

# Asthma: Addressing consistency in results from basic science, clinical trials, and observational experience

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The basic science understanding of the pathophysiology of a disease often serves as the basis for clinical investigations. This knowledge is used to propose new directions in care and confirm initial concepts. The basic science of asthma demonstrates that the most comprehensive management of inflammation appears to be associated with the use of inhaled corticosteroids and proposes a mechanism for combination therapy with the addition of salmeterol. Randomized clinical trials are performed to confirm these initial observations and demonstrate both the safety and efficacy of therapeutic agents. These investigations are either placebo-controlled or direct comparisons of 2 medications. For the treatment of asthma, these studies have all consistently demonstrated that inhaled corticosteroids are the most effective primary controller therapy. Greater improvement in both lung function and patient-oriented symptom control is observed with the use of inhaled corticosteroids. For patients whose symptoms are not controlled with single-drug therapy, the addition of a long-acting bronchodilator appears to be the most effective add-on treatment with the greatest improvement in lung function and symptom control. Clinical trials have been used for the purposes of cost modeling. Therapies that produce the greatest effect size at the lowest incremental costs produce the greatest improvement in cost-effectiveness. Retrospective claims analysis, more recently, have been used to validate these observations from clinical trials. These studies measure both resource use and costs or charges. These analyses have confirmed that initial treatment with inhaled corticosteroids and combined treatment with inhaled corticosteroids and long-acting bronchodilators are the most effective stepwise approaches to the treatment of asthma. (*J Allergy Clin Immunol* 2002;109:S490-S502.)

**Key words:** *Asthma, bronchodilators, corticosteroids*

Asthma is defined as “a lung disease with the following attributes: (1) airflow obstruction that is reversible, either spontaneously or with treatment; (2) airway inflammation; and (3) increased airways responsiveness

## Abbreviations used

|        |                                           |
|--------|-------------------------------------------|
| BAL:   | Bronchoalveolar lavage                    |
| BDP:   | Beclomethasone dipropionate               |
| bid:   | Twice daily                               |
| ICS:   | Inhaled corticosteroid                    |
| LT:    | Leukotriene                               |
| LTRA:  | Leukotriene receptor antagonist           |
| NHLBI: | National Heart, Lung, and Blood Institute |
| PEFR:  | Peak expiratory flow rate                 |

to a variety of stimuli.” The principles of the basic science of asthma have led to the development of therapeutics to modify and potentially reverse the pathophysiology of this disease. Over the past 10 years, great strides have been made in researching therapies that attempt to achieve the goals established by the National Heart, Lung, and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma.<sup>1</sup> The goals are as follows:

1. Maintain (near) “normal” pulmonary function
2. Maintain normal activity levels (including exercise and other physical activity)
3. Prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the night, in the early morning, or after exertion)
4. Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
5. Provide optimal pharmacotherapy with minimal or no adverse effects
6. Meet patients’ and families’ expectations of and satisfaction with asthma care

In summary, the objective of management is to control asthma effectively and safely and minimize the impact of the disease on an individual’s daily life by reducing symptoms and exacerbations. Asthma is defined as a chronic inflammatory disease, characterized by reversible airflow obstruction, wheezing, and heightened airway responsiveness (or “twitchiness”) to a variety of stimuli. These 3 components are interrelated in a complex manner. Guidelines recommend that an inhaled corticosteroid (ICS) be used as the initial management of persistent asthma for most patients. Cromolyn sodium, nedocromil, leukotriene antagonists, and sustained-release theophylline have been considered as alternative maintenance medications for persistent asthma. Not all patients respond to single con-

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troller therapy with an ICS; for this reason, additional maintenance medications are recommended. For patients with persistent asthma who are unable to achieve the goals of therapy with an ICS alone, one option is the addition of an inhaled, long-acting  $\beta_2$ -agonist. Other options include increasing the dose of the ICS or adding a leukotriene antagonist or long-acting theophylline to the baseline ICS dose.

As discussed elsewhere in this supplement, the selection of a medication is based on evidence demonstrating the best therapeutic index. Although much has been written about therapies that may be more effective for patients with a specific genotype,<sup>2</sup> there are limited data at present to support this approach and no means of identifying appropriate patients. Determining who will respond to an asthma medication and the best medication for a particular patient are the topics of much research in the field of pharmacogenetics.

At present, there are 3 fundamental areas of research that should be taken into account when a therapeutic decision is formulated. First, does the basic science conceptually support the clinical approach? Second, is the science confirmed by the randomized clinical trials? (For example, there are many excellent scientific hypotheses that do not make it from the bench to practice.) Third, does rigorous analysis of clinical experience support the conclusion of the science and randomized clinical trials? Clinical experience can be rigorously evaluated when formal methodology and statistical analysis are applied.

## PATHOPHYSIOLOGY OF ASTHMA

Although the science of asthma has progressed significantly since the publication of the 1997 NHLBI asthma guidelines, the components and basic understanding of asthma have not changed. This consensus document therefore serves as a good platform for the discussion about the pathophysiology of asthma.

Asthma is a disease in which smooth muscle dysfunction and airway inflammation combine to result in airflow obstruction and airways hyperresponsiveness.<sup>1</sup> Although the process is incompletely understood, inflammatory cells such as T lymphocytes, eosinophils, and mast cells are recruited into the airways of patients with asthma. A large number of studies in which bronchoscopy with airway biopsy was performed have provided evidence for T-lymphocyte activation within the airways of subjects with asthma. The  $T_H2$  lymphocyte plays a critical role in the pathogenesis of asthma by producing cytokines involved in the initiation and maintenance of allergic inflammation. Cytokines produced by  $T_H2$  cells such as IL-3, GM-CSF, and IL-5 play a critical role in the differentiation, proliferation, survival, and activation of eosinophils.<sup>3-5</sup> Eosinophils, by virtue of their ability to secrete cytotoxic granule proteins and to produce lipid-derived proinflammatory mediators such as leukotriene C4 (LTC4), and platelet-activating factor, mediate much of the damage to the airway epithelium seen in chronic asthma.<sup>6</sup> IL-3 and, to a lesser extent, IL-4 are critical to the development of

mast cells, which play a prominent role in the acute-phase allergic response, whereas IL-4 and IL-13 are required for the isotype switch to IgE.<sup>7-9</sup> IL-1 and TNF- $\alpha$  are potent proinflammatory cytokines that are involved in the up-regulation of adhesion molecules on vascular endothelium, an essential step in the migration of leukocytes to sites of inflammation.

