

## **Difficult asthma: Assessment and management, Part 2**

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### **ABSTRACT**

*Patients with severe asthma have considerable morbidity related to their asthma and are at risk for serious, life-threatening exacerbations. Their management requires an intensive and comprehensive approach, including attention to reducing exposure to environmental inciters of airway inflammation and triggers of symptoms, patient education (including an asthma action plan), and opportunity for close patient-provider communication. Approved medical options include the lipoxigenase inhibitor, zileuton; the anti-immunoglobulin E monoclonal antibody, omalizumab; and bronchial thermoplasty. Nonapproved interventions of potential benefit are ultrahigh-dose inhaled corticosteroids, anticholinergic bronchodilators (tiotropium), macrolide antibiotics, and vitamin D supplementation for the vitamin D-deficient patient. Potentially toxic, "steroid-sparing" therapies such as methotrexate, cyclosporine, and etanercept are best reserved for patients participating in clinical trials. Recognition of specific subtypes of patients with therapy-resistant asthma permits more targeted treatment approaches, such as for aspirin-sensitive asthma, persistent eosinophilic asthma, asthma complicated by allergic bronchopulmonary aspergillosis, asthma with persistent airflow obstruction, and asthma with life-threatening (near fatal) asthmatic attacks. Novel therapies based on an improved understanding of the pathobiology of therapy-resistant asthma are greatly needed.*

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**I**n Part 2 of our review of difficult asthma, we turn attention to the medical treatment of severe, refractory asthma. We make the assumption that a thorough evaluation of the patient has been made by an asthma specialist, with consideration of potential contributing factors that may explain why the patient's asthma has been difficult to control. As discussed in Part 1,<sup>1</sup> this systematic assessment includes examination of the following: exposures to inciting agents, especially inhaled allergens, that may worsen the underlying asthmatic inflammation of the airways; comorbidities that may aggravate asthma; potential issues of medication non-adherence; and alternative diagnoses that may mimic asthma. On-going consideration and reconsideration of these potential impediments to improvement are essential and can be performed concurrently with the introduction of new therapies used to treat the patient's condition.

We will consider the role of treatments approved by the U.S. Food and Drug Administration (FDA), specif-

ically the lipoxigenase inhibitor, zileuton; the anti-immunoglobulin E (IgE) monoclonal antibody, omalizumab; and bronchial thermoplasty. We will touch on medications approved by the FDA that can be applied to the treatment of difficult asthma in nonapproved ways; and we will make mention of steroid-sparing immunosuppressive agents that, because of their toxicity, are best used only in the context of a clinical trial. We will not give consideration to the role of allergen immunotherapy for difficult asthma, in part because adequate analysis of the topic is beyond the scope of this article and in part because of concerns that patients with difficult asthma are those at greatest risk for adverse outcomes, including death, from this form of treatment.

It is worth emphasizing that the management of difficult asthma involves more than the addition of novel medications. We have already stressed the importance of allergen and airway irritant avoidance; correction of aggravating conditions, such as rhinosinusitis and gastroesophageal reflux; and assistance with medication compliance. Besides achieving improved asthma control and minimizing medication side effects, an important goal of treatment for patients with difficult asthma is protection from life-endangering asthmatic attacks. All patients with difficult asthma should have a clearly articulated, written "asthma action plan" for managing deterioration in their status; and we would encourage availability of a personal

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peak flowmeter for tracking expiratory flow and for improved communication with treating providers. Besides a quick-acting bronchodilator of short duration of action by metered-dose inhaler, such as albuterol, levalbuterol, or pirbuterol, some patients will have a compressor and nebulizer for home administration of nebulized rescue bronchodilator; others will have an epinephrine prefilled syringe available for emergency use in a very severe asthmatic attack. In addition, as part of their asthma action plan, some patients will have available at home oral corticosteroids, such as prednisone, to be initiated early during the course of severe attacks according to physician-prescribed guidelines. One can not overstate the value of having an asthmatic patient be well-informed about his/her disease and its treatment and equipped with the medications needed to avert disastrous deterioration.

### FDA-APPROVED TREATMENTS FOR THERAPY-RESISTANT ASTHMA

In this section we consider the benefits, limitations, and potential adverse effects of zileuton, omalizumab, and bronchial thermoplasty.

#### Zileuton

Zileuton (Zyflo; Cornerstone Therapeutics, Inc., Cary, NC) is an inhibitor of the intracellular enzyme, 5-lipoxygenase, which together with the 5-lipoxygenase activating protein converts cell membrane-derived arachidonic acid to leukotriene  $A_4$  and initiates the pathway of leukotriene synthesis. Zileuton not only acts to reduce production of the cysteinyl leukotrienes (leukotrienes  $C_4$ ,  $D_4$ , and  $E_4$ ) but also inhibits synthesis of leukotrienes  $B_4$ , a potent neutrophil chemoattractant. It is administered orally as extended-release tablets in a dose of 1200 mg twice daily.

In a double-blind, crossover trial of patients with aspirin-exacerbated respiratory disease, zileuton as add-on therapy to "usual care" was compared with placebo.<sup>2</sup> Thirty-nine of the 40 patients in this study were taking an inhaled corticosteroid (ICS; beclomethasone or budesonide) at a dose of  $\geq 1000$   $\mu\text{g}/\text{day}$  or oral corticosteroids (at 4–25 mg/day). Each treatment period lasted 6 weeks with a 4-week washout phase between crossover periods. Patients randomized to receive zileuton had a significant improvement in lung function (forced expiratory volume in 1 second [ $\text{FEV}_{1\text{L}}$ ], and morning and evening peak flow values) compared with placebo (Fig. 1); other favorable outcomes included decreased bronchial hyperreactivity, less need for rescue bronchodilator, and improved nasal symptoms.

