evening percent predicted PEF and percent symptom-free days and nights. No significant difference was observed for FEV<sub>1</sub> or for relief medication use. The study demonstrated superior efficacy of low-dose fluticasone to cromolyn in this group of children with mild to moderate asthma.

In addition to the studies previously summarized, 7 reports with similar study conditions (in general, conducted in patients with mild to moderate asthma, with a duration of 6 weeks to 6 months, and in a double-blind, parallel study design) provided results similar to those reviewed.<sup>42-48</sup> These studies compared cromolyn in varying doses with ICS at doses averaging 400 µg/d. Overall, when the effects of cromolyn and ICS were compared in

the same studies, ICS were superior or equal to cromolyn therapy in all studies and never less effective. Furthermore, the ICS were generally administered in a low- to medium-dose schedule.

### Nedocromil sodium

Two studies comparing nedocromil with ICS are summarized in Table IV. Bel et al<sup>49</sup> compared nedocromil, 4 mg QID, versus BDP, 100 µg QID, versus placebo for 4 months. FEV<sub>1</sub> did not change with nedocromil or placebo but increased with BDP (from 88.9% to 96.4% of predicted value). In addition, PC<sub>20</sub> improved 3-fold with nedocromil and BDP (almost 2 doubling doses). Svendsen et al<sup>50</sup> evaluated the efficacy of nedocromil compared with BDP on pulmonary function and on BHR in a crossover study with 6 weeks per treatment arm. Nedocromil was as effective as BDP on pulmonary function but less effective when evaluated on asthma severity, overall opinion, patient symptom score, and bronchodilator use.

Harper et al<sup>51</sup> compared the effects of BDP, 400 µg/d, with nedocromil, 16 mg/d, in adults. Seventeen subjects were enrolled in this double-blind crossover study with 2 8-week treatment phases. Both drugs resulted in

**TABLE VI.** Comparison of long-acting  $\beta_2$ -agonists with ICS

| Parameter                           | ICS                                               | Duration and significance | Comparator                                                |
|-------------------------------------|---------------------------------------------------|---------------------------|-----------------------------------------------------------|
| FEV <sub>1</sub>                    |                                                   |                           |                                                           |
| Simons et al (1997) <sup>54</sup>   | BDP 400 $\mu$ g/d                                 | 12 mo<br>NS               | Salmeterol 50 $\mu$ g/BID                                 |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>+10.0%                       | 12 mo<br>$P < .0001$      | Salmeterol 50 $\mu$ g/BID<br>−4.5%                        |
| PEF                                 |                                                   |                           |                                                           |
| Simons et al (1997) <sup>54</sup>   | BDP 400 $\mu$ g/d<br>+35 L/min                    | 12 mo<br>NS               | Salmeterol 50 $\mu$ g/BID<br>+41 L/min                    |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>+60 L/min                    | 12 mo<br>NS               | Salmeterol 50 $\mu$ g/BID<br>+49 L/min                    |
| BHR                                 |                                                   |                           |                                                           |
| Simons et al (1997) <sup>54</sup>   | BDP 400 $\mu$ g/d<br>>1 doubling dilution higher  | 12 mo<br>$P = .003$       | Salmeterol 50 $\mu$ g/d<br>< 1 doubling dilution higher   |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>+2.02 doubling dilutions     | 12 mo<br>$P < .0001$      | Salmeterol 50 $\mu$ g/BID<br>−0.73 doubling dilutions     |
| Symptoms                            |                                                   |                           |                                                           |
| Simons et al (1997) <sup>54</sup>   | BDP 400 $\mu$ g/d<br>92% of days without symptoms | 12 mo<br>NS               | Salmeterol 50 $\mu$ g/BID<br>88% of days without symptoms |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>55% asymptomatic last 2 wk   | 12 mo<br>NA               | Salmeterol 50 $\mu$ g/BID<br>36% asymptomatic last 2 wk   |
| $\beta_2$ -agonist use              |                                                   |                           |                                                           |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>use 0.07 puffs/d             | 12 mo<br>$P = .0001$      | Salmeterol 50 $\mu$ g/BID<br>use 0.44 puffs/d             |
| Other                               |                                                   |                           |                                                           |
| Simons et al (1997) <sup>54</sup>   | BDP 400 $\mu$ g/d<br>Average growth: 3.96 cm      | 12 mo<br>$P = .004$       | Salmeterol 50 $\mu$ g/BID<br>Average growth: 5.40 cm      |
| Verberne et al (1997) <sup>55</sup> | BDP 400 $\mu$ g/d<br>Average growth: 4.7 cm       | 12 mo<br>$P = .007$       | Salmeterol 50 $\mu$ g/BID<br>Average growth: 6.1 cm       |

