

# Emerging Therapeutic Options for Asthma

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## Abstract

Asthma is characterized by eosinophilic airway inflammation and elevated serum immunoglobulin E (IgE) levels. Due to these pathologic features, the foundation of asthma treatment has historically been anti-inflammatory therapy with inhaled corticosteroids (ICSs). Numerous factors in addition to IgE and eosinophils, however, likely play important roles in mediating the airway inflammatory response characteristic of asthma. ICSs are effective therapy for some patients with persistent asthma, but clinical trials have shown that even increasing doses of ICSs under carefully controlled situations does not always result in acceptable asthma control. Consequently, other classes of medications, in addition to ICSs, are recommended in those patients with more severe asthma. The class of medication most commonly used in more severe asthma, along with ICSs, is long-acting inhaled beta<sub>2</sub>-agonists, but leukotriene modifying agents and anti-IgE monoclonal antibodies may also be used. Agents such as tiotropium, a long-acting inhaled anti-muscarinic agent, and those aimed at inhibiting cytokines, such as mepolizumab, daclizumab, and etanercept, hold promise in the treatment of asthma. Other agents under investigation include phosphodiesterase type 4 inhibitors and oligonucleotides. Bronchial thermoplasty, a nonpharmacologic option, may also be beneficial in patients with poorly controlled asthma. As our understanding of the complex pathophysiology of asthma increases, it will enable the development of novel therapeutic approaches for patients who are not responding well to traditional treatments. Although more studies are necessary to ensure the efficacy and safety of both pharmacologic and nonpharmacologic approaches, there is future promise for therapeutic advances in severe, persistent asthma.