Patients with aspirin-sensitive asthma tend to have high basal levels of leukotriene production and are logical candidates for intense leukotriene pathway

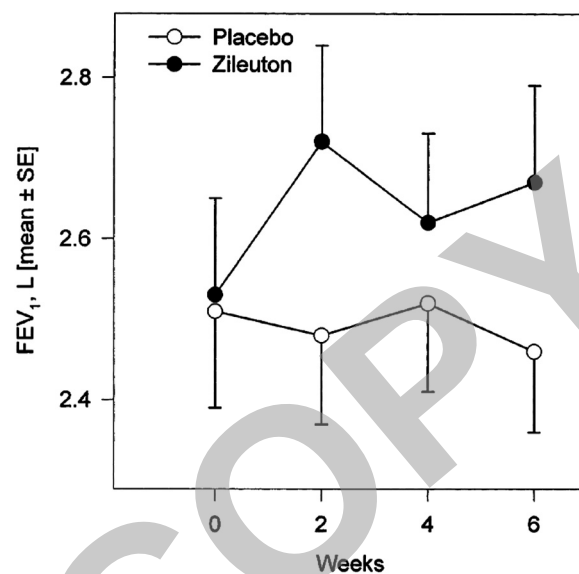


**Figure 1.** Zileuton versus placebo in aspirin-sensitive asthma. Lung function (forced expiratory volume in 1 second [ $\text{FEV}_{1\text{L}}$ ]) is displayed for zileuton- and placebo-treated patients during the 6 weeks of therapy. The differences between groups were statistically significant at 2 and 6 weeks. (Reprinted with permission from Dahlén B, Nizankowska E, Szczeklik A, et al., Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 157: 1187–1194, 1998.)

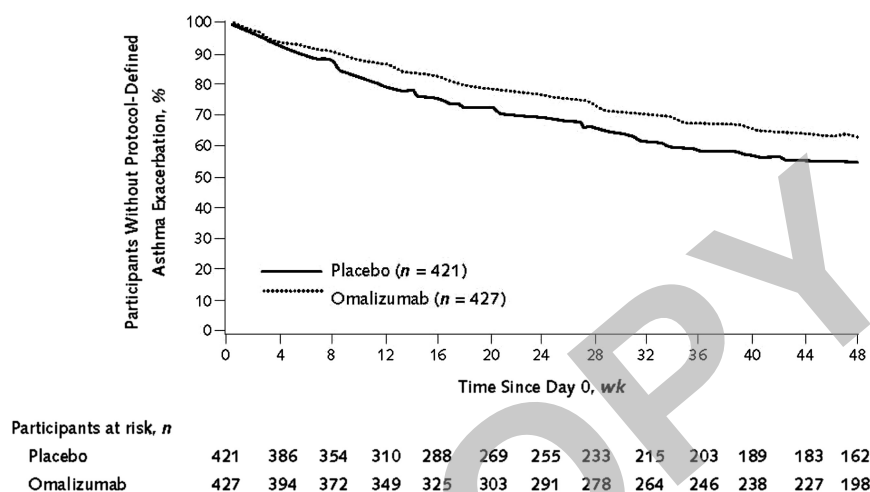
blockade. However, data are lacking to establish a role for zileuton in patients with therapy-resistant asthma who are not aspirin sensitive, the vast majority of our patients even among this subgroup with severe asthma.

Zileuton is generally well tolerated with a low risk of side effects. Two to 4% of patients develop hepatotoxicity, most often within the first 6 months of treatment. This drug-induced hepatitis is reversible with medication discontinuation, although fatalities have been reported. Consequently, it is recommended that liver function (serum aspartate aminotransferase and alanine aminotransferase) be monitored monthly for the first 3 months, and then every 2–3 months for the remainder of the 1st year and periodically thereafter.

#### Omalizumab

Omalizumab (Xolair; Genentech, San Francisco, CA) is a humanized (mouse-derived) anti-IgE monoclonal antibody. It binds to the Fc fragments of the IgE heavy chains at the same site where IgE is bound to its high-affinity receptor (Fc- $\epsilon$ -RI) on mast cells, basophils, and dendritic cells. Omalizumab reduces the concentration of circulating unbound IgE by 95%<sup>3</sup> and over time leads to a significant decrease in the density of high-affinity receptor molecules expressed on its target cell surfaces.<sup>4</sup> Omalizumab-IgE complexes are cleared from

**Figure 2.** Impact of omalizumab on risk of asthmatic exacerbations. Compared with placebo, omalizumab significantly reduced the time to first asthmatic exacerbation, as displayed in this Kaplan-Meier plot. Exacerbations were defined as worsening asthma symptoms requiring treatment with systemic corticosteroids for  $\geq 3$  days, or, for patients receiving long-term oral corticosteroids, as a  $\geq 20$ -mg increase in the average daily dose of oral prednisone. (Reprinted with permission from Hanania NA, Alpan O, Hamilos DL, et al., *Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial.* *Ann Intern Med* 154:573–582, 2011.)



the blood by the reticuloendothelial system and have not been implicated as a cause of antigen–antibody complex deposition diseases such as glomerulonephritis or serum sickness.