NS, Not statistically significant; NA, statistical analysis not available.

improvement, with most measures comparable for the 2 study drugs. A few measures (ie,  $\beta_2$ -agonist use, morning tightness, nocturnal asthma scores) favored BDP.

Similar to cromolyn, in studies in which the effect of nedocromil was compared with ICS, the effect of nedocromil—if not comparable—was usually less than that of ICS but was never greater. Furthermore, in these studies the dosages for ICS were generally in a low-to-medium range.

### Methylxanthines

Two studies are presented in Table V in which the results of treatment with sustained-release theophylline were compared with those of low-dose ICS. The first study compared 336  $\mu$ g of BDP with sustained-release theophylline in 747 patients entered into a year-long study.<sup>52</sup> The second study compared fluticasone propionate, 100 or 200  $\mu$ g/d, with theophylline in 353 patients over a 12-week period.<sup>53</sup> Pulmonary function improved significantly with fluticasone propionate compared with theophylline. There was no significant difference between BDP and theophylline. However, reductions in BHR, asthma symptoms, requirement for rescue  $\beta_2$ -agonists, and need for emergency department visits or hospitalization were significantly better with BDP than with theophylline. Significantly more patients met the criteria for asthma stability with fluticasone propionate than with

theophylline. There were no favorable outcomes, in either study, that occurred more often in the theophylline-treated subjects than in those receiving the ICS.

### Long-acting $\beta_2$ -agonists

Two recent pediatric studies compared the efficacy and safety of therapy with the long-acting  $\beta_2$ -agonist salmeterol to low-dose BDP for a period of 1 year (Table VI).<sup>54,55</sup> Symptoms of asthma in the first study<sup>54</sup> and home-monitored PEF measurements in both studies were not statistically significantly different between the 2 treatment groups.<sup>54,55</sup> FEV<sub>1</sub> improved more with BDP than with salmeterol in the first study; in the second study there was no statistically significant difference in FEV<sub>1</sub> between the 2 treatment groups. Rescue  $\beta_2$ -agonist use of albuterol was significantly lower with BDP in the first study.<sup>54</sup> BHR was significantly improved with BDP compared with salmeterol in both studies. The only examined variable that favored salmeterol was an increase in height, which was significantly greater in the children receiving salmeterol than in those receiving ICS.

### Leukotriene pathway modifiers

A number of studies presented at recent medical meetings have evaluated the impact of LTD<sub>4</sub> antagonists in comparison with low-dose inhaled BDP on specific efficacy parameters (Table VII).<sup>56-62</sup> In each of the 7 studies,