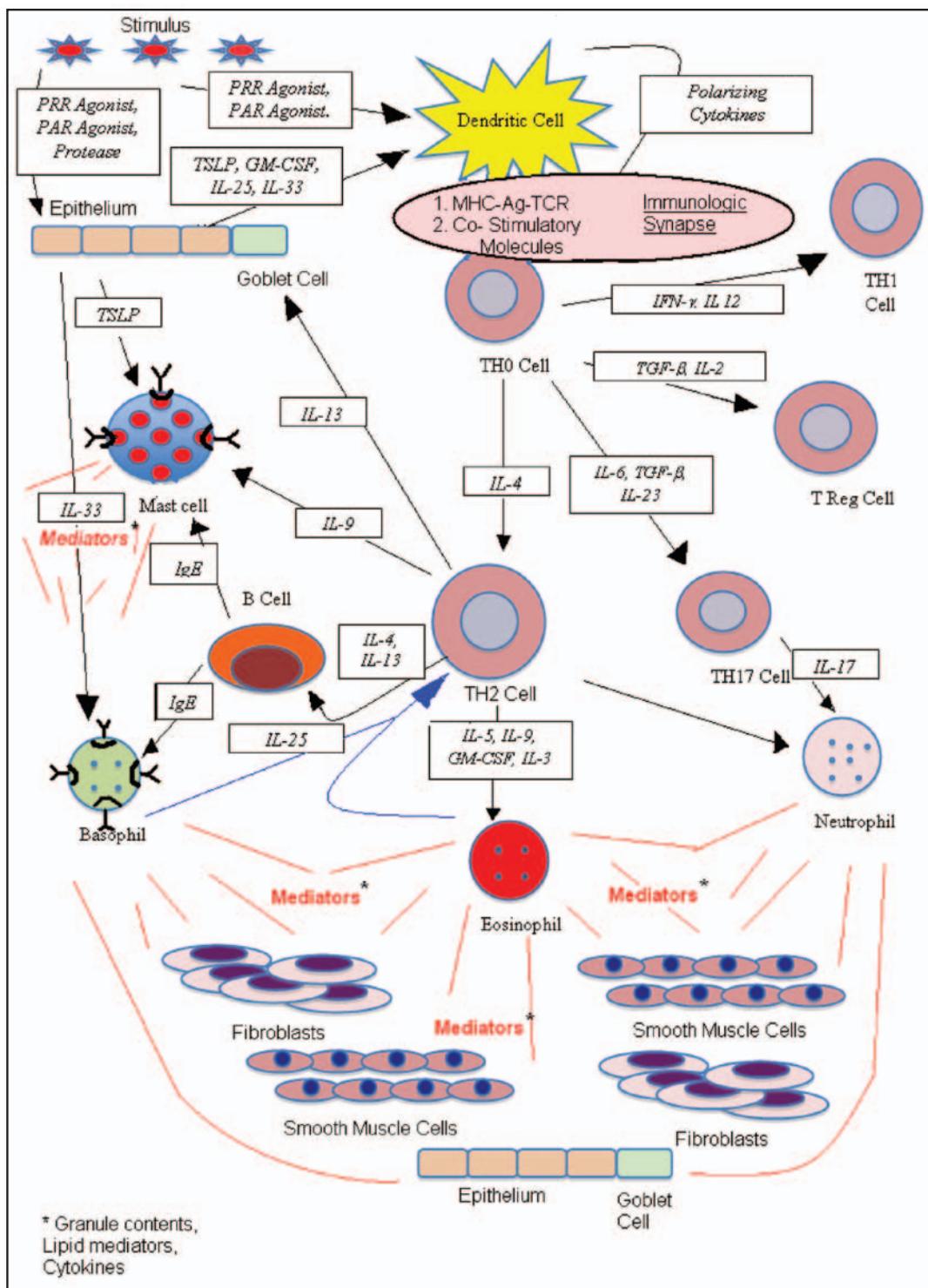
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Asthma is usually a relatively straightforward disease to diagnose. Patients typically present with some combination of 4 basic symptoms: cough, wheeze, chest tightness, and shortness of breath.<sup>1</sup> These symptoms may be episodic or persistent. Asthma patients often have wheezing on physical examination and some combination of airway obstruction and/or bronchial hyperresponsiveness on physiologic testing. Patients with asthma usually also have a history of eczema and allergic rhinitis. The combination of asthma, eczema, and allergic rhinitis is considered the "atopic triad," because these 3 conditions are believed to involve a specific type of inflammatory reaction to extrinsic allergens called atopy. The inflammatory reactions in atopic disease are mediated by immunoglobulin E (IgE) and involve eosinophils. Asthma is characterized by eosinophilic airway inflammation and elevated serum IgE levels.<sup>1</sup> Due to these pathologic features, the foundation of asthma treatment has historically been anti-inflammatory therapy with inhaled corticosteroids (ICSs).<sup>1</sup> Although the clinical presentation of asthma might be straightforward, we are learning that the pathophysiology of asthma is far more complex than we believed. This is an important point because we are also learning that ICS therapy will not adequately control asthma in all patients.

As shown in the **Figure**, numerous factors in addition to IgE and eosinophils likely play important roles in mediating the airway inflammatory response characteristic of asthma. Cytokines (eg, interleukins, lymphokines, tumor necrosis factor [TNF], interferons) and other cell types (eg, lymphocytes, mast cells, airway epithelial cells, airway smooth muscle cells) have all been implicated as mediators of airway inflammation.<sup>2</sup> Understanding how these inflammatory mediators and cells contribute to the pathophysiology of asthma will be crucial next steps in our approach to better managing asthma, because current pharmacologic treatment approaches do not always ensure asthma control. ICSs are effective therapy for some patients with persistent asthma, but clinical trials have shown that even increasing doses of ICSs under carefully controlled situations does not always result in acceptable asthma control.<sup>3</sup> This article is intended to review newer methods of treating asthma, both pharmacologic and nonpharmacologic, as a basis for understanding how these approaches may be used to manage patients not responding to standard treatment with ICSs.