## T-cell activation

Over the past decade, a large body of literature has accumulated implicating inappropriate T-cell activation within the airways of patients with asthma. Numerous studies have documented elevated numbers of T cells within the bronchoalveolar lavage (BAL) fluid and within the epithelium and submucosa of patients with asthma compared with nonasthmatic subjects. In a landmark study published in 1992, Robinson et al<sup>10</sup> performed bronchoscopy in 15 subjects with mild atopic asthma and 10 nonatopic, nonasthmatic control subjects. Bronchoalveolar cells were isolated and evaluated for cytokine messenger RNA expression by means of in situ hybridization. When compared with the nonasthmatic control subjects, subjects with asthma had elevated numbers of T cells expressing mRNA for the classic  $T_H2$  cytokines GM-CSF, IL-3, IL-4, and IL-5. This study was among the first to demonstrate activation of  $T_H2$  cells in patients with chronic asthma. A follow-up study sought to determine whether activation of  $T_H2$  cells also contributed to poorly controlled asthma.<sup>11</sup> The investigators found a relationship between up-regulation of proinflammatory cytokines and poorly controlled asthma. These studies enhanced our understanding of the mechanism of glucocorticoids as an effective therapy for asthma because of their inhibition of the production of cytokines involved in the pathogenesis of airway inflammation (see below).

## Role of eosinophils

Eosinophils have long been known to be associated with asthma. Horn et al<sup>12</sup> were among the first researchers to describe this relationship more than 25 years ago, when they reported an inverse relationship between lung function and the number of circulating eosinophils among adults with moderate to severe asthma. Since then, numerous studies have further strengthened the concept that activated eosinophils contribute to airway epithelial damage and associated lung function abnormalities. In another landmark publication, Bousquet et al<sup>13</sup> found eosinophilia within the BAL fluid, lung tissue, and circulation among the patients with asthma they studied. In addition, eosinophilia was associated with multiple parameters of asthma disease severity, including clinical severity and lung function abnormalities. Other studies have also shown significant correlations between airway eosinophils and lung function, peak expiratory flow rate (PEFR) variability, and bronchial hyperresponsiveness.<sup>14</sup> In summary, the predominance of data suggests that the greater the number of airway eosinophils, the greater is the degree of airflow obstruction and level of bronchial hyperresponsiveness. When

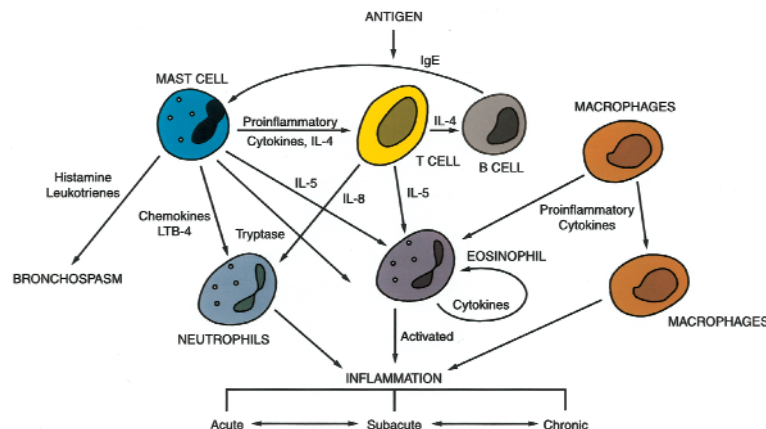


FIG 1. Allergic inflammatory process in patients with asthma.<sup>1</sup>

eosinophils are activated by cytokines such as IL-5 and GM-CSF, they release several cytotoxic proteins (including major basic protein and eosinophilic cationic protein), which results in airway epithelial desquamation and heightened bronchial responsiveness.<sup>15</sup> The strength of these findings is the concordance of physiologic and pathologic parameters.

### Epithelial cell disruption

The airway epithelium also plays an important role in the pathogenesis of asthma. The epithelium normally has a protective role as a barrier to inhalation of noxious compounds. With epithelial cell disruption, as seen in asthma, this airway defensive function is undermined and may contribute to heightened bronchial responsiveness. Jeffery et al<sup>16</sup> evaluated the relationship between the degree of epithelial cell disruption or desquamation and the degree of bronchial hyperresponsiveness. These investigators found a significant, direct correlation between increased epithelial desquamation and increased bronchial hyperresponsiveness. The epithelium also contributes to airway inflammation and subsequent airway remodeling or repair. Damaged airway epithelial cells produce cytokines, such as GM-CSF,<sup>17</sup> that further contribute to airway inflammation by activating eosinophils, the cells believed to cause the initial epithelial cell damage. Thus, the interplay between recruited inflammatory cells and resident cells, as in the airway epithelium, results in the complex allergic inflammatory process noted in patients with asthma, as shown in Fig 1.<sup>1</sup>

### Smooth muscle dysfunction and airway inflammation/remodeling

Smooth muscle dysfunction and airway inflammation are distinct, yet interrelated, aspects of the abnormalities seen in asthma.<sup>1</sup> For example, airway inflammation contributes directly and indirectly to bronchoconstriction and airway hyperresponsiveness.<sup>18</sup> Inflammation and the release of inflammatory mediators significantly contribute to bronchial hyperresponsiveness. In addition, airway edema contributes to chronic airflow obstruction.

Conversely, airway smooth muscle cells can release mediators that contribute to the inflammatory response within the airways. Asthma can be triggered by a multitude of agents, including allergens, viral infections, and airway irritants, that induce inflammation and produce both airway hyperresponsiveness and airflow obstruction (Fig 2).<sup>1</sup> Airflow obstruction in asthma results from one of a number of events, including acute bronchoconstriction, airway edema, mucus plug formation, and airway remodeling.

Other pathologic findings in an asthmatic airway, including thickening of the basement membrane or lamina reticularis, goblet cell hyperplasia, neovascularization, and smooth muscle hypertrophy and hyperplasia,<sup>19,20</sup> appear to occur as part of the reparative process associated with chronic inflammation. Only recently has attention been focused on the reparative processes involved in chronic asthma. The term *airway remodeling* has been coined to describe this process in patients with asthma. Patients with asthma and "remodeled" airways display thickened basement membranes, goblet cell hyperplasia, and smooth muscle hypertrophy. Although not proven, airway remodeling may eventually result in a fixed obstructive, or irreversible, lung disease. The concern regarding the eventual development of fixed airflow obstruction has led many investigators to recommend early intervention with anti-inflammatory agents in an attempt to prevent the need for repair and airway remodeling.

Despite great interest in this topic, there is a paucity of published literature on airway remodeling and its relationship to asthma severity. In one of the most thought-provoking studies to date, Chetta et al<sup>21</sup> performed bronchoscopy with bronchial biopsies in 27 patients with asthma. These investigators found an inverse association between basement membrane thickness (their measure of the severity of airway remodeling) and FEV<sub>1</sub> and methacholine PC<sub>20</sub> values. In addition, PEFR variability increased as basement membrane thickness increased. In a follow-up study, the same investigators found a direct association between clinical asthma severity score and thickness of the basement membrane.<sup>22</sup> In addition, all

the patients with asthma displayed significantly thickened basement membranes when compared with nonasthmatic control subjects. Even patients with mild asthma had a significant, 3-fold greater basement membrane thickening when compared with the nonasthmatic control subjects.