TABLE VII. Comparison of leukotriene modifiers with ICS

| Parameter                             | ICS                                        | Duration and significance                                                       | Comparator                                                               |
|---------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| FEV <sub>1</sub>                      |                                            |                                                                                 |                                                                          |
| Ind et al (1998) <sup>56</sup>        | BDP 336 µg/d<br>+0.35 L                    | 12 wk<br>NA                                                                     | Pranlukast 900 mg/d<br>+0.23 L                                           |
| Wenzel et al (1997) <sup>57</sup>     | BDP 336 µg/d<br>+0.35 L                    | 12 wk<br>NA                                                                     | Pranlukast<br>600 mg +0.19 L<br>900 mg +0.23 L                           |
| Ind et al (1998) <sup>56</sup>        | BDP 336 µg/d<br>+0.40 L                    | 9 mo<br>NA                                                                      | Montelukast 10 mg/d<br>+0.26 L                                           |
| Knorr et al (1997) <sup>58</sup>      | BDP 252 µg/d<br>+0.28 L (14.3%)            | 4 mo<br>NA                                                                      | Montelukast 5 mg/d (pediatric)<br>+0.22 L (12.4%)                        |
| Reiss et al (1997) <sup>59</sup>      | BDP 400 µg/d<br>+16%                       | 9 mo<br>NS                                                                      | Montelukast 10 mg/d<br>+11%                                              |
| Laitinen et al (1997) <sup>60</sup>   | BDP 400-500 µg/d<br>+8%                    | 6 wk<br><i>P</i> < .01 (vs 40 mg)                                               | Zafirlukast<br>40 mg +2%<br>160 mg +7%                                   |
| PEF                                   |                                            |                                                                                 |                                                                          |
| Laitinen et al (1997) <sup>60</sup>   | BDP 400-500 µg/d<br>+10%                   | 6 wk<br><i>P</i> < .01 (vs 40 mg)                                               | Zafirlukast<br>40 mg +6%<br>160 mg +8%                                   |
| Westbrook et al (1997) <sup>61</sup>  | FP 200 µg/d<br>+28 L/min                   | 2 wk<br><i>P</i> < .05                                                          | Zafirlukast 40 mg/d<br>+6 L/min                                          |
| BHR                                   |                                            |                                                                                 |                                                                          |
| Ind et al (1998) <sup>56</sup>        | BDP 400-500 µg/d<br>+1.04 mg/mL            | 6 wk<br>NA                                                                      | Zafirlukast 160 mg/d<br>+0.41 mg/mL                                      |
| Westbrook et al (1997) <sup>61</sup>  | FP 200 µg/d<br>+1.61 mg/mL                 | 2 wk<br><i>P</i> < .05                                                          | Zafirlukast 40 mg/d<br>0.99 mg/mL                                        |
| Symptoms                              |                                            |                                                                                 |                                                                          |
| Ind et al (1998) <sup>56</sup>        | BDP 400-500 µg/d<br>Night -49%<br>Day -40% | 6 wk<br>Night NS<br>Day <i>P</i> < .01 (vs 40 mg)<br><i>P</i> < .05 (vs 160 mg) | Zafirlukast<br>40 mg -36% night, -24% day<br>160 mg -35% night, -28% day |
| Reiss et al (1997) <sup>59</sup>      | BDP 400 µg/d<br>Day -27%                   | 9 mo<br>NS                                                                      | Montelukast 10 mg/d<br>-23%                                              |
| Wenzel et al (1997) <sup>57</sup>     | BDP 336 µg/d<br>-31%                       | 12 wk<br>NA                                                                     | Pranlukast<br>600 mg -27%<br>900 mg -34%                                 |
| β <sub>2</sub> -Agonist use           |                                            |                                                                                 |                                                                          |
| Laitinen et al (1997) <sup>60</sup>   | BDP 400-500 µg/d<br>-35%                   | 6 wk<br>NS                                                                      | Zafirlukast<br>40 mg -26%<br>160 mg -22%                                 |
| Reiss et al (1997) <sup>59</sup>      | BDP 400 µg/d<br>-37%                       | 9 mo<br>NS                                                                      | Montelukast 10 mg/d<br>-36%                                              |
| Wenzel et al (1997) <sup>57</sup>     | BDP 336 µg/d<br>-33%                       | 12 wk<br>NA                                                                     | Pranlukast<br>600 mg -30%<br>900 mg -40%                                 |
| Quality of life                       |                                            |                                                                                 |                                                                          |
| Ind et al (1998) <sup>56</sup>        | FP 200 µg/d<br>+0.97                       | 2 wk<br>NA                                                                      | Pranlukast 900 mg/d<br>+0.90                                             |
| Knorr et al (1997) <sup>58</sup>      | BDP 252 µg/d<br>+1.03                      | 4 mo<br>NS                                                                      | Montelukast 5 mg/d<br>+0.75                                              |
| Chervinsky et al (1997) <sup>62</sup> | BDP 336 µg/d<br>Significant                | 12 wk                                                                           | Pranlukast<br>600 mg NS<br>900 mg Significant                            |

