

# Asthma: Newer Tx options mean more targeted therapy

It's an exciting era of asthma management, with the introduction of several novel modalities, including biological therapy and bronchial thermoplasty.

## PRACTICE RECOMMENDATIONS

› Consider inhaled corticosteroids (ICS) as your first choice for a long-term control agent to treat asthma; add a long-acting beta agonist (LABA) when needed. **(A)**

› Use long-acting muscarinic antagonists (LAMA) as add-on therapy for patients whose asthma is uncontrolled despite the use of low-dose ICS-LABA, or as an alternative to high-dose ICS-LABA. **(A)**

› Consider biological therapies for patients with asthma exacerbations that require steroids at least twice a year. **(B)**

› Use azithromycin as an add-on therapy to ICS-LABA for a select group of patients with uncontrolled persistent asthma (neutrophilic phenotype). **(C)**

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

**R**ecent advances in our understanding of asthma pathophysiology have led to the development of new treatment approaches to this chronic respiratory condition, which affects 25 million Americans or nearly 8% of the population.<sup>1</sup> As a result, asthma treatment options have expanded from just simple inhalers and corticosteroids to include biological therapies, immunotherapy, bronchial thermoplasty, and anti-inflammatory agents. This review will focus on the newer therapeutic options and provide guidance on when to seek expert pulmonary consultation (TABLE 1). But before we begin, it's important to briefly review the pathophysiology of asthma and several key diagnostic considerations.

## The pathophysiology of asthma provides key targets for therapy

There are 2 basic phenotypes of asthma—neutrophilic predominant and eosinophilic predominant—and 3 key components to its pathophysiology<sup>2</sup>:

■ **Airway inflammation.** Asthma is mediated through either a type 1 T-helper (Th-1) cell or a type 2 T-helper (Th-2) cell response, the pathways of which have a fair amount of overlap (FIGURE). In the neutrophilic-predominant phenotype, irritants, pollutants, and viruses trigger an innate Th-1 cell-mediated pathway that leads to subsequent neutrophil release. This asthma phenotype responds poorly to standard asthma therapy.<sup>2-4</sup>

In the eosinophilic-predominant phenotype, environmental allergic antigens induce a Th-2 cell-mediated response in the airways of patients with asthma.<sup>5-7</sup> This creates a downstream effect on the release of interleukins (IL) including IL-4, IL-5, and IL-13. IL-4 triggers immunoglobulin (Ig) E release, which subsequently induces mast cells to release inflammatory cytokines, while IL-5 and IL-13 are responsible for eosinophilic response. These cytokines and eosinophils induce

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TABLE 1

## When to consider pulmonary consultation

Multiple exacerbations
Symptoms not controlled on high-dose ICS-LABA combination
Asthma-COPD overlap syndrome
Patient with history of intubation
Symptoms are only cough or are exercise induced
Asthma with predominant severe seasonal/environmental allergies
Patients on chronic prednisone therapy
Potential asthma mimics: upper airway cough syndrome, paradoxical vocal cord movement disorder, laryngopharyngeal reflux disease
Asthma with systemic signs of vasculitis
Uncontrolled asthma with peripheral blood count showing eosinophils > 150 cells/mcL or IgE > 30 IU/mL <sup>15</sup>
Asthma with abnormal parenchymal lung findings on chest x-ray or CT

COPD, chronic obstructive pulmonary disease; CT, computed tomography; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta-agonist.

➤ It is important to determine whether patients with asthma-COPD overlap syndrome are asthma predominant or COPD predominant, because appropriate first-line treatment will differ.

airway hyperresponsiveness, remodeling, and mucus production. Through repeated exposure, chronic inflammation develops and subsequently causes structural changes related to increased smooth muscle mass, goblet cell hyperplasia, and thickening of lamina reticularis.<sup>8,9</sup> Understanding of this pathobiological pathway has led to the development of anti-IgE and anti-IL-5 drugs (to be discussed shortly).