Omalizumab is administered by subcutaneous injection every 2–4 weeks, depending on dosing. The recommended dose is based on the patient’s weight and pretreatment total serum IgE level and approximates 0.016 mg of drug per kilogram of patient weight/serum IgE level in international units per milliliter. Omalizumab has been approved for patients aged  $\geq 12$  years who have serum IgE levels of 30–700 IU/mL and evidence by skin or blood testing of sensitization to one or more perennial aeroallergens.

Among asthmatic patients already taking inhaled high-dose steroids and long-acting  $\beta$ -agonist (LABA) bronchodilators and experiencing at least one exacerbation of their asthma requiring oral steroid treatment within the prior 12 months, omalizumab but not placebo led to a significant reduction in the frequency of asthma exacerbations over the ensuing 48 weeks of study (Fig. 2).<sup>5</sup> Omalizumab-treated patients also reported symptomatic improvement through asthma quality-of-life questionnaires (AQLQs). However, no differences between the omalizumab and placebo groups were seen in the frequency of rescue bronchodilator use, daily asthma symptom score, or lung function. The results of this large randomized trial ( $n = 850$  subjects) confirmed an earlier report of another randomized, placebo-controlled trial showing benefit among a smaller number of patients with therapy-resistant asthma. That study also found fewer asthmatic attacks among omalizumab-treated patients (after a *post hoc* adjustment for between-group differences in pretreatment exacerbation rates).<sup>6</sup> A sizeable percentage of patients with difficult asthma will be treated with daily or alternate-day prednisone in an effort to maintain adequate asthma control. Omalizumab may enable some of these patients to discontinue their sys-

temic steroids, thereby reducing their risk of serious, long-term adverse side effects.<sup>5–7</sup>

A limitation of anti-IgE therapy is its expense (upward of \$25,000/yr for drug alone). Among adult patients with asthma, a large percentage with therapy-resistant disease will be ineligible for treatment because of serum IgE levels outside of the approved dosing range ( $<30$  or  $>700$  IU/mL) or lack of evidence for allergic sensitization by skin or blood testing. Furthermore, once therapy is initiated (perhaps based on a single serum IgE level determination), there is no guidance available for determining the appropriateness of omalizumab dosing. In patients receiving omalizumab, routine laboratory determination of serum IgE measures both free IgE and IgE bound to omalizumab. Measurement of unbound IgE, a reduction of which is the intermediate goal of treatment, is not clinically available. Also unanswered is the question, When can patients with difficult-to-control asthma who have derived benefit from anti-IgE therapy discontinue treatment without likely clinical deterioration? At present, individualized patient management requires an empiric approach that can be difficult for both clinical and health insurance reasons.

Adverse effects of omalizumab include a small ( $\sim 1$  in 1000 injections) risk of anaphylactic reactions, including reactions that may be delayed by several hours after injection.<sup>8,9</sup> In initial trials an increased risk of malignancies of multiple different types was associated with omalizumab use compared with placebo and compared with the anticipated rate of malignancy in the general population.<sup>10</sup> However, interim analysis of a large-scale prospective, nonrandomized, observational study of omalizumab among persons with moderate-to-severe asthma (“An Epidemiologic Study of Xolair (Omalizumab) Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma,” [EXCELS]<sup>11</sup>) has not found any association between cancers and omalizumab use.<sup>12</sup> Find-

ings in the EXCELS trial have raised the possibility of increased adverse cardiovascular and cerebrovascular events among patients receiving omalizumab.<sup>13</sup> However, differences in the treatment groups at the start of the study (greater prevalence of diabetes and hypertension in the omalizumab-treated versus placebo-treated group) may account for this finding. Finally, reduced circulating IgE antibody may predispose to more frequent or serious parasitic infections in areas where parasites are endemic.

### Bronchial Thermoplasty

The concept underlying bronchial thermoplasty is that thermal energy applied endobronchially along the course of major bronchi can be used to disrupt bronchial smooth muscle fibers and reduce bronchial hyperresponsiveness in asthma.<sup>14</sup> In this FDA-approved procedure, a specially designed catheter is deployed through the channel of a fiberoptic bronchoscope and heat transferred through the mucosal surfaces to the underlying submucosal tissues. In three outpatient sessions, each ~1 hour in duration and spaced 3 weeks apart, the entire lengths of accessible subsegmental, segmental, and lobar bronchi can be treated. Contraindications to use of this treatment, based on the exclusion criteria for entry into a seminal clinical trial (Asthma Intervention Research [AIR2] Trial),<sup>15</sup> include the following: severe baseline airflow obstruction (prebronchodilator FEV<sub>1</sub> < 60% of predicted); daily oral steroids (at a dose of prednisone at 10 mg/day or more); four or more oral steroid bursts or hospitalizations for asthma in the past year; three or more lower respiratory tract infections in the past year; chronic sinusitis; and a history of near-fatal asthma.