NA, Statistical analysis not available; NS, not statistically significant; FP, fluticasone propionate.

the improvement in FEV<sub>1</sub> was greater with BDP. In one study the differences were significant and in one not significant; and in 4, statistical comparisons were not given. PEFs were significantly improved with BDP compared

with zafirlukast in the 2 studies in which they were reported. BHR also improved to a statistically more significant degree in the one study in which statistical analysis was provided. Symptoms of asthma and β<sub>2</sub>-agonist

use were improved more with BDP in 2 studies. In a third study the results were better with BDP than with 600 mg of pranlukast, but better results were achieved with a 900-mg dose of pranlukast than with BDP. When statistical analysis was provided, difference in symptoms was significant in one study favoring BDP but not in the other. Finally, BDP was associated with an improved quality of life over the comparator LTD<sub>4</sub> antagonists in 2 studies in which values were reported. In one case no statistical comparison was provided; in one case the difference was not significant; and in one case BDP significantly improved the quality of life, whereas the lower dose of LTD<sub>4</sub> antagonist did not. There was no statistical comparison provided in any of the studies that favored the LTD<sub>4</sub> antagonist over BDP.

### **EFFECT OF LONG-TERM-CONTROL MEDICATIONS ON ASTHMA SYMPTOMS WHEN ADDED TO ICS**

In addition to consideration as an alternative to ICS at step 2 (ie, mild persistent asthma) of the EPR-2 Guidelines, the long-term-control medications may also be appropriate as add-on therapy in patients already receiving ICS in steps 3 and 4 (ie, moderate persistent and severe persistent asthma, respectively). There is evidence that each of the alternative long-term-control medications, except cromolyn, can be used in this manner to improve asthma control and to reduce the dose of ICS.

#### **Cromolyn sodium**

Four reported studies failed to show reduction in ICS therapy when cromolyn was added.<sup>63-66</sup>

#### **Nedocromil sodium**

Svendsen and Jørgensen<sup>67</sup> evaluated 35 patients with asthma in a randomized, double-blind, placebo-controlled, parallel-group study of inhaled nedocromil, 16 mg daily, as an additional treatment to high-dose (1000 µg) ICS. Statistically significant treatment differences in favor of the addition of nedocromil were observed in morning PEF and daytime symptoms during weeks 5 through 8, and for overall clinical opinion. These findings suggest that the addition of nedocromil to an ICS regimen in patients with moderate to severe asthma can produce improvements in symptom control and pulmonary function.

O'Hickey and Rees,<sup>68</sup> in a double-blind, placebo-controlled trial, evaluated the effect of nedocromil, 32 mg/d, in patients receiving ICS at doses up to 1000 µg/d. Over a 6-week treatment period with nedocromil or placebo, only asthma symptoms and physician opinion favored nedocromil, with morning PEF approaching statistical significance. Wong et al<sup>69</sup> assessed the steroid-sparing potential of inhaled nedocromil (16 mg/d) in a randomized, double-blind, placebo-controlled study of 69 subjects with asthma controlled with inhaled BDP in the dose range of 1000 to 2000 µg daily over a 4-week period. Nedocromil permitted reduction of the ICS dose by

80% versus placebo (65%), but the comparison did not reach statistical significance.

Several other studies attempted to evaluate the ability to reduce the oral steroid dose on addition of nedocromil therapy. Goldin and Bateman<sup>70</sup> evaluated the steroid-sparing effect of nedocromil in 50 adult patients with asthma. There was no difference in the ability to reduce oral prednisolone in the comparison of nedocromil with placebo; and no significant change in symptoms, lung function, or inhaler use was observed in either group. Using a similar study design, Boulet et al<sup>71</sup> examined the efficacy of nedocromil as an oral steroid-sparing agent in a group of 37 patients with severe, oral steroid-dependent asthma, all receiving daily or alternate-day prednisone. These adult patients with asthma were followed up for 12 weeks to determine whether the oral steroid dose could be reduced in a comparison of nedocromil, 16 mg daily, and placebo. The nedocromil group achieved a greater reduction in oral steroid dose: 8 totally eliminated use of oral steroids compared with none in the placebo group. There was a reduction of 4.6 mg per day in the oral prednisone dose for the nedocromil group versus a reduction of 2 mg per day prednisone for the placebo group.