■ **Figure.** Schematic Depiction of the Components of the Airway Allergic Inflammatory Response<sup>2</sup>



Ag indicates antigen; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; MHC, major histocompatibility complex; PAR, protease activated receptor; PRR, pattern recognition receptor; TCR, T-cell receptor; TGF, transforming growth factor; TH, T helper cell; TSLP, thymic stromal lymphopoietin.

Arrows indicate the direction in which the identified signal is acting. Red lines indicate the discharge of cellular mediators (including granular contents, lipid mediators, and cytokines).

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### Current Approach to Categorizing Asthma Severity and Treating Asthma

As discussed in the previous article by Dr Long,<sup>4</sup> the Expert Panel Report 3 (EPR3) published by the National Heart, Lung, and Blood Institute recommends a stepwise approach to managing persistent asthma.<sup>1</sup> The EPR3 emphasizes that there are 2 goals of this stepwise approach to asthma pharmacotherapy: the first is to achieve asthma control, which is the elimination of daytime and nocturnal symptoms, normalization of lung function, and reduction in the risk of exacerbations; the second is to minimize the likelihood of adverse events and costs related to asthma pharmacotherapy. To achieve these goals, the stepwise approach requires that physicians estimate asthma severity; asthma pharmacotherapy will vary depending upon the severity category. For mild, persistent asthma, recommended therapy consists of low dose ICSs, education, and removal of environmental triggers. For patients with moderate-to-severe persistent asthma, however, treatment is more complex. Increasing doses of ICSs are used in these patients, as well as additive therapy. The class of medication most commonly used in more severe asthma, along with ICSs, is long-acting inhaled beta<sub>2</sub>-agonists (LABAs), but leukotriene modifying agents (LMAs) and anti-IgE monoclonal antibodies may also be used. Unfortunately, healthcare providers are suboptimally managing asthma. For example, a survey of patients with asthma being treated by primary care physicians in Canada showed that almost 60% did not have well-controlled asthma, and that healthcare providers often did not appreciate the lack of control.<sup>5</sup> In this survey, patients with suboptimal asthma control were significantly more likely to need urgent care visits for asthma management ( $P < .001$ ).

There are 3 important reasons for the lack of success in achieving asthma control. 1) Many patients with asthma simply do not adhere to recommended treatment. In a retrospective database analysis of medical records and pharmacy claims, overall adherence to ICS use by patients with asthma was found to be only 50%. There was a clear relationship between poor adherence with ICS use and worse outcomes, including asthma-related hospitalizations.<sup>6</sup> 2) Physicians may fail to appreciate asthma severity in the individual patient. To appropriately use the EPR3 step-up approach to asthma pharmacotherapy, physicians must first make the appropriate link between accurately categorizing asthma severity and choosing the appropriate pharmacotherapeutic regimen. Telephone surveys have suggested that the majority of patients with asthma have mild disease.<sup>7</sup> However, my colleagues and I found that more than 90% had moderate-to-severe persistent asthma using information obtained from

diary cards completed daily by patients not using ICSs.<sup>8</sup> Similarly, Fuhlbrigge et al found that over three-quarters of asthma sufferers had moderate or severe persistent asthma.<sup>9</sup> A prospective, longitudinal study from a managed care consortium showed that physicians often underestimated asthma severity. The consequence of underestimating asthma severity in that study was undertreatment.<sup>10</sup> 3) There are subsets of patients with persistent asthma who do not respond to ICSs. A recent editorial by Drs Bhat and Calhoun speculated that 10% to 15% of patients with severe persistent asthma may be refractory to the best currently available pharmacotherapy.<sup>11</sup> For such patients, newer therapies are needed, and efforts such as those by the Severe Asthma Research Program are helping us determine how to better manage these patients.<sup>12</sup>