Bronchial thermoplasty was assessed in a randomized, double-blind, sham procedure-controlled trial of nearly 300 patients aged 18–65 years with therapy-resistant asthma.<sup>15</sup> All subjects were receiving high-dose ICSs and LABA bronchodilators on entry into the trial. Their mean score on the AQLQ at entry into the trial was 4.3. The primary end point of the study was the AQLQ score measured at 6, 9, and 12 months after the procedure. More patients treated with bronchial thermoplasty experienced sustained improvements in their AQLQ scores by a clinically meaningful amount (0.5) than in the sham procedure-treated group. Other favorable outcomes in the group treated with bronchial thermoplasty were fewer asthmatic attacks, emergency department visits, and days missed from work or school over the course of the year after thermoplasty (Fig. 3). Bronchial thermoplasty did not alter lung function, medication use, or other symptom score measurements (e.g., symptom-free days or asthma control questionnaire score).<sup>15</sup>

Very limited data are available regarding long-term outcomes among patients treated with bronchial thermoplasty, although a small cohort of patients monitored for

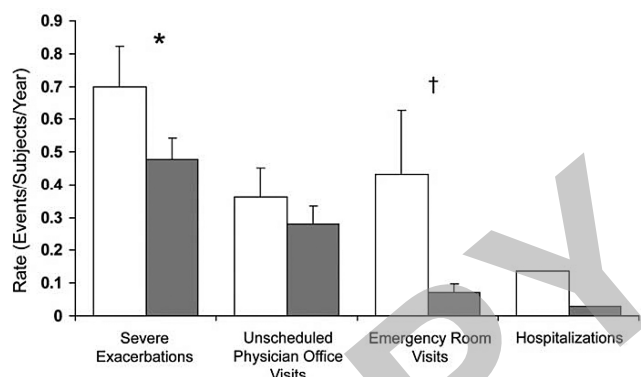


**Figure 3.** Effect of bronchial thermoplasty on asthma morbidity during the year after treatment. Statistically significant differences were found between bronchial thermoplasty and sham bronchoscopic procedures for the frequency of asthmatic exacerbations (defined as an increase in asthma symptoms requiring treatment with oral corticosteroids or a doubling of the dose of inhaled corticosteroids) and for emergency department visits. Open bars represent the sham procedure-treated group; shaded bars represent the bronchial thermoplasty-treated group. \*Indicates a posterior probability of superiority = 95.5%; †Indicates a posterior probability of superiority = 99.9%. (Reprinted with permission from Castro M, Rubin AS, Laviolette M, et al., Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 181:116–124, 2010.)

5 years had sustained benefit without delayed adverse effects.<sup>16</sup> The presumed mechanism of action of bronchial thermoplasty—reduced capacity for airway smooth muscle constriction—was not assessed in the AIR2 trial, and other histological consequences of thermal injury to the airways are unknown. It is uncertain whether bronchial thermoplasty will allow patients to reduce their burden of daily medications, including oral steroids. The cost of the procedure and the three bronchoscopies that it entails is likely to vary from institution to institution, with estimates in the range of \$5000–15,000.

Prolonged bronchoscopic procedures among patients with difficult-to-control asthma can be expected to entail significant morbidity. In the AIR2 trial, 8% of patients required hospitalization for complications surrounding their bronchoscopies, including asthma exacerbations, segmental atelectasis, hemoptysis, and lower respiratory tract infections. There have not been reports of bronchial strictures or perforations after thermoplasty.<sup>15</sup>

### Potentially Beneficial Treatments for Therapy-Resistant Asthma, Used in Nonapproved Ways, with Low Risk of Serious Toxicity

Physicians treating therapy-resistant asthma are constantly seeking new approaches to reduce disease morbidity and drug toxicities, including novel application of therapies already available. In this section we will

consider the pros and cons of the following therapeutic interventions: ultrahigh-dose inhaled steroids, alternative long-acting bronchodilators, macrolide antibiotics, and vitamin D supplementation.

*Ultrahigh-Dose Inhaled Steroids.* As recommended in asthma treatment guidelines,<sup>17,18</sup> high-doses of inhaled steroids consist of fluticasone at 1000  $\mu\text{g}/\text{day}$  or the equivalent. This dose can be achieved with as little as 1–2 inhalations of medication taken twice daily, making good compliance with this high-dose regimen easily achievable. For the patient whose asthma remains poorly controlled despite regular use of these high doses of inhaled steroids, especially those who continue to manifest sputum eosinophilia, further increasing the dose of inhaled steroids is an option. This approach is particularly compelling for the patient who improves on systemic steroids and worsens with withdrawal of systemic steroids. One approach is to double the dose of inhaled steroids (e.g., to fluticasone 2000  $\mu\text{g}/\text{day}$ ), another is to add a different steroid preparation, such as one with smaller average particle size in the aerosol plume (smaller median mass aerodynamic diameter) and therefore having the possibility of improved delivery onto smaller, more peripheral airways (e.g., beclomethasone at 80  $\mu\text{g}/\text{puff}$ , 4 puffs twice daily).<sup>19</sup>

Potential concerns with long-term application of this strategy are local and systemic steroid side effects. Locally, tissue atrophy is a theoretical concern; might ultrahigh-dose inhaled steroids lead to laryngeal atrophy with permanent dysphonia and to tracheal atrophy and risk of tracheomalacia? Systemic absorption of inhaled steroids is dose dependent and a predictable consequence of very high doses. The risk of recognized steroid side effects, including cataracts,<sup>20</sup> increased intraocular pressure and open-angle glaucoma,<sup>21</sup> skin bruising, adrenal suppression, and bone loss contributing to osteoporosis,<sup>22</sup> are all increased. Long-term risks such as these are only justified if the patient's quality of life is improved to a major extent and/or if the dose of oral steroid tablets can be reduced as the result of use of ultrahigh-dose inhaled steroids.