Marin et al<sup>72</sup> evaluated the effect of nedocromil in 26 patients with steroid-resistant asthma in a randomized, double-blind, placebo-controlled trial. They reported that nedocromil, 16 mg daily, but not placebo, resulted in a mean increase in FEV<sub>1</sub> of 11.4% after 12 weeks of therapy ( $P = .05$ ) and of 12.4% ( $P = .04$ ) and 15% ( $P = .02$ ) in morning PEF after 8 and 12 weeks of treatment, respectively. Six of the 12 patients treated with nedocromil who completed the treatment showed a "good response," defined as a reduction in albuterol use of 50% and an increase in morning PEF of more than 20% from baseline; however, there were no clinical predictors of this response.

Nedocromil, either in addition to the ICS dose or in conjunction with a reduced ICS dose, may add some beneficial effects for certain parameters of efficacy in patients with moderately severe asthma. However, its effect is not remarkable, and the response varies between studies.

#### **Methylxanthines**

Theophylline, when added to either an inhaled or alternate-day oral corticosteroid therapy regimen, has been demonstrated to decrease symptoms, improve pulmonary function, and decrease the requirement for additional oral steroids.<sup>73</sup> When long-term administration of theophylline was discontinued in a group of patients, there was a significant increase in symptoms and decrease in pulmonary function, despite the patients' continuing use of ICS (mean dose, 1500 µg/d).<sup>19</sup> When a group of patients with asthma began receiving either budesonide, 800 µg/d, plus theophylline or budesonide alone at a dose of 1600 µg/d, both PEF and spirometry measurements increased more in the group receiving theophylline plus the lower dose of ICS. However, there was no difference in the requirement of the 2 groups for inhaled  $\beta_2$ -agonist rescue medication.<sup>74</sup>

## Long-acting $\beta_2$ -agonists

For patients who have inadequate control of symptoms with ICS alone, 2 large studies have compared the results of doubling or more than doubling the dose of ICS or of adding the long-acting inhaled  $\beta_2$ -agonist salmeterol.<sup>75,76</sup> In each study the standard parameters of asthma control—daytime and nighttime symptoms, use of rescue  $\beta_2$ -agonists, and pulmonary function test results—indicated greater control of asthma with the combination of lower-dose ICS and salmeterol therapy than with higher-dose ICS alone.

In a study comparing 2 doses of budesonide with and without the addition of the long-acting  $\beta_2$ -agonist formoterol, the long-acting inhaled  $\beta_2$ -agonist decreased the number of both mild and severe exacerbations of asthma and provided improved levels of pulmonary function when added to budesonide (at either dose level).<sup>77</sup>

## Leukotriene pathway modifiers

Patients receiving moderately high-dose ICS had their dose halved and then were randomized to either pranlukast, an LTD<sub>4</sub> antagonist, or placebo.<sup>78</sup> Although the asthma control in patients receiving placebo deteriorated progressively over the following 6 weeks, patients receiving pranlukast continued to experience control as well as they did with the higher dose of ICS. Particularly striking was the increase in 2 markers of airway inflammation—serum eosinophil cationic protein and exhaled nitric oxide—in the placebo group, which was largely blocked by the addition of pranlukast.

Patients who had symptoms while receiving BDP, 336  $\mu\text{g}/\text{d}$ , were randomized to 13 weeks of treatment with either BDP, 336  $\mu\text{g}/\text{d}$ , plus either zafirlukast, 40 or 80 mg/d, or BDP, 672  $\mu\text{g}/\text{d}$ . Both doses of zafirlukast plus low-dose inhaled BDP were as effective in improving symptom control and PEF as was the higher dose of BDP.<sup>79</sup> These studies differ from studies of the addition of long-acting inhaled  $\beta_2$ -agonists to BDP or to budesonide, in which the addition proved more efficacious than the doubling of the ICS dose.