Airway remodeling may contribute to the response to ICS therapy. In 2 studies published several years ago, one in children and the other in adults,<sup>23,24</sup> the investigators made the intriguing observation that the longer an individual had asthma before institution of ICS therapy, the smaller was the improvement in pulmonary function after institution of therapy. Although neither group of investigators used bronchoscopy and biopsy to evaluate the airway, the implication is that the longer airway inflammation is unchecked before institution of ICS therapy, the more likely it is that airway remodeling has occurred and the less likely it is that the individual will respond to therapy. In summary, the available evidence suggests that airway remodeling occurs even in patients with mild asthma, and the magnitude of these changes is associated with disease severity. It should be stressed that our understanding of this complex issue remains incomplete, and further investigation is warranted.<sup>25,26</sup> Advances in our knowledge of the basic science of asthma allow for the development of more rational and effective therapies.

## EFFECTS OF ASTHMA THERAPIES

### Glucocorticoids

As discussed previously, the inflammatory response in asthma is associated with the production of cytokines, the up-regulation of adhesion molecules on both leukocytes and vascular endothelium, the influx of inflammatory cells into the airway, and the production of mediators of inflammation including histamine, leukotrienes, prostaglandins, platelet-activating factor, and the eosinophil-derived basic proteins.<sup>27</sup> Glucocorticoids have profound inhibitory effects on nearly every aspect of this inflammatory response. Although incompletely understood, the anti-inflammatory effects of glucocorticoids likely come from their ability to inhibit the transcription of cytokines. By inhibiting the production of essentially all the cytokines involved in allergic inflammation, these agents can significantly suppress the inflammatory response. Specifically, in vitro exposure to glucocorticoids results in inhibition of the production of IL-1,<sup>28</sup> IL-2,<sup>29</sup> IL-3,<sup>30</sup> IL-4,<sup>31,32</sup> IL-5,<sup>33,34</sup> IL-6,<sup>35</sup> IL-13, GM-CSF,<sup>36</sup> and TNF- $\alpha$ .<sup>37</sup> Many, if not all, of these cytokines are believed to be involved in airway inflammation.

Studies evaluating the effect of ICS therapy on allergic inflammation in patients with asthma have often used bronchoscopy with BAL and/or endobronchial biopsy before and after a course of ICS therapy. One of the first controlled studies evaluated the effect of budesonide (1200  $\mu$ g/d) or terbutaline for 3 months on airway inflammation in 14 adult patients with asthma.<sup>38</sup> Budesonide was associated with an increase in the number of intact ciliated epithelial cells lining the airway epithelium and a reduction in the number of eosinophils within the airway

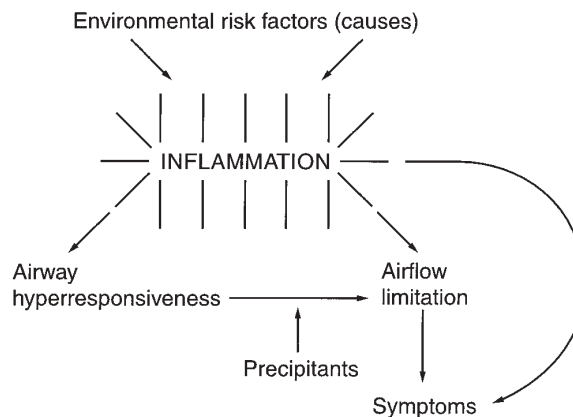


FIG 2. Triggers of asthma.<sup>1</sup>

epithelium. Reductions in the number of eosinophils and activated T lymphocytes (CD25<sup>+</sup>) obtained from BAL fluid of patients with asthma treated with high-dose beclomethasone dipropionate (BDP) have also been noted.<sup>39</sup> A recent placebo-controlled study by Trigg et al<sup>40</sup> evaluated the effect of high-dose BDP therapy (1000  $\mu$ g/d) for 4 months in a group of 25 patients with mild asthma. These investigators found significant reductions in tissue eosinophils, diminished epithelial expression of GM-CSF, and a reduction in the thickness of the lamina reticularis with BDP compared with placebo.

Fluticasone propionate has also been shown to result in significant reductions in airway inflammatory cells and mediators of inflammation from both BAL fluid and airway tissue of adults with asthma.<sup>41</sup> Even short-term (6-week), low-dose fluticasone propionate (500  $\mu$ g/d) resulted in reduced airway inflammation.<sup>42</sup> Associated with the decrease in airway inflammation was a reduction in the thickness of the lamina propria, suggesting that fluticasone propionate can also modulate the intensity of airway remodeling. These studies demonstrated a parallel between resolution of the pathologic changes of asthma and an improvement in the physiologic parameters of lung function and bronchial hyperresponsiveness.

Exhaled nitric oxide levels are often elevated in patients with asthma and may serve as a noninvasive marker of allergic inflammation. In a 3-week study, exhaled nitric oxide levels fell from 203 to 120 ppb with budesonide (1600  $\mu$ g/d) but remained unchanged with placebo.<sup>43</sup> Therapy with ICS also down-regulates T-lymphocyte activation in the peripheral blood of patients with asthma.<sup>44</sup> Of interest, ICS therapy has also been shown to be effective in “repairing” the disruption in the airway epithelium in adults with recently diagnosed asthma.<sup>38</sup> In addition, ICS may prevent dysfunction of  $\beta_2$ -adrenergic receptors by inhibiting the release of cytokines.<sup>45</sup> Laboratory data suggest that the regular use of glucocorticoids may allow  $\beta_2$ -agonists to be more effective by protecting against  $\beta_2$ -receptor down-regulation and the development of tolerance to  $\beta_2$ -agonists.<sup>46</sup>

In summary, ICS therapy is very effective in inhibiting airway inflammation, with reductions in mediator and

cytokine production and release, as well as inhibition of inflammatory cell infiltration into airway submucosa and epithelium. Clinical improvement (in terms of the degree of bronchial hyperresponsiveness and baseline lung function) is associated with reductions in airway inflammation. In addition, preliminary data suggest that ICS therapy can reduce the thickness of the lamina reticularis and possibly attenuate airway remodeling. These data support the hypothesis that ICSs act topically by suppressing allergic inflammation, and with suppression of inflammation, comes improved asthma control. Further study is needed to determine whether early intervention with ICSs can prevent airway remodeling.