*Alternative Long-Acting Bronchodilators.* The introduction of LABA bronchodilators in the mid-1990s had a dramatic impact on difficult-to-control asthma. When combined with inhaled steroids, LABAs proved highly effective in reducing symptoms (especially nocturnal awakenings due to asthma), improving lung function, and enhancing quality of life.<sup>23</sup> However, clinical data have suggested that not everyone responds to sustained  $\beta$ -agonist stimulation in the same way. Some patients derive less bronchodilator benefit, and it has been suggested that repeated stimulation of the  $\beta$ -agonist receptor can lead to worsening lung function in a

minority of asthmatic patients.<sup>24</sup> As discussed in Part 1, efforts are ongoing to determine whether genotypic variants in the  $\beta$ -receptor molecule can predict those who will experience worse outcomes with use of LABAs.<sup>25</sup>

In a recent study of patients whose asthma was not well controlled on low-dose inhaled steroids, addition of the once-daily, long-acting anticholinergic bronchodilator, tiotropium, to low-dose inhaled steroids was compared with two other treatment strategies: adding a LABA to low-dose inhaled steroids or increasing the dose of inhaled steroids.<sup>26</sup> Using a noninferiority analysis, when added to low-dose inhaled steroids, tiotropium proved equally effective as salmeterol for the outcomes of morning and evening peak flow measurements, proportion of asthma control days, and daily symptom scores; and it was superior in terms of the prebronchodilator FEV<sub>1</sub>. (Both adding tiotropium and adding a LABA to low-dose inhaled steroids was more effective than increasing the dose of inhaled steroids alone.) This study did not address whether addition of tiotropium to the combination of inhaled steroids and LABA might be beneficial in some patients.

Tiotropium has few known side effects, other than dry mouth. Urinary retention in persons with prostatism is a theoretical adverse effect that occurs only rarely. Concerns about increased cardiovascular adverse effects (heart attacks and strokes) from regular use of anticholinergic bronchodilators<sup>27</sup> were not borne out in a large-scale, 4-year trial of tiotropium among a population of predominantly middle-aged men.<sup>28</sup> Given a favorable side effects profile and long-term safety, a trial of tiotropium in persons with therapy-resistant asthma seems warranted, despite the limited available information about its use in asthma. What is not known is whether some patients would do better if a long-acting anticholinergic bronchodilator were substituted for a LABA rather than added to it, and whether both short- and long-acting anticholinergic bronchodilators (ipratropium and tiotropium) should be substituted for all  $\beta$ -agonist bronchodilators, on the possibility that withdrawal of  $\beta$ -agonist stimulation might improve asthma control in a subset of therapy-resistant patients.

Slow-release theophylline preparations are another alternative bronchodilator to LABAs.<sup>29</sup> Because of their limited bronchodilator effectiveness, frequent side effects, multiple drug interactions, variable metabolism necessitating blood level measurements, and risk of life-threatening toxicities from overdoses, we will not give further consideration to their use.

*Macrolide Antibiotics.* The rationale for use of macrolide antibiotics to treat refractory asthma is twofold. First, it is possible that intracellular microbes such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* or

their toxic byproducts contribute to the pathogenesis of asthma in some patients.<sup>30</sup> Second, long-term use of macrolide antibiotics has proven effective in the treatment of neutrophilic inflammatory lung diseases such as cystic fibrosis, panbronchiolitis, and chronic obstructive pulmonary disease (COPD) and might, by analogy, be adjunctive therapy in a subset of asthmatic patients with neutrophilic airway inflammation.<sup>31</sup>

To date, clinical trials of macrolide antibiotics in asthma have for the most part been small in scale and short in duration. Variable treatment regimens have been proposed, including weekly administration of azithromycin for 6 weeks (after an initial loading dose given daily for 3 days)<sup>32</sup> and daily administration of clarithromycin for 6 weeks.<sup>33</sup> Some studies have found benefit only among patients with evidence for mycoplasma or chlamydial infection of the airways.<sup>33</sup> In a study with a negative outcome, the Asthma Clinical Research Network reported a 16-week randomized, placebo-controlled trial of daily clarithromycin versus placebo among 92 subjects with asthma poorly controlled despite low-dose inhaled steroids (fluticasone at 88  $\mu$ g twice daily). They found no change in asthma control among the two groups, regardless of the presence or absence of polymerase chain reaction evidence on bronchial biopsy for *M. pneumoniae* or *C. pneumoniae* infection.<sup>34</sup>

There is ample experience regarding the safety of long-term macrolide therapy from experience treating atypical mycobacterial pulmonary infections and from a 1-year, randomized trial of azithromycin in COPD.<sup>35</sup> The most common side effect of long-term use is hearing loss.<sup>35</sup> A broader concern is the potential for selection of macrolide-resistant organisms, although the emergence of infections caused by resistant pathogens has not been observed in trials involving patients with asthma.