## EVIDENCE OF FAVORABLE TRENDS IN HEALTH STATISTICS ASSOCIATED WITH INCREASED USE OF ICS

### Increased use of ICS results in decreased hospitalization rates for asthma

In a study by Gottlieb et al,<sup>80</sup> asthma hospitalization rate was positively correlated with poverty rate and proportion of nonwhite residents and inversely correlated with the ratio of inhaled anti-inflammatory (steroids and cromolyn/nedocromil) to  $\beta_2$ -agonist medication use ( $r = .55$ ,  $P = .008$ ). The investigators concluded that underuse of inhaled anti-inflammatory medication may be one of the many factors that contributes to excess hospitalization for treatment of asthma in the economically disadvantaged population.

In a study by Vollmer et al,<sup>81</sup> it was observed that patients treated by allergists tended to have more severe

asthma ( $P < .01$ ), to be older, to have a higher incidence of atopy, and to have perennial rather than seasonal asthma. In addition, patients cared for by an allergist were considerably more likely than generalists' patients to report use of inhaled anti-inflammatory agents ( $P < .01$ ) regardless of the degree of asthma severity (mild, 69% vs 43%; moderate-to-severe, 92% vs 42%). Allergists' patients were also more likely to have received their most recent medical care for an asthma exacerbation in a clinic rather than an emergency department or hospital ( $P < .01$ ) (mild, 14% vs 29%, respectively; moderate-to-severe, 23% vs 33%, respectively). They also reported significantly better quality of life, as measured by several dimensions of the Short Form General Health Survey (ie, the SF-36 scale).

Donahue et al<sup>82</sup> retrospectively evaluated the use of ICS and the risk of hospitalization for treatment of asthma over a 3-year period. Of 16,941 eligible persons with asthma, 742 (4.4%) were hospitalized because of asthma. The overall relative risk (RR) of hospitalization among those who received ICS was 0.5 (95% CI, 0.4–0.6), a 50% reduction. Cromolyn was also associated with reduced risk, especially among children (RR, 0.8; 95% CI, 0.7–0.9).

It was concluded that ICS and, to a lesser extent, inhaled cromolyn confer significant protection against exacerbations of asthma leading to hospitalization. These results support the use of ICS by individuals who require more than occasional  $\beta_2$ -agonist use to control asthma symptoms.

In a study of Swedish children with asthma, aged 2 to 18 years, Wennergren et al<sup>83</sup> reported that the number of asthma hospital days per year gradually decreased to less than one third ( $P < .001$ ) and asthma admissions decreased by 45% ( $P < .05$ ) during the period from 1985 to 1993. The changes were most marked in those children older than 5 years of age. The major reason for the decrease in asthma hospitalization in children aged 2 to 18 years was attributed to the increased use of anti-inflammatory treatment with ICS in Sweden. Studies are not available for any of the other medications with anti-inflammatory properties.

### Increased use of ICS results in decreased deaths from asthma

Ernst et al<sup>84</sup> evaluated the risk of fatal and near-fatal asthma in relation to ICS use. After accounting for the risk associated with the use of other medications and adjusting for markers of risk of adverse events related to asthma, Ernst et al<sup>84</sup> found that subjects who had been dispensed, on average, one or more metered-dose inhalers of BDP per month over a 1-year period had a significantly lower risk of fatal and near-fatal asthma (odds ratio, 0.1; 95% CI, 0.02–0.6). These data support recent guidelines from several countries, which recommend the use of ICS in patients with moderate and severe asthma.

Campbell et al<sup>85</sup> examined an age-specific trend in the asthma-related mortality rate between 1983 and 1995 in England and Wales, concluding that deaths in age groups 5 years to 74 years peaked before 1989 and then showed

a downward trend. Deaths in the group aged 75 to 84 years peaked between 1988 and 1993 and subsequently dropped. All trends were highly statistically significant. These downward trends in asthma-related mortality rates in Britain may be related to increased use of prophylactic treatment.