### Inhaled Corticosteroids in Combination With Other Drugs

ICSs are the foundation of therapy for patients with persistent asthma.<sup>1</sup> ICSs are the most effective anti-inflammatory medications currently available for asthma. They block late-phase reactions to allergens, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.<sup>1</sup> ICSs are the only class of medications which have been proved, by bronchoscopy biopsy studies, to effectively reduce airway inflammation in patients with asthma.<sup>13-15</sup> By controlling airway inflammation, the use of ICSs reduces symptoms and improves lung function.<sup>16</sup> Regular use of ICSs has been associated with reduced asthma exacerbations<sup>17</sup> and possibly decreased asthma mortality.<sup>18</sup> However, carefully conducted controlled clinical trials have shown that a substantial minority of patients do not achieve asthma control, even with high-dose ICSs. In the GOAL (Gaining Optimal Asthma control) study, the use of ICSs alone resulted in well-controlled asthma in only 68% of patients at the end of 1 year of treatment.<sup>3</sup>

The EPR 3 recognizes that ICSs alone, even at increased doses, may be insufficient to control asthma in all patients, particularly those with moderate-to-severe disease.<sup>1</sup> Consequently, they recommend adding other classes of medications to ICSs in those patients with more severe asthma. LABAs are the medication most commonly added to the regimen of patients whose asthma is not controlled by an ICS. The addition of a LABA to an ICS was hypothesized to provide benefits compared with simply increasing the dose of the ICS, by improving lung function and symptom control more rapidly. The GOAL study directly compared the effectiveness of higher doses of an ICS (fluticasone propionate) with the combination therapy of an ICS plus a LABA (salmeterol) in achieving asthma control.<sup>3</sup> The combination of

the ICS and LABA was associated with patients achieving well-controlled status faster. Also, a significantly higher percentage of patients achieved asthma control with the combination compared with those receiving the ICS alone. The combination approach was also associated with fewer asthma exacerbations. Although the combination of an ICS with a LABA was more effective in this study, it is remarkable to note that only 77% of patients treated with an ICS and a LABA achieved well-controlled asthma status at study end.

Another combination that may be effective for patients poorly controlled by ICSs alone is ICS therapy plus an LMA. Although LMAs are recommended as an alternative to ICSs in patients with mild, persistent asthma, the combination of an LMA plus an ICS may help some patients with more severe symptoms. Virchow et al performed a 6-month open-label study in which patients (n = 1681) were given montelukast (10 mg) in addition to their ICS or ICS plus LABA therapy.<sup>19</sup> At the end of the study, there was a dramatic improvement in the patients' asthma control. Using Asthma Control Test score categories, the percentage of patients with uncontrolled (57.5%) or poorly controlled (25.0%) asthma at baseline decreased at month 6 to 17.6% and 21.7%, respectively. Furthermore, the percentage of patients with well-controlled (13.9%) or completely controlled (1.2%) asthma at baseline increased at month 6 to 47.5% and 11.4%, respectively. Similar improvements were seen in 2 recent Canadian studies.<sup>20,21</sup> Although LMAs provide benefits when combined with an ICS, the LABA and ICS combination seems more effective. Nelson et al randomized patients with asthma suboptimally controlled on an ICS alone to additionally receive a LABA or an LMA.<sup>22</sup> Patients improved with both combinations, but the addition of a LABA to an ICS resulted in significantly greater improvements in lung function and overall asthma control.

Selected patients may benefit from the combination of an ICS plus the humanized monoclonal anti-IgE antibody omalizumab. Rodrigo et al examined data from 8 placebo-controlled clinical trials that assessed the safety and efficacy of an ICS plus omalizumab in patients with moderate to severe persistent asthma.<sup>23</sup> They calculated that the asthma exacerbation rate during the stable phase was almost halved in patients receiving omalizumab compared with placebo (37.6 per 100 patient-years in the omalizumab group vs 69.9 in the placebo group; RR= 0.57, 95% confidence interval [CI], 0.48-0.66). The percentage of patients with at least 1 asthma exacerbation was 17.2% in the omalizumab group versus 30.9% in the placebo group (RR = 0.55, 95% CI, 0.47-0.64). Patients treated with omalizumab were significantly more likely to tolerate ICS reduction. Equally important, the