**Vitamin D.** Recently, interest has newly focused on the role of vitamin D as a modulator of immune responses<sup>36</sup>; and, in particular, several lines of evidence suggest a potential role for vitamin D in asthma. For instance, there are vitamin D receptors on activated T and B lymphocytes and dendritic cells. Lower vitamin D levels are associated with worse asthma control<sup>37</sup>; and it has been suggested that children of mothers with low vitamin D dietary intake during pregnancy are more likely to develop asthma.<sup>38</sup> Children with low vitamin D levels tend to have more asthma exacerbations,<sup>39</sup> and in one study low vitamin D levels were associated with an increased steroid usage, possibly because of decreased steroid responsiveness.<sup>40</sup>

None of these studies has shown that treating persons with low serum vitamin D levels improves asthma. Studies to test this hypothesis are ongoing. In the meantime, administering vitamin D to asthmatic

patients with vitamin D insufficiency (blood levels  $\leq 30$  ng/mL) represents a low-risk intervention. The dose of vitamin D needed to optimize immune function in asthma is unknown. Current research trials are testing the potential benefits for persons with vitamin D insufficiency of doses varying from 400 to 4000 IU/day.<sup>41</sup>

### **Potentially Beneficial Treatments, Used in Nonapproved Ways, for Therapy-Resistant Asthma with High Risk of Serious Toxicity**

The search for steroid-sparing therapies in patients with steroid-dependent asthma has led investigators to adopt treatments effective in other inflammatory/immune-mediated conditions for potential treatment of asthma. An example is methotrexate, which is accepted as a steroid-sparing and disease-modifying therapy in rheumatoid arthritis and psoriasis. Initial reports describing its use in asthma were encouraging.<sup>42</sup> Once-weekly doses from 10–25 mg given orally or intramuscularly seemed to enable asthmatic patients to reduce their dose of oral steroids and in some cases to discontinue their use altogether. However, subsequent studies did not uniformly describe favorable outcomes in asthma, and meta-analyses have suggested marginal benefit at best.<sup>43,44</sup> Given its limited effectiveness and risk of side effects (particularly nausea and vomiting) and long-term adverse consequences (liver inflammation and fibrosis), use of methotrexate for severe asthma has largely fallen out of favor.

Cyclosporine (along with other calcineurin inhibitors) is the cornerstone of immunosuppressive therapy in solid organ transplantation. Its potent inhibitory action on lymphocytes makes it a logical choice as experimental therapy for steroid-dependent asthma. A limited number of publications have described improved asthma control and reduced steroid requirement when cyclosporine was used to treat therapy-resistant asthma.<sup>45,46</sup> However, cyclosporine is difficult to use (in large part because of its many drug interactions and narrow therapeutic window), and the high risk of renal toxicity and irreversible renal failure with long-term use or with supratherapeutic blood levels makes it an unacceptable alternative for most practitioners.

TNF- $\alpha$  inhibition has proven highly effective in rheumatoid arthritis and may prove to be steroid sparing in sarcoidosis. An initial randomized, crossover trial of twice-weekly etanercept or placebo in asthma found significant improvement in lung function and asthma quality-of-life scores with reduced bronchial hyperresponsiveness in response to etanercept.<sup>47</sup> However, this favorable outcome could not be duplicated in subsequent studies.<sup>48,49</sup> It may be that the benefit of TNF- $\alpha$  inhibition in asthma is limited to persons with neutrophilic airway inflammation. Treatment specifically tar-

Table 1 Clinically defined asthma subtypes and management options for each group

| Asthma Subtype                                                | Special Management Considerations                                                                                                                                                                                                                            |
|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aspirin-sensitive asthma                                      | Leukotriene modifiers, including lipoxygenase inhibitor, aspirin desensitization and maintenance therapy, and avoidance of cyclooxygenase 1 inhibitors                                                                                                       |
| Persistent eosinophilic asthma                                | Ultrahigh-dose inhaled steroids; anti-IL-5 monoclonal antibody (in clinical trials)                                                                                                                                                                          |
| Asthma complicated by allergic bronchopulmonary aspergillosis | Systemic corticosteroids; ultrahigh-dose inhaled steroids and oral antifungal azoles                                                                                                                                                                         |
| Asthma with persistent airflow obstruction                    | Appropriately adjusted target of optimal lung function, regular exercise (including possible outpatient pulmonary rehabilitation), and potential dose reduction of anti-asthmatic medications                                                                |
| Life-threatening (near fatal) asthma                          | Focus on prevention of severe asthmatic attacks, including peak flowmeter, asthma action plan, portable nebulizer or epinephrine prefilled syringe, oral steroids available at home, accessible emergency care, and well-informed family/friends for support |

geted at this subpopulation of patients with therapy-resistant asthma has yet to be reported.

For many years allergists have used lipid-based preparations of steroids for intramuscular administration to treat refractory seasonal rhinitis and conjunctivitis. Using this repository formulation might provide improved symptom control, ensure medication compliance, and perhaps induce fewer systemic steroid side effects than long-term oral administration. In small studies describing its use in refractory, steroid-dependent asthma, high-dose intramuscular triamcinolone brought about sustained improvement (6–12 months) with a reduction in total steroids doses.<sup>50,51</sup> We have used intramuscular steroids as a form of “directly observed therapy” for difficult-to-control asthma when medication compliance appeared to be an issue. Avoiding patient self-adjustment of his/her oral steroid dose may indeed lead to less total systemic steroid burden. However, long-term treatment with intramuscular steroids induces the same iatrogenic Cushing’s syndrome as oral steroids, and may induce adrenal insufficiency. Local side effects at the site of administration may include skin hypopigmentation and atrophy of the subcutaneous tissue.