### Leukotriene-modifying agents

Leukotrienes are potent lipid-derived mediators of inflammation produced and released from eosinophils, mast cells, and basophils. The cysteinyl leukotrienes are potent bronchospastic agents, stimulate mucus production, and result in increased vascular permeability.<sup>47</sup> In animal models, leukotrienes are chemotactic agents involved in the recruitment of proinflammatory cells into the airway. Whether leukotrienes serve as chemotactic agents in humans has been a matter of debate. Mulder et al<sup>48</sup> sought to address this issue by performing inhalation challenges with a number of agents, including methacholine, LTD<sub>4</sub>, and allergen, in adults with asthma. All agents resulted in significant bronchoconstriction within minutes of the inhalation challenge. Inhalation of LTD<sub>4</sub> resulted in a >30% drop in FEV<sub>1</sub> within minutes of inhalation and a spontaneous return to near-baseline lung function after 60 minutes. The study participants then underwent serial induced sputum challenges over a 24-hour period with evaluation of sputum eosinophilia. Somewhat surprisingly, although LTD<sub>4</sub> was associated with significant bronchospasm, it was not associated with the influx of eosinophils during the ensuing 24-hour period. In contrast, allergen inhalation was associated with both bronchospasm and subsequent airway eosinophilia. The investigators concluded that although LTD<sub>4</sub> causes bronchospasm, it did not induce the influx of inflammatory cells associated with the development of a late-phase allergic response.

The extent of the anti-inflammatory effects profile of the leukotriene-modifying agents has yet to be determined. Although leukotriene receptor antagonists (LTRAs) have been researched over the past 2 decades, their shorter time of commercial availability may explain the limited literature on their anti-inflammatory effects when compared with the data on ICSs. To date, there is only one published biopsy study with pranlukast (an LTD<sub>4</sub> receptor antagonist not available in the United States) demonstrating significant reductions in airway inflammation in adults with asthma.<sup>49</sup> Two recent studies in children with asthma have demonstrated that montelukast reduces exhaled nitric oxide levels.<sup>50,51</sup> The available data suggest that the major action of the LTRA is to provide bronchoprotection rather than broad anti-inflammatory effects. Therapy with LTRA is targeted at

blocking the airway leukotriene receptors.<sup>52</sup> In clinical studies of montelukast, patients with asthma have exhibited modest improvement in lung function, as well as a reduction of symptoms.<sup>53,54</sup>

Although there have been only a few studies comparing the efficacy of an ICS with that of a leukotriene-modifying agent, these investigations have consistently shown that ICSs are more effective in terms of improving baseline lung function, improving symptom control, and reducing bronchial hyperresponsiveness.<sup>55,56</sup> The ICSs generally result in a 10% to 15% improvement in baseline lung function (as reviewed by Spahn and Szefer<sup>55</sup>), whereas LTRAs such as montelukast result in a 5% to 7.5% improvement in FEV<sub>1</sub> values.<sup>51-53</sup> In a well-designed, randomized, placebo-controlled study by Malmstrom et al,<sup>56</sup> the effectiveness of montelukast (10 mg/d), low-dose inhaled BDP (200 µg, administered twice daily [bid] with a spacer device), and placebo was studied in nearly 900 adults with chronic asthma for 12 weeks. Lung function (FEV<sub>1</sub>) improved by 13.1% with BDP as compared with 7.4% with montelukast and 0.7% with placebo. In addition, both BDP and montelukast were associated with significant improvements in PEF, symptom scores, quality-of-life measurements, and reduced nocturnal asthma symptoms. The clinical effect for all of these outcomes was significantly greater with BDP than with montelukast ( $P < .01$ ). The latter agent had a more rapid initial effect observed during the first 2 days. In a recent study in which low-dose fluticasone and montelukast were compared in adults with moderate asthma, Busse et al<sup>57</sup> reported results consistent with those of the study by Malmstrom et al, which demonstrated greater lung function improvement and clinical outcomes in those patients treated with fluticasone (see Table I). All of the present clinical trials demonstrate a smaller effect size of the targeted therapy with an LTRA compared with the more broad-spectrum approach of the ICSs.

### β<sub>2</sub>-Agonists

Long-acting inhaled β<sub>2</sub>-agonists, such as salmeterol xinafoate and formoterol fumarate, are potent bronchodilators. The primary role of these agents in asthma management is as add-on therapy to ICSs. Although the NHLBI guidelines classify β<sub>2</sub>-agonists as being included in the controller class of asthma medications, these agents are not recommended as primary maintenance medications. Even though β<sub>2</sub>-agonists have not been regarded as primary anti-inflammatory medications for asthma, long-acting inhaled β<sub>2</sub>-agonists may exert a positive effect on certain aspects of the inflammatory response in asthma, such as inhibition of microvascular leakage<sup>46</sup> and potentiation of eosinophil cell death caused by ICSs.<sup>58</sup> The combination of ICS and long-acting β-agonists has been demonstrated to be more effective than doubling the dose of ICS. Recent bench research suggests that β<sub>2</sub>-agonists can activate the glucocorticoid receptor in primary human lung fibroblasts and vascular smooth muscle cells.<sup>59</sup> With activation comes heightened translocation of the glucocorticoid receptor

complex into the nucleus and subsequent enhanced binding to glucocorticoid response elements. Although the concept is speculative, enhanced glucocorticoid response element binding may explain the clinical synergistic effects when long-acting  $\beta$ -agonists and ICSs are used in combination.

### Theophylline

Sustained-release theophylline was used extensively in the treatment of asthma in the 1980s. As safer and more effective medications have been developed, theophylline is now considered an alternative to other controller medications. Although theophylline exhibits some evidence of an anti-inflammatory effect,<sup>60,61</sup> it functions primarily as a bronchodilator and is now considered a secondary or tertiary alternative treatment because of its lower therapeutic index.

### Cromolyn sodium

The scientific basis for using cromolyn sodium in the treatment of asthma has produced many theories but little consensus. The literature on the efficacy of this agent is inconclusive. One published study demonstrated that zafirlukast and cromolyn sodium produce equivalent improvement in lung function and asthma symptom control.<sup>62</sup> However, a recent systematic review of all published, controlled trials failed to demonstrate significant improvement in lung function with cromolyn sodium as a maintenance medication for the treatment of asthma.<sup>63</sup> In the largest placebo-controlled trial in childhood asthma ever published, the Childhood Asthma Management Program, nedocromil was no more effective than placebo with regard to most efficacy parameters studied.<sup>64</sup> Although safe, the cromolyn/nedocromil class of asthma therapies is less effective than the ICS class.

### Summary: Controller therapy

What controller has the best therapeutic index for the management of persistent asthma? The NHLBI guidelines recommend low-dose ICS therapy with cromolyn sodium, theophylline, and the LTRAs as alternatives for patients with mild, persistent asthma. The basic science also supports this recommendation based on the extensive body of literature demonstrating the efficacy and broad anti-inflammatory effects of inhaled corticosteroids. In addition, studies demonstrating the long-term safety of the ICSs have finally been performed,<sup>64,65</sup> which should alleviate many of the concerns with respect to long-term use in children with mild, persistent asthma.