placebo and omalizumab treatment groups had similar safety profiles. There were no indications of increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms in patients receiving omalizumab. One limitation of therapy with omalizumab is the requirement that elevated IgE levels be documented prior to initiation. Also, because of the risk of immediate hypersensitivity reactions to this product, the US Food and Drug Administration requires careful monitoring of patients during and immediately after administration of omalizumab.

Recent work has suggested that another option to consider for patients with uncontrolled asthma on ICSs is the addition of tiotropium, a long-acting inhaled anti-muscarinic agent (LAMA).<sup>24</sup> This anticholinergic drug is currently approved for the management of chronic obstructive pulmonary disease, but not asthma. Peters et al studied tiotropium, in combination with an ICS, for the treatment of asthma.<sup>25</sup> Using a double-blind, triple-dummy crossover trial design, they compared the efficacy of 3 different treatment approaches in patients with uncontrolled asthma on standard ICS therapy (n = 210). Following a 4-week run-in period with ICS therapy (beclomethasone 80 µg twice daily), patients with confirmed poorly controlled asthma were given 3 different treatments in a crossover fashion: (1) doubling the dose of the ICS (beclomethasone 160 µg twice daily); (2) normal dose ICS (beclomethasone 80 µg twice daily) plus the LABA salmeterol xinafoate (50 µg twice daily); or (3) normal dose ICS (beclomethasone 80 µg twice daily) plus tiotropium bromide (18 µg each morning). Each of the treatment approaches provided some benefits, but the LAMA and LABA additions provided consistently better improvements in overall asthma control than doubling the dose of the ICS. The addition of tiotropium was superior to doubling the dose of the ICS with regard to improving morning and evening peak expiratory flows (PEF), forced expiratory volume in 1 second (FEV<sub>1</sub>), and daily symptom scores. The combination of tiotropium plus the ICS provided comparable improvements in asthma-control days as the ICS plus LABA combination, but significantly greater improvements in prebronchodilator FEV<sub>1</sub>.<sup>25</sup> Although the use of a LAMA is not included in the EPR 3 recommendations, these results are promising. Future studies are needed to understand which patients may respond to a LAMA versus a LABA as add-on therapy to an ICS.

### New Agents Aimed at Inhibiting Cytokines

There has been considerable interest in developing inhibitors of other inflammatory mediators thought to be involved in asthma pathophysiology, specifically interleukins (IL). IL-5 has been identified as playing an important role, in both

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animal and human studies, in mediating eosinophil mobilization, maturation, activation, and survival. The development of an IL-5 antagonist through monoclonal antibody technology, mepolizumab, was greeted with great interest by the asthma community.