### Therapy based on Phenotypic Subtypes

It is likely that in the (near) future we will abandon a “one-shoe-fits-all” approach to the treatment of refractory asthma in favor of therapies tailored to specific subgroups of patients. For now, we can identify subgroups based on their clinical and pathophysiological presentations. In the future, molecular mapping and genetic profiling<sup>52</sup> will provide information to help pinpoint specific therapeutic targets unique to some patients with asthma and not others. Novel therapies

based on this sort of information have already begun to emerge in cystic fibrosis.<sup>53</sup>

The method of cluster analysis has allowed investigators to identify distinct cluster groups of patients with severe asthma in children and adults.<sup>54,55</sup> Others have proposed categorization by biological and pathophysiological endotypes, leading the description of six recognizable subgroups of patients with distinctive asthma characteristics.<sup>56</sup> What follows is our personal subgrouping of patients with therapy-resistant asthma, based on observations in our own practices (Table 1).

*Aspirin-Sensitive Asthma.* It is estimated that 3–5% of adult patients with asthma will experience abrupt deterioration in their asthma after ingestion of a cyclooxygenase-1 inhibitor such as aspirin or other nonsteroidal anti-inflammatory drug (NSAID). In descriptive series of patients with difficult asthma, aspirin-sensitive asthma (or aspirin-exacerbated respiratory disease) constitutes a disproportionate fraction of patients, as many as 20%.<sup>57</sup> They are typically self-identified based on their prior asthmatic exacerbations after taking aspirin or other NSAIDs. Their distinctive biochemical characteristic is overproduction of cysteinyl leukotrienes at baseline and after challenge with aspirin or other NSAIDs.<sup>58</sup>

As we have already discussed, this subgroup of patients with refractory asthma are logically treated intensively with leukotriene modifiers, such as cysteinyl leukotriene receptor antagonists or a lipoxygenase inhibitor.<sup>2</sup> Future studies might explore the use of both classes of leukotriene modifier in combination or higher than conventional doses of leukotriene receptor antagonists. Another approach in specialized centers

has been aspirin-desensitization followed by aspirin maintenance therapy.<sup>59</sup>

*Persistent Eosinophilic Asthma.* Some patients with asthma have persistent blood eosinophilia despite appropriate treatment for allergic exposures. A subgroup has adult-onset asthma and no demonstrable allergic sensitivities. Detailed evaluation fails to provide an alternative explanation for their eosinophilia, such as parasitic infection, Churg-Strauss vasculitis, or hyper-eosinophilic syndrome.<sup>60</sup> Other patients manifest with persistent sputum eosinophilia despite reliable and intensive treatment with inhaled corticosteroids. (In our clinical practices, sputum eosinophilia is identified in the hospital clinical cytology laboratory on review of standard sputum samples by cytopathologists). It is reasonable to suspect that their persistent airway eosinophilia is a contributing factor to their therapy-resistant asthma. Many of these patients require daily oral steroids to suppress their blood and sputum eosinophilia and control symptoms.<sup>61</sup>

In this subgroup of patients with refractory asthma, we encourage a trial of ultrahigh-dose inhaled steroids, as mentioned earlier in this article. A promising future approach is treatment with an anti-interleukin (IL)-5 monoclonal antibody, such as reslizumab or mepolizumab. Clinical trials of anti-IL-5 monoclonal antibodies have shown promise in this patient population.<sup>62,63</sup> For instance, in one published study of anti-IL-5 monoclonal antibody therapy in patients with persistent eosinophilic asthma despite high-dose inhaled steroids, four monthly infusions of reslizumab led to improved asthma control questionnaire scores and higher FEV<sub>1</sub> values compared with placebo and were associated with few side effects.<sup>63</sup>

*Allergic Bronchopulmonary Aspergillosis.* Among asthmatic patients with persistent eosinophilia, some will be found to have colonization of their airways by *Aspergillus*. The intense type-1 immune-mediated response to *Aspergillus* causes bronchiectasis with a characteristic distribution, predominantly in proximal airways. Patients with allergic bronchopulmonary aspergillosis (ABPA) manifest with a mixture of allergic and infectious features. They may have eosinophilic pneumonia or bacterial infection of bronchiectatic airways (such as with *Staphylococcus* and *Pseudomonas*). Cough, sputum production, and mucus plugging (including mucoid impaction of dilated airways seen on chest imaging) are characteristic features.<sup>64</sup>

Treatment of ABPA has traditionally focused on suppression of the immune response with systemic steroids and ICSs. Evidence now supports adjunctive therapy with anti-fungal azoles (such as itraconazole or voriconazole), which have permitted dose reduction of systemic steroids.<sup>65</sup> Treatment often includes intermit-

tent or continuous suppressive use of antibiotics to treat bacterial superinfections, similar to the management of other patients with bronchiectasis.

*Asthma with Persistent Airflow Obstruction.* Although asthma is commonly thought of as a disease characterized by fully reversible airflow obstruction, it is well recognized that some persons with asthma develop permanent, irreversible airflow obstruction.<sup>66</sup> The pathology is poorly characterized but presumably involves a component of bronchial and peribronchial fibrosis. Other than cigarette smoking, risk factors for the development of irreversible airflow obstruction in asthma are likewise uncertain, with possibilities including undertreatment of long-standing airway inflammation, severe asthmatic exacerbations,<sup>67</sup> and comorbid viral or immune-mediated bronchiolitis. Patients with severe persistent airflow obstruction have features in common with patients suffering from COPD, including impaired exercise capacity and limited functional reserve in the setting of exacerbations, especially those triggered by respiratory tract infections.