### EVIDENCE FROM RANDOMIZED CLINICAL TRIALS AND RETROSPECTIVE CLAIMS ANALYSES

The next level of evidence is consideration of the results of randomized clinical trials and companion retrospective claims analyses. Randomized clinical trials usually present measures of lung function (either FEV<sub>1</sub> or PEFR) as the primary endpoints. Patient-oriented out-

**TABLE I.** Fluticasone propionate benefits versus montelukast

| All changes from baseline          | Fluticasone | Montelukast |
|------------------------------------|-------------|-------------|
| Δ Morning FEV <sub>1</sub> (%)     | 21.9*       | 14          |
| Δ Daytime asthma symptom score     | -0.85*      | -0.60       |
| Δ Total $\beta_2$ -agonist use (%) | -61.0*      | -43.7       |
| Δ Morning PEFR (L/min)             | 68.5*       | 34.1        |
| Δ Evening PEFR (L/min)             | 53.9*       | 28.7        |
| Δ Nocturnal awakenings (%)         | -65*        | -50         |

Data from J Allergy Clin Immunol 2001;107:461-8.<sup>71</sup>

\*P < .001 fluticasone versus montelukast for each endpoint.

comes—including daytime and nighttime symptoms, need for rescue albuterol, and symptom-free days—are frequently used as the secondary endpoints. It is important to note that in most comparative studies, the medication that produces the greatest improvement in lung function is also the medication that produces the greatest improvement in secondary outcomes measured with symptom scores and use of short-acting  $\beta$ -agonists.

The prevention of recurrent exacerbations of asthma is a primary goal of the NHLBI guidelines. These events are infrequent in clinical trials but are observed more frequently in retrospective claims analysis. It is for this reason that both types of analyses are important. The importance of FEV<sub>1</sub> as a predictor of asthma exacerbations in children has been reported in a retrospective cohort analysis that assessed the association with several different models.<sup>66</sup> A strong association was apparent between the FEV<sub>1</sub> percent predicted and the risk of an asthma attack (Fig 3). The results of this study support the concept that appropriately designed and powered randomized clinical trials should parallel the findings of rigorous observational analysis. This analysis confirmed results of previous studies that support the use of physiologic measurements in the assessment of asthma.<sup>67,68</sup>

Randomized clinical trials have been the gold standard for the assessment of comparative efficacy of therapeutic agents. As discussed previously in this supplement, these trials are limited by the same attributes that contribute to their demonstration of internal validity, namely, well-defined populations and frequent monitoring of outcome parameters. Observational claims analyses have more generalizable populations and the ability to study patients over long periods, thus enabling the recording of less-frequent, but equally important, outcomes such as hospitalizations and emergency department visits. Observational analyses can therefore be used to complement and add robustness to the findings of randomized clinical trials.

### ICSs and LTRAs

By using an evidence-based approach, the second NHLBI Expert Panel Report on the diagnosis and management of asthma determined that inhaled glucocorticoids were the primary maintenance treatment for persistent disease.<sup>1</sup> Since the publication of these guidelines, LTRAs have become available. All data at the highest level of evidence (direct head-to-head, randomized, controlled

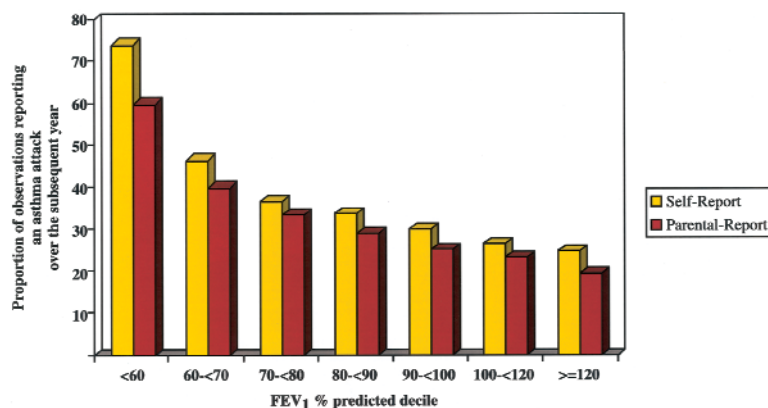


FIG 3. Association between FEV<sub>1</sub> percentage and risk of an asthma attack. (Reprinted with permission from J Allergy Clin Immunol 2001;107:61-7.<sup>66</sup>)

comparisons) have indicated that inhaled glucocorticoids are superior to the LTRAs for first-line maintenance therapy.<sup>56,69-71</sup> Two trials have compared fluticasone and zafirlukast and two have compared montelukast with inhaled fluticasone or beclomethasone. When the effect size in these reports is assessed, it is important to study the baseline characteristics, pre-randomization medication use, and statistical analyses performed.

In the study by Bleecker et al, patients randomly assigned to receive fluticasone had a 2-fold greater improvement in FEV<sub>1</sub> and 4-fold greater improvement in morning PEFR when compared with those who received zafirlukast.<sup>69</sup> The study subjects were symptomatic at the time of enrollment and were receiving inhaled  $\beta$ -agonists as needed. The magnitude of improvement in morning PEFR associated with fluticasone was irrespective of the subject's baseline FEV<sub>1</sub>. The greater effect size, 65% to 165% favoring fluticasone, was seen with all other clinical parameters, such as symptom-free days and nights and rescue-free days. Westbrook et al<sup>70</sup> assessed the effects of fluticasone and zafirlukast on bronchial hyperresponsiveness. Their 2-week crossover study demonstrated that fluticasone was associated with greater protection of the airways as assessed by provocation with histamine. These 2 studies produced complementary results. Placebo-controlled trials comparing ICSs with leukotriene-modifying agents have all reached the same conclusion: ICSs are the more effective class of medications.

Retrospective claims analysis can be used to address the same comparison of fluticasone and zafirlukast as primary controller therapy, but under actual practice conditions rather than in a clinical trial. The study population is analogous and more generalizable. In one such analysis, patients were controller-naïve for 9 months and using inhaled  $\beta$ -agonists as the only asthma medication.<sup>72</sup> They then began receiving ICSs or LTRAs to improve asthma control. The patients were continuously enrolled members from 1 of 13 United HealthCare-affiliated plans with enrollment of 1.4 million lives. They were identified with at least one *International Classification of Diseases, Ninth Revision* (493.XX) claim for asthma. Instead of

random assignment to treatment groups, the patients had an index event, which was their initial prescription for either inhaled fluticasone or zafirlukast. The subjects could not have had a claim for any ICS or oral LTRA in the 9 months before initiation of fluticasone or zafirlukast therapy. They were subsequently followed up for 12 months. This study had a conceptual design similar to that of the randomized clinical trial by Bleecker et al,<sup>69</sup> in which patients received no controller medications for 2 weeks before the initiation of active treatment and were then followed up for 12 weeks. However, as is typical of retrospective claims analysis, the pretreatment and post-treatment periods were significantly longer in the United HealthCare study.