Haldar et al performed a randomized, double-blind, placebo-controlled, parallel-group study in patients ( $n = 61$ ) with refractory eosinophilic asthma and a history of recurrent severe exacerbations.<sup>26</sup> Patients received 12 monthly infusions of mepolizumab (750 mg;  $n = 29$ ) or placebo ( $n = 32$ ). At the end of the 50-week study, patients treated with mepolizumab had significantly fewer severe exacerbations compared with those receiving placebo (mean exacerbations per subject, 2.0 vs 3.4, respectively; RR= 0.57; 95% CI, 0.32-0.92;  $P = .02$ ). Furthermore, improvement in Asthma Quality of Life Questionnaire (AQLQ) scores were significantly greater in the group receiving mepolizumab (mean increase from baseline, 0.55 vs 0.19; mean difference between groups, 0.35; 95% CI, 0.08-0.62;  $P = .02$ ). A similar but smaller study was conducted by Nair et al.<sup>27</sup> This randomized, double-blind, parallel-group study included patients with persistent sputum eosinophilia and symptoms despite prednisone treatment. Patients received mepolizumab (5 monthly infusions of 750 mg each;  $n = 9$ ) or placebo ( $n = 11$ ) while continuing to receive prednisone. After the 5 infusions, there were 12 asthma exacerbations in 10 patients who received placebo and only 1 exacerbation in those who received mepolizumab ( $P = .002$ ). In addition, patients receiving mepolizumab were able to reduce their prednisone dose by a mean of 84% of their maximum possible dose, as compared with only a 48% reduction in those receiving placebo ( $P = .04$ ).<sup>27</sup> Although mepolizumab significantly depleted circulating and sputum eosinophils, it only partially reduced bronchial mucosal evidence of eosinophil infiltration, even at the highest doses.<sup>28</sup> Newer products, such as MEDI-563, a humanized monoclonal antibody directed against the  $\alpha$  chain of the IL-5 receptor, may more effectively deplete eosinophils than antibodies directed against circulating IL-5.<sup>29,30</sup> The availability of this product should enable investigators to determine whether a more aggressive approach to inhibiting IL-5 will impact asthma control.

IL-2 is postulated to have multiple pro-inflammatory effects in asthma by stimulating Th2 lymphocyte proliferation and cytokine secretion. Daclizumab is a monoclonal antibody that binds to the  $\alpha$  chain of the high-affinity IL-2 receptor and inhibits the biological activity of IL-2. Busse et al performed a small, randomized, double-blinded, placebo-controlled study in adults with moderate-to-severe persistent asthma who required ICS treatment for asthma control.<sup>31</sup>

During the first 12 weeks of the study, all patients were maintained on a stable dose of an ICS and received daclizumab (2 mg/kg loading dose, 1 mg/kg maintenance dose;  $n = 88$ ) or placebo ( $n = 27$ ) every 2 weeks. Over the next 8 weeks of the study, efforts were made to taper the ICS dose. Patients were followed for an additional 16 weeks without therapy as a washout period. During the first 12 weeks of the study, there was a small but significant increase in FEV<sub>1</sub> in the daclizumab group (daclizumab, 4.4% vs placebo, 1.5%;  $P = .05$ ), along with reduced daytime asthma symptoms ( $P = .018$ ) and short-acting inhaled beta<sub>2</sub>-agonist use ( $P = .009$ ). Daclizumab treatment did not allow ICS tapering, but did prolong the time to the first asthma exacerbation ( $P = .024$ ).

Both IL-4 and IL-13 mediate IgE production, mucus hypersecretion, bronchial hyperresponsiveness, and the differentiation of Th2 lymphocytes. A variety of products have been developed which block the effect of IL-4, including soluble IL-4 receptors, and anti-IL-4 humanized monoclonal antibodies. Unfortunately, these products have not demonstrated adequate clinical efficacy.<sup>32</sup> Because the IL-4 receptor  $\alpha$  chain is used by both IL-4 and IL-13, antagonists directed at IL-4R $\alpha$  have been developed. In a small phase 2 study, Corren and colleagues randomized patients with moderate-to-severe asthma on stable doses of an ICS to receive AMG 317, a monoclonal antibody that blocks IL-4R $\alpha$ , or placebo.<sup>33</sup> Improvements in asthma symptom scores were not found with AMG 317 treatment compared with placebo. Wenzel et al studied the effect of pitrakinra, a recombinant IL-4 variant which inhibits the IL-4R complex in patients with atopic asthma with a documented late phase response to an inhaled allergen.<sup>34</sup> Both inhaled and subcutaneous pitrakinra somewhat attenuated the late phase FEV<sub>1</sub> response to an inhaled allergen, but effects on overall asthma control were difficult to detect. Studies have examined the efficacy of suplatast tosilate, which suppresses both IL-4 and IL-5, in patients with asthma, and there have been some encouraging results.<sup>35,36</sup>