Patients with persistent airflow obstruction in asthma may have few daily respiratory symptoms other than exertional dyspnea. They may have none of the frequent cough, wheezing, and chest tightness typical of other patients with therapy-resistant asthma, and they may not experience frequent asthma exacerbations. Their management requires a re-setting of therapeutic expectations. The goals of treatment become defining and then preserving their maximal level of lung function, maintenance of exercise capacity through regular exercise, prevention of respiratory infections with appropriate vaccinations, and in some instances “stepping down” asthma treatment that does not further improve lung function or quality of life.

*Life-Threatening (near Fatal) Asthma.* Regardless of their biological and pathophysiological characteristics, persons with severe asthma are at increased risk of suffering life-threatening asthmatic attacks. In the epidemiology and natural history of asthma: outcomes and treatment regimens trial referenced in Part 1 of this review, the prevalence of having ever been intubated for respiratory failure due to asthma was 8% among those whose FEV<sub>1</sub> was  $\geq 80\%$ , 12% among those with an FEV<sub>1</sub> of 60–80%, and 20% among those with an FEV<sub>1</sub>  $\leq 60\%$ .<sup>68</sup> Intubation for respiratory failure represents a near-fatal event in asthma. Had the resources for intubation and mechanical ventilation not been available, the patient would likely have died. Furthermore, in a follow-up study among patients who were treated in an intensive care unit for their asthma, the estimated mortality over the ensuing 6 years was ~23%.<sup>69</sup>

Patients who have experienced life-threatening asthmatic attacks should receive special attention not only to their optimal maintenance therapy but also to strategies for dealing with worsening asthmatic symptoms. Items to include in a "life-threatening asthma" checklist might include home peak flowmeter, asthma action plan, portable compressor and nebulizer, epinephrine prefilled syringe, oral corticosteroids available to the patient at all times, and emergency contacts for medical help. Care of such patients also includes intense education of both patient and family members or close friends who might be called on to help in an acute asthmatic crisis.

### Experimental Therapies

Despite the advances in asthma care over the last 20 years and the impressive decline in hospitalizations and deaths due to asthma in the United States since the mid-1990s, it is clear that persons with therapy-resistant asthma, almost by definition, are in need of new, more effective, and safer medications to treat their unique types of asthma. Like patients with other therapy-resistant diseases, such as many forms of cancer or idiopathic pulmonary fibrosis, one option available to them should be participation in early phase trials of novel, experimental therapies. At the Partners Asthma Center one such randomized, controlled trial is currently underway, testing the utility of imatinib (Gleevec; Novartis, East Hanover, NJ) in severe asthma, based on the activity of this tyrosine kinase inhibitor to inhibit mast cell function by blocking the activity of stem cell factor at its receptor (c-Kit).

Another example, for which there is initial supportive evidence, is inhibition of IL-13 with the monoclonal antibody, lebrikizumab. In a published, 6-month pilot study, patients with severe asthma and persistent airflow obstruction had greater improvement in prebronchodilator FEV<sub>1</sub> when randomized to monthly injections of lebrikizumab as opposed to placebo, although other outcomes were indistinguishable between groups (asthma symptom scores, need for rescue medications, frequency of nocturnal awakenings, or rates of exacerbations).<sup>70</sup> Higher levels of periostin (a protein released from epithelial cells in response to IL-13 stimulation) predicted a larger bronchodilator response to lebrikizumab, indicating a potential biomarker for lebrikizumab responsiveness.<sup>70</sup>

Patients interested in participating in research in difficult-to-control asthma can be directed to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### SUMMARY

Severe asthma remains a source of major morbidity for millions of people in the United States and worldwide. Although highly effective and well-tolerated medications successfully control asthma in the vast

majority of patients, a small minority continue to suffer reduced quality of life and frequent asthmatic attacks despite appropriate treatment with maximal guidelines-directed therapy. In this review we have proposed a systematic approach to the evaluation of such patients with difficult-to-control asthma. The assessment begins with evaluation of medication adherence to the medically prescribed treatment program and exclusion of alternative diagnoses that may be mimicking or complicating asthma. Also important are allergy assessment and avoidance and attention to complicating conditions, such as rhinosinusitis and gastroesophageal reflux, which may prevent good asthma control unless corrected.

Some patients will be found to have disease that is truly resistant to conventional therapy. Options for their care include lipoxigenase inhibitor therapy, anti-IgE monoclonal antibody therapy, and bronchial thermoplasty. Unconventional approaches that have proven effective in some patients include ultrahigh-dose inhaled steroids, use of alternative bronchodilators (such as the long-acting anticholinergic bronchodilator, tiotropium), macrolide antibiotics, and correction of vitamin D deficiency. We may be able to refine our treatment approach by identifying specific subtypes of patients with therapy-resistant asthma, such as aspirin-sensitive asthma and asthma with persistent eosinophilia, and applying current and emerging therapies to these specific biological subtypes.

In the end, we acknowledge that our current understanding of the mechanisms driving therapy-resistant asthma is limited and our therapies imperfect. National and international consortia have been formed to investigate the pathobiology underlying refractory asthma, and trials are ongoing to test the efficacy of novel and emerging therapies. In the meantime, we encourage a collaborative approach to these challenging patients, bringing together allergists and pulmonologists, as well as other consultants (*e.g.*, otolaryngologists, speech pathologists, gastroenterologists, cardiologists, psychiatrists, social workers, and endocrinologists) into an integrated medical team. In this way we can best hope to achieve our goals of preventing life-threatening asthmatic attacks, improving asthma-related quality of life, minimizing medication side effects, and, ultimately, achieving the same good asthma control possible for others with asthma.

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