## SUMMARY

Recent guidelines have supported the use of ICS as the preferred long-term-control medication. Nonsteroidal long-term-control medications are available but remain alternatives to ICS. To date, all of these medications show most often lesser, at the most equivalent, but never greater effects than ICS. In most of these studies, the ICS were used at low- to moderate-dose ranges, and it is assumed that the effect of ICS could have been greater with higher doses. The nonsteroidal long-term-control medications do seem to play a role in supplementing ICS and even in facilitating a reduction in high-dose corticosteroid therapy. These adjunct effects may reduce the need for high-dose ICS, as well as the potential concern associated with long-term use of higher steroid doses. Future studies demonstrating the effect of these combinations on reducing airway inflammation would be supportive of the clinical data.

Although cromolyn and nedocromil are recognized as very safe long-term-control medications, they are most effective in patients with mild-to-moderate persistent asthma. Only nedocromil has been shown to be effective in facilitating a reduction in ICS dosages during concomitant therapy. Cromolyn and nedocromil are considered safe alternatives to ICS for first-line intervention in young children; however, long-term studies are needed to determine whether they are as effective as ICS in preventing irreversible changes in pulmonary function.

Theophylline was considered the preferred first-line-control medication in the late 1970s and 1980s. However, the recognition of the benefits of ICS and the potential significant adverse effects associated with theophylline resulted in a subsequent change in the direction of pharmacologic management away from theophylline. In some studies theophylline has shown clinical equivalence to ICS and has also had an effect on some of the inflammatory cells. With the introduction of leukotriene antagonists with a similar spectrum of beneficial effects (eg, oral, long-acting, immediate effects on pulmonary function and feasibility of once-daily dosing), it appears that theophylline use will continue to decline. Theophylline remains a valuable supplement to ICS therapy, especially in patients with moderate-to-severe persistent asthma.

As previously mentioned, the leukotriene modifiers offer a significant challenge to ICS as a preferred medication, especially with the development of once-daily formulations. The increased use of these medications will determine whether the safety profile claim is sustained. It is also important to conduct studies to determine the effects of long-term use on asthma outcomes, especially pulmonary function and

modulation of inflammatory cells. Studies are needed to determine whether leukotriene modifiers can be as effective as ICS in preventing irreversible changes in pulmonary structure and function. As with the other alternative long-term-control medications, a major use for the leukotriene modifiers may be in combination with ICS to allow more effective asthma control with lower steroid doses.

The role for long-acting bronchodilators (salmeterol and formoterol) as controllers appears to be as additive to ICS. These medications demonstrate no significant anti-inflammatory effect but do increase lung function.

## Prospectus

At present, ICS have set the gold standard for long-term-control therapy by clearly demonstrating an effect on reducing inflammation. In addition, studies with ICS in asthma therapy demonstrate decreased hospitalization rates, reduced need for rescue therapy, improved pulmonary function, and altered BHR. ICS have also been shown to reduce subepithelial fibrosis considered to be secondary to collagen deposition. To date, no other asthma medication has shown the extent or degree of clinical improvement noted with ICS.

The recent National Heart, Lung, and Blood Institute guidelines have recommended the institution of long-term-control therapy earlier in the course of disease. In severe asthma, the use of high-dose ICS is justified because the alternative use of systemic steroids has a greater potential for adverse effects. In mild asthma, the use of low-dose ICS appears to have a good therapeutic index, but long-term studies are necessary to alleviate lingering concerns regarding the risk for systemic effects. Cromolyn and nedocromil appear to have some of the clinical benefits of ICS, but these effects are generally less pronounced. The long-term safety of these medications is generally recognized. Theophylline does have some anti-inflammatory effects and remains a potential alternative or supplemental medication. Leukotriene modifiers appear to have less efficacy than ICS. Their effect on long-term modulation of airway inflammation and long-term safety await further study. The 1997 National Heart, Lung, and Blood Institute Guidelines identify ICS as preferred treatment for persistent asthma. The review of the evidence from clinical trials to date confirms this recommendation.

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