TNF plays an important role in chronic inflammatory disorders involving the Th1 immune response and neutrophils. Although asthma is generally thought to be mediated by Th2 immune response and eosinophils, increased levels of TNF- $\alpha$  have been found in patients with asthma on the surface of peripheral blood monocytes<sup>37</sup> and in bronchial lavage fluid.<sup>38</sup> In these 2 small studies, treatment with the TNF antagonist etanercept, an immunoglobulin G11-TNF p75 receptor fusion protein, yielded encouraging results with improvements in asthma symptoms and lung function. These encouraging results were not confirmed, though, by a later study. Morjaria et al performed a randomized, double-blind, placebo-controlled parallel group study that compared etan-

except (50 mg administered by subcutaneous injection once weekly for 12 weeks) with placebo in 39 patients with severe corticosteroid-refractory asthma.<sup>39</sup> Etanercept was associated with a significant decrease in Asthma Control Questionnaire scores compared with placebo (-1.11 [95% CI -1.56 to -0.75] and -0.52 [95% CI -0.97 to -0.07], respectively;  $P = .037$ ), but there were no significant differences among the treatment groups with respect to AQLQ scores, PEF, and bronchial hyperresponsiveness. Infliximab, a human-murine chimeric monoclonal antibody that binds and neutralizes TNF- $\alpha$ , has also been studied in asthma. Erin et al performed a double-blind, placebo-controlled, parallel-group design study in 38 patients with moderate asthma who were symptomatic despite treatment with ICSs. Patients received infliximab (5 mg/kg intravenously at weeks 0, 2, and 6) or placebo.<sup>40</sup> At the end of the study, there was no significant difference in the primary end point (the change in morning PEF at end of study compared with end of run-in phase), but significantly fewer patients given infliximab had exacerbations compared with those given placebo (29% vs 78%, respectively;  $P = .01$ ). The authors of this study described these findings as encouraging and warranting further studies with infliximab.

### Novel Anti-Inflammatory Agents

Phosphodiesterase type 4 inhibitors may also be useful for some patients with asthma. Bateman et al conducted a double-blind, parallel-group, phase 2/3 study in which patients with asthma ( $n = 693$ ) were randomized to receive 100, 250, or 500  $\mu\text{g}$  of roflumilast or placebo once daily for 12 weeks.<sup>41</sup> At the end of the study, all roflumilast doses were shown to increase FEV<sub>1</sub> from baseline ( $P < .001$ ), with the highest dose associated with the greatest increase in FEV<sub>1</sub> (100  $\mu\text{g}$  resulted in a 260 mL increase; 250  $\mu\text{g}$ , a 320 mL increase; and 500  $\mu\text{g}$ , a 400 mL increase in FEV<sub>1</sub>).

Bousquet et al compared roflumilast (500  $\mu\text{g}$  once daily) with inhaled beclomethasone dipropionate (BDP) (200  $\mu\text{g}$  twice daily) in a double-blind, double-dummy, randomized, noninferiority study in patients with persistent asthma ( $n = 499$ ).<sup>42</sup> At the end of the 12-week study, both medications significantly improved FEV<sub>1</sub> (roflumilast, 12% increase; BDP, 14% increase) and forced vital capacity (FVC) (roflumilast, 270 mL increase; BDP, 330 mL increase). Bousquet et al did not find any significant differences among the 2 medications with regard to FEV<sub>1</sub> and FVC values. Also, both agents were associated with similar reductions in the need for rescue inhalants.