A total of 725 individuals were identified as new users of fluticasone and 309 were new users of zafirlukast.<sup>72</sup> Compared with zafirlukast, fluticasone was associated with a 70% reduced risk for hospitalization ( $P = .0232$ ), a 49% lower risk for an emergency department event ( $P = .0546$ ), and a 51% reduction in combined emergency department events and hospitalizations ( $P = .0268$ ). Adjusted annual asthma care costs declined significantly for fluticasone and increased for zafirlukast. The adjusted mean difference in annual asthma costs was \$215 less per patient with fluticasone ( $P < .0001$ ). Asthma care costs decreased for patients treated with fluticasone compared with an increase for patients treated with zafirlukast. This retrospective claims analysis demonstrated that fluticasone was associated with a significantly lower risk of asthma-related hospitalization when compared with zafirlukast. The results confirm those reported in the study by Bleecker et al,<sup>69</sup> who found more symptom-free and rescue-free days with fluticasone compared with zafirlukast. Furthermore, fluticasone was associated with lower costs. In addition, the improved outcomes with fluticasone were noted even though compliance was lower with the inhaled glucocorticoid than with zafirlukast. There were 5.06 claims per year for zafirlukast and 3.07 claims per year for fluticasone. Despite this lower rate of refill persistence with fluticasone, the odds ratio for resource use was lower, favoring fluticasone. There was

a 70% reduction in the risk of hospitalization and a 49% reduction in emergency department use. This finding supports the conclusion that efficacy is a more important variable than effectiveness.

Indicators for indirect costs are difficult to collect. Because of employee confidentiality, these dollar figures are frequently not available. The data from studies in which retrospective claims analysis was used indicate that all indexes of patient symptoms are reduced with ICSs. Better sleep and more rescue-free days should lead to greater work productivity. The parameters associated with fewer emergency department visits and hospital stays might suggest more productive days at school or work.

No published studies have compared the efficacy of the available LTRAs, zafirlukast and montelukast (the latter being the most frequently prescribed of the two). The main difference between these medications appears to be the dosing frequency and dosing in relation to meal-times. The results of randomized clinical trials and retrospective claims analyses comparing montelukast and ICSs have been similar to those for zafirlukast. Two randomized clinical trials have compared montelukast and ICSs. The first trial, by Malmstrom et al<sup>56</sup> (as discussed earlier in this article), compared montelukast (10 mg/d) with low-dose beclomethasone (200 µg, given bid). This study was conducted in controller-naïve patients (subjects could continue taking stable doses of theophylline) who had baseline FEV<sub>1</sub> values of 50% to 85% of predicted values. For all clinical measures of lung function, beclomethasone was statistically and clinically more effective than montelukast ( $P < .01$ ). The only parameter for which the 2 medications were equally effective was the reduction of circulating eosinophil counts. The clinical significance of this finding is unclear because it is discordant with the other results. Nielson and Dahl<sup>73</sup> have suggested that peripheral eosinophilia might be a marker of the systemic effect of the medication rather than an indicator of disease improvement.

In a second randomized clinical trial, Busse et al<sup>71</sup> compared inhaled fluticasone and montelukast. The study enrolled symptomatic patients who were receiving only as-needed  $\beta$ -agonists for their asthma. The baseline FEV<sub>1</sub> of 50% to 80% of predicted value and baseline use of short-acting  $\beta$ -agonists were similar to those found in the study by Malmstrom et al.<sup>56</sup> Once again, the effect size for FEV<sub>1</sub> (58%) and morning PEFR (100%) was significantly greater with fluticasone as compared with montelukast. Parallel to the improvement noted in lung function was the finding that patient asthma symptom scores, nighttime awakenings, symptom-free days, and use of rescue albuterol all favored the use of fluticasone ( $P < .001$ ). The statistical methods used in this study included analyses of variance and Cochran-Mantel-Haenszel analyses to adjust for baseline comparability, similar to the regression methods used in the retrospective claims analysis described in the following paragraph. For all major clinical outcome parameters, these two studies demonstrated consistently greater improvement with either fluticasone or beclomethasone when compared with montelukast.

If the findings of the controlled clinical trials are applicable in clinical practice, one should be able to demonstrate these changes with formal analysis of retrospective claims data. The following retrospective claims analysis<sup>74</sup> was designed to test this hypothesis. The analysis was performed by PharMetrics Integrated Outcomes, a company that evaluates medical and pharmaceutical claims databases from more than 23 managed health care plans across the United States. Similar in design to the randomized clinical trial by Busse et al,<sup>71</sup> the retrospective analysis was an observational study in which pharmacy and medical claims were used to determine whether there are differences in the cost of asthma care between patients who are beginning treatment with montelukast or low-dose fluticasone (88 µg bid). Patients were identified who had at least one *International Classification of Diseases, Ninth Revision* (493.XX) claim for asthma and as an indexed event were prescribed inhaled fluticasone, 44 µg, or montelukast, 5 or 10 mg. As in the study by Busse et al,<sup>71</sup> the patients were controller-naïve for the 9 months before the first prescription claim for either fluticasone or montelukast. Resource use was then monitored for the next 9 months. Multivariate regression analysis was used to determine the influence of these single-controller therapies on post-index asthma-related costs.

Asthma-related costs were adjusted for age, sex, health plan, comorbidities, pre-index asthma medication use, and pre-index asthma care costs. The results of the multivariate regression analysis, adjusted for baseline covariates, indicated that fluticasone was associated with significantly lower post-index total asthma-related costs than montelukast ( $P < .001$ ). Adjusted least-squares mean total asthma care costs for the 9-month post-index period were US\$694.04 for fluticasone compared with US\$1027.71 for montelukast. This difference in costs was related to the lower cost of medication and lower rates of resource use for hospitalization and emergency department events among the patients receiving fluticasone. On average, patients receiving montelukast had 4.6 prescription claims for this medication during the treatment period, whereas those receiving fluticasone averaged 3.4 prescription claims for this agent during the same period. Again, greater compliance with LTRA did not produce better outcomes.

When the criteria for selection of a primary controller single therapy for asthma are assessed, the basic science, randomized clinical trials, and retrospective claims analysis all yield the same confirmatory conclusions. Inhaled glucocorticoids have a broader range of sites of activity in reducing airway inflammation of asthma. These agents have a greater impact on objective improvement of lung function, which is associated with greater improvement in patient-oriented outcomes. Retrospective claims analyses demonstrate parallel improvement by a reduction in resource use in the hospital and emergency department. Finally, claims analyses demonstrate large cost savings when ICSs are selected over LTRAs.<sup>72</sup>

The evidence is consistent for the use of ICS therapy for primary controller therapy. The clinical trials with

TABLE II. Controlled comparative trials of combination therapy

| Treatment                                                                                            | Patients (n)   | Duration (wk) | Significant differences                    |                  |          | Reference |
|------------------------------------------------------------------------------------------------------|----------------|---------------|--------------------------------------------|------------------|----------|-----------|
|                                                                                                      |                |               | Lung function<br>(FEV <sub>1</sub> or PEF) | Albuterol<br>use | Symptoms |           |
| Salmeterol, 42 µg bid, and<br>zafirlukast, 20 mg bid                                                 | 289 (80% ICS)  | 4             | ↑                                          | ↓                | ↓        | 78        |
| Salmeterol, 50 µg bid, and<br>montelukast, 10 mg/d                                                   | 467 (100% ICS) | 12            | ↑                                          | ↓                | ↓        | 79        |
| Fluticasone, 100 µg bid/salmeterol,<br>50 µg bid, and fluticasone<br>100 µg bid/montelukast, 10 mg/d | 447 (100% ICS) | 12            | ↑                                          | ↓                | ↓        | 80        |

their high internal validity all demonstrate greater efficacy of ICSs as compared with LTRAs, and these results are confirmed in the observational retrospective analysis with their high external validity. The greater effect size produced with ICSs in the clinical trials more than compensates for their lower refill persistence in claims analysis.

### Dual controller therapies

For many patients, the use of single controller therapy for asthma does not provide complete control, and additional treatment is desirable. Salmeterol and montelukast are the two medications most commonly prescribed as add-on controllers in patients treated with ICSs. Salmeterol is a potent, long-acting, selective  $\beta_2$ -agonist that has been shown to be more effective than doubling the dose of ICS in patients who are symptomatic while receiving low to moderate doses of ICSs.<sup>75</sup> Nine studies with more than 3800 subjects have demonstrated the greater improvement of salmeterol plus ICS, and additional studies have demonstrated the additive effect of formoterol plus ICS. Leukotriene receptor antagonists are considered by some to be a potential alternative because of their protective effects against the cysteinyl leukotrienes, which are potent mediators. Montelukast has also been shown to produce incremental improvement in lung function when added to beclomethasone.<sup>76</sup> The effect size noted in the study by Laviolette et al<sup>76</sup> demonstrated a 5.08% improvement in FEV<sub>1</sub> and a 2.53% improvement in PEF. In a recent study by Simons et al,<sup>77</sup> there was a 1.9% improvement in FEV<sub>1</sub> and a 3% change in PEF with the addition of montelukast to a fixed dose of budesonide.

The direct comparisons of the addition of salmeterol or montelukast to ICS should address the question of which agent is the best add-on therapy. Is the consistent message from science, clinical trials, and observational studies observed in the studies of monotherapy also apparent with dual controller treatment?

Three randomized clinical studies that address the issue of the comparative benefits of using inhaled salmeterol, montelukast, or zafirlukast as add-on therapy for asthma have been published or presented.<sup>78-80</sup> All 3 of these studies reached the same conclusion by demonstrating greater efficacy with the addition of salmeterol (Table II). The initial study was a 4-week, double-blind

trial involving 289 patients  $\geq 12$  years of age who had persistent asthma.<sup>78</sup> More than 80% of the patients were receiving concomitant ICS therapy when they were randomly assigned to receive zafirlukast, 20 mg bid, or salmeterol, 42 µg bid. Patients randomly assigned to receive salmeterol had greater improvement in pulmonary function and symptoms, as well as a reduced need for rescue albuterol. Morning PEF improved by 29.6 L/min in the salmeterol group as compared with 13.0 L/min in the zafirlukast group. Salmeterol therapy also resulted in significantly greater improvements than zafirlukast with regard to evening PEF, percentage of symptom-free days, and percentage of days and nights without need for rescue albuterol.

Fish et al<sup>79</sup> studied the addition of either salmeterol or montelukast to treatment regimens for patients who were symptomatic despite the use of an ICS. In this 12-week trial, 467 patients  $\geq 15$  years of age were randomly assigned to receive either salmeterol inhalation powder 50, µg bid, or oral montelukast, 10 mg/d, in addition to their currently used ICS. The addition of salmeterol provided significantly greater improvements in morning and evening PEF, percentage of symptom-free days, percentage of rescue-free days, and overall daytime symptoms when compared with montelukast. Both drugs were well tolerated, and no significant differences were seen in adverse events or exacerbations between groups.

The third study, reported by Nelson et al,<sup>80</sup> used the most standardized protocol. The study enrolled 447 patients with asthma who were symptomatic despite receiving fluticasone, 100 µg bid. The patients continued to receive this dose of fluticasone with the addition of either inhaled salmeterol, 50 mg bid, or oral montelukast, 10 mg/d, and were followed up for the next 12 weeks. The addition of salmeterol produced significantly greater improvement in morning FEV<sub>1</sub> and morning and evening PEF ( $P < .01$ ). The salmeterol group used significantly less albuterol during the treatment phase and had a significantly lower rate of asthma exacerbations. These 3 clinical studies demonstrate consistency in their results and warrant confirmation of their findings by retrospective claims analysis.

Retrospective claims analysis has also been used to address the question of the most effective complementary therapy in patients whose asthma is not controlled with

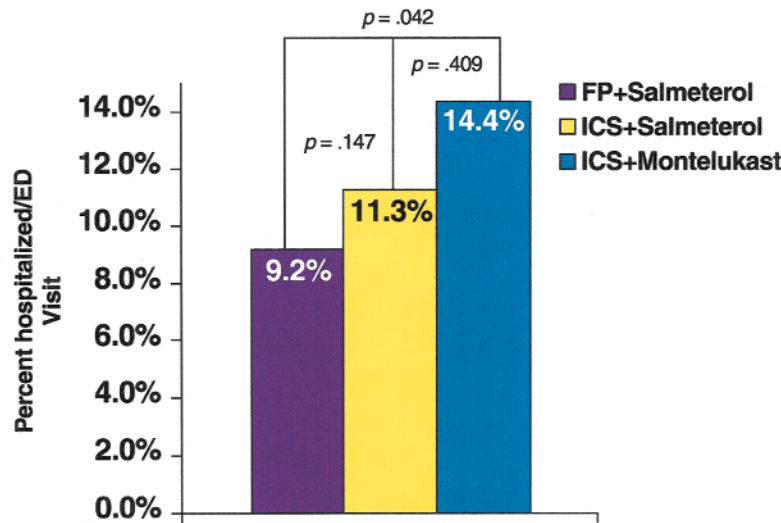


**FIG 4.** Adjusted hospitalization and emergency department rates during the 1-year follow-up. FP, Fluticasone propionate. (Reprinted with permission from Stempel DA, Mayer JW, O'Donnell JC. The combination of salmeterol and fluticasone improves asthma-related outcomes at a lower cost compared to inhaled corticosteroids and montelukast [abstract]. *J Allergy Clin Immunol* 2001;107(suppl):S101.)

ICS alone. These analyses address whether the greater improvements in lung function and symptom control and decreased  $\beta$ -agonist use are validated in these observational investigations. A study was designed to assess the comparative impact on healthcare use and cost of 3 common dual-controller therapies: (1) fluticasone plus salmeterol, (2) other inhaled ICSs plus salmeterol, and (3) ICSs plus montelukast.<sup>81</sup> This investigation used a 24-month pretreatment–post-treatment retrospective design to compare asthma-related service use and costs among patients continuously enrolled in 1 of 14 United HealthCare plans. Outcomes assessed were post-index pharmacy costs, rates of emergency department visits and hospitalizations, number of filled prescriptions for canisters of short-acting  $\beta$ -agonists, and total asthma-related costs.