### Oligonucleotides

Oligonucleotides target ribonucleic acid (RNA) or proteins to alter cellular signaling. Due to the complex array of patho-

physiologic processes involved in asthma, there are numerous oligonucleotides in development that may benefit patients with asthma.<sup>43</sup> Oligonucleotides cover a broad range of drugs and can be either RNA-targeting agents such as antisense, small interfering RNA, deoxyribozymes, and microRNA, or protein-targeting agents such as RNA decoy, immunostimulatory sequence drugs, and aptamers. At present, the development of oligonucleotides for the treatment of asthma is still in its infancy, and most studies are in animal models of asthma. Several preliminary clinical studies, however, have been conducted with these products. A phase 2 crossover study by Gauvreau et al assessed the safety and efficacy of TPI ASM8, which consists of 2 modified phosphorothioate antisense oligonucleotides that may attenuate the allergic inflammation response by targeting C-C chemokine receptor type 3 and the beta chain of IL-3, IL-5, and granulocyte macrophage colony-stimulating factor receptors.<sup>44</sup> A total of 17 patients with mild atopic asthma were randomized to inhale 1500  $\mu\text{g}$  TPI ASM8 or placebo by nebulizer once daily for 4 days. On day 3, subjects underwent an allergen inhalation challenge. Compared with placebo, TPI ASM8 inhibited sputum eosinophil influx by 46% and blunted the increase in total cells (63%) after the allergen challenge. Additional studies are underway.

Another oligonucleotide of interest is CYT003-QbG10.<sup>45</sup> This is an immunostimulatory sequence drug encapsulated in a virus-like particle. A phase 2 trial was completed, but results have yet to be published. A press release, however, noted that patients stabilized on ICS therapy were given CYT003-QbG10 or placebo as their ICS dose was gradually reduced. At the end of the 12-week study, average asthma symptom score increased 29% in patients given placebo and decreased 33% in patients given CYT003-QbG10.

### Bronchial Thermoplasty

A nonpharmacologic option that may be beneficial in patients with poorly controlled asthma is bronchial thermoplasty. This technique uses the application of heat to the airways to reduce airway smooth muscle mass. Asthma is characterized by increased airway smooth muscle mass which presumably plays a role in the bronchoconstriction and bronchial hyperresponsiveness characteristic of the disease. Precisely calibrated heat is applied to the airway walls by a series of bronchoscopic procedures. In animals, local application of precisely calibrated heat to segments of the airway wall resulted in reduction of airway smooth muscle with replacement by loose connective tissue. There were corresponding decreases in bronchial hyperresponsiveness in the animals studied.<sup>46</sup> In humans undergoing lung resection, bronchial thermoplasty was performed prior to the surgery

and treated airway sections were histologically analyzed. As demonstrated in the animal studies, bronchial thermoplasty reduced airway smooth muscle mass without causing airway inflammation.<sup>46</sup> In a large, multicenter trial, patients with severe asthma were randomized to receive bronchial thermoplasty or sham control for 3 bronchoscopy procedures. The primary outcome, scores on the AQLQ, was improved in both the treatment and control groups, but scores were slightly better in the bronchial thermoplasty group (AQLQ score increased  $1.35 \pm 1.10$  versus an increase of  $1.16 \pm 1.23$  in the sham group). There were no differences between the treatment groups in FEV<sub>1</sub>, symptom-free days, and rescue medication use. There were, however, safety concerns with bronchial thermoplasty. Ten (5%) of 190 patients treated with bronchial thermoplasty required hospitalization for management of worsened respiratory symptoms on the day of bronchoscopy. More studies are needed to confirm the long-term risk-benefit profile of this procedure.<sup>47</sup>

### Conclusion

Management of asthma must be improved. Patients with asthma must be convinced of the value in using their medications, particularly ICSs, regularly. Physicians should be more effectively educated on the complexities of estimating asthma severity and appropriately initiating asthma pharmacotherapy. Learning more about the complexities of asthma pathophysiology will enable the development of novel therapeutic approaches for patients who are not responding well to traditional treatments. Although more studies are necessary to ensure the efficacy and safety of both pharmacologic and nonpharmacologic approaches, there is future promise for therapeutic advances in severe, persistent asthma.

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