Compared with the patients using fluticasone plus salmeterol, those using ICS plus montelukast in the post-index period were 5 times more likely to have an asthma-related hospitalization and 2 times more likely to have an asthma-related emergency department visit or hospitalization than subjects using fluticasone plus salmeterol ( $P \leq .05$ ). Only those patients receiving fluticasone plus salmeterol had a significant reduction in asthma exacerbations as measured by a decrease in hospitalizations and emergency department visits (Fig 4). Subjects in the fluticasone-plus-salmeterol group also had fewer post-index claims for short-acting  $\beta$ -agonists when compared with the subjects in either of the other two groups ( $P \leq .05$ ). In the post-index period, patients in the ICS-plus-montelukast group had 56% greater use of inhaled short-acting  $\beta$ -agonists than those treated with fluticasone plus salmeterol. Total adjusted asthma costs in the ICS-plus-montelukast group were more than 60% higher than costs in the 2 groups using salmeterol as add-on medication ( $P \leq .0001$ ). The costs associated with ICS plus montelukast were US\$594 more per

patient per year when compared with the use of fluticasone plus salmeterol. Compared with the addition of montelukast to ICS, the use of salmeterol and fluticasone was associated with a significant reduction in the use of short-acting  $\beta$ -agonists, the risk of an emergency department or hospital event, and total asthma costs. Similarly, the addition of salmeterol to all other ICSs predicted lower costs for short-acting  $\beta$ -agonists and total asthma care compared with the addition of montelukast to ICS. The lower number of asthma exacerbations, as reflected in this study by the lower risk for hospitalization and emergency department events, is consistent with the findings from the study by Nelson et al,<sup>80</sup> which demonstrated a significant reduction in exacerbations. In addition, both this randomized clinical trial and the by Nelson et al<sup>80</sup> demonstrate the parallel reductions in the use of short-acting  $\beta$ -agonists.

A second retrospective claims analysis was performed to compare asthma-related health care use and expenditures for patients prescribed 1 of 3 dual-controller treatments: fluticasone plus salmeterol, ICS (excluding fluticasone) plus salmeterol, and ICS plus an LTRA. This study was performed by Health Benchmarks with the use of asthma-related medical and pharmacy claims.<sup>82</sup> Again, the study period covered 12 months before and after the initiation of dual therapy. The study focused on 1325 patients  $\geq 12$  years of age who were using ICS but not using a second controller treatment during the pre-index period. The index event was the first prescription for 1 of the 2 indexed medications. The members were required to have a claim for an ICS in the post-index period. Multivariate regression analyses were used to assess differences in asthma-related expenditures. All cost variables were log-transformed to compensate for positive skew.

The results demonstrated that the risk-adjusted total asthma-related costs for the patients receiving fluticasone

plus salmeterol ( $n = 121$ ), ICS plus salmeterol ( $n = 844$ ), and ICS plus LTRA ( $n = 360$ ) were US\$975, US\$1089, and US\$1268, respectively. Risk-adjusted pharmacy costs were US\$813, US\$841, and US\$996, respectively. Generalized linear modeling, controlling for baseline covariates, indicated that compared with ICS plus LTRA therapy, both groups receiving ICS plus salmeterol had a significant reduction in asthma-related total costs ( $P = .0014$ ) and pharmacy costs ( $P = 0.001$ ). Similar results were found when the ICS-plus-salmeterol and ICS-plus-LTRA groups were compared ( $P = .0001$ ). The number of inpatient, outpatient, and emergency department visits and their corresponding costs were lower with fluticasone plus salmeterol, but not significantly so ( $P > .05$ ). Furthermore, the use of short-acting  $\beta$ -agonists was significantly less frequent in the fluticasone-plus-salmeterol group than in either of the 2 other cohorts and was consistent with the data from the United HealthCare analysis.<sup>81</sup> Results from these 2 real-world managed-care claims analyses suggest that treatment with ICS plus salmeterol yields important cost savings when compared with treatment with an ICS plus an LTRA.

The use of a second therapeutic agent frequently produces incremental costs because of the additional expenditure for the second pharmaceutical agent. Reductions in emergency department use rates, hospitalizations, or both may compensate, in part, for the cost of the second maintenance medication. Pharmaceuticals are an important investment in the treatment of patients with asthma. The best investment is the medication that produces the best outcomes with good safety (defined as limited adverse effects, as well as limiting the morbidity from the treated disease) with the lowest use of medical resources. All the data presented, whether from randomized clinical trials or retrospective claims analyses, have yielded consistent findings. The retrospective claims analyses of dual asthma therapy have all demonstrated consistently greater improvement with the addition of salmeterol as compared with either of the LTRAs. These results have usually been statistically different with a significant effect size. Furthermore, the findings noted in the randomized clinical trials have been confirmed in the 2 retrospective claims analyses. The strongest evidence occurs when multiple clinical trials confirm the findings. This is further strengthened when the results are confirmed with differing methodologies. The most consistent finding for dual therapy for the treatment of asthma appears to be that the combination of ICSs and salmeterol yielding the greatest improvement in lung function and symptom scores with the lowest rate of exacerbation and at the lowest incremental cost when compared with the use of an ICS and LTRA. Furthermore, the use of fluticasone plus salmeterol is associated with a greater reduction in albuterol use than either of the comparator groups.

Retrospective claims analyses may be used to confirm the results of randomized clinical trials in a more generalizable population. The patients studied are from daily practice situations. Their access to medical care is more typical than that in a randomized clinical trial, and emer-

gency department visits and hospitalizations are more common events. The improvement noted in these observational studies included reduced claims for emergency department visits and hospitalizations. If pharmaceuticals are the investment in health care, lower claims for the treatment of exacerbations are the return on this investment. The data are consistent and support the 1997 guidelines advocating the use of an ICS as the primary controller for persistent asthma.<sup>1</sup> For patients who are unable to achieve the goals of asthma despite the use of ICSs, this comprehensive combination of data from randomized clinical trials and retrospective claims analyses would support the use of ICSs and salmeterol.

The best evidence for a therapeutic decision occurs when different methodologies produce consistent and complementary results. The basic scientific understanding of the disease pathophysiology poses clinical questions. These hypotheses are next answered in clinical trials with selected patient populations. Finally, the use of observational databases, including medical and pharmacy claims, permits the further confirmation of the findings of clinical trials in a more generalizable population. These analyses all support the conclusions of the 1997 NHLBI Guidelines for the Diagnosis and Management of Asthma<sup>1</sup>: ICSs are the primary controller medications. For patients who do not achieve the goals of care despite this treatment, long-acting bronchodilators such as salmeterol offer appropriate step-up care.

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