■ **Airway obstruction.** Early asthmatic response is due to acute bronchoconstriction secondary to IgE; this is followed by airway edema occurring 6 to 24 hours after an acute event (called late asthmatic response). The obstruction is worsened by an overproduction of mucus, which may take weeks to resolve.<sup>10</sup> Longstanding inflammation can lead to structural changes and reduced airflow reversibility.

■ **Bronchial hyperresponsiveness** is induced by various forms of allergens, pollutants, or viral upper respiratory infections. Sympathetic control in the airway is mediated via beta-2 adrenoceptors expressed on airway smooth muscle, which are responsible for the effect of bronchodilation in response to albuterol.<sup>11,12</sup> Cholinergic pathways may further contribute to bronchial hyperresponsiveness and form the basis for the efficacy of anticholinergic therapy.<sup>12,13</sup>

## What we've learned about asthma can inform treatment decisions

Presentation may vary, as asthma has many forms including cough-variant asthma and exercise-induced asthma. Airflow limitation is typically identified through spirometry and characterized by reduced (< 70% in adults) forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) or bronchodilator response positivity (an increase in post-bronchodilator FEV<sub>1</sub> > 12% or FVC > 200 mL from baseline).<sup>2</sup> If spirometry is not diagnostic but suspicion for asthma remains, bronchial provocation testing or exercise challenge testing may be needed.

Additional diagnostic considerations may impact the treatment plan for patients with asthma:

■ **Asthma and COPD.** A history of smoking is a key factor in the diagnosis of chronic obstructive pulmonary disease (COPD)—but many patients with asthma are also smokers. This subgroup may have asthma-COPD overlap syndrome (ACOS). It is important to determine whether these patients are asthma predominant or COPD predominant, because appropriate first-line treatment will differ. Patients who are COPD predominant demonstrate reduced diffusion capacity (DLCO) and abnormal PaCO<sub>2</sub> on arterial blood gas. They also may show more structur-

al damage on chest computed tomography (CT) than patients with asthma do. Asthma-predominant patients are more likely to have eosinophilia.<sup>14</sup>

■ **Patients with severe persistent asthma or frequent exacerbations**, or those receiving step-up therapy, may require additional serologic testing. Specialized testing for IgE and eosinophil count, as well as a sensitized allergy panel, may help clinicians in selecting specific biological therapies for treatment of severe asthma (further discussion to follow). We recommend using a serum allergy panel, as it is a quick and easy way to identify patients with extrinsic allergies, whereas skin-based testing is often time consuming and may require referral to a specialist.<sup>2,5,15</sup>

■ **Aspergillus.** An additional consideration is testing for Aspergillus antibodies. Aspergillus is a ubiquitous fungus found in the airways of humans. In patients with asthma, however, it can trigger an intense inflammatory response known as allergic bronchopulmonary aspergillosis. ABPA is not an infection. It should be considered in patients who have lived in a damp, old housing environment with possible mold exposure. Treatment of ABPA involves oral corticosteroids; there are varying reports of efficacy with voriconazole or itraconazole as suppressive therapy or steroid-sparing treatment.<sup>16-18</sup>

### Getting a handle on an ever-expanding asthma Tx arsenal

The goals of asthma treatment are symptom control and risk minimization. Treatment choices are dictated in part by disease severity (mild, moderate, severe) and classification (intermittent, persistent). Asthma therapy is traditionally described as step-up and step-down; **TABLE 2** summarizes available pharmacotherapy for asthma and provides a framework for add-on therapy as the disease advances.

Over the past decade, a number of therapeutic options have been introduced or added to the pantheon of asthma treatment.

#### Inhaled medications

This category includes inhaled corticoste-

roids (ICS), which are recommended for use alone or in combination with long-acting beta-agonists (LABA) or with long-acting muscarinic agonists (LAMA).

■ **ICS** is the first choice for long-term control of persistent asthma.<sup>2</sup> Its molecular effects include activating anti-inflammatory genes, switching off inflammatory genes, and inhibiting inflammatory cells, combined with enhancement of beta-2-adrenergic receptor expression. The cumulative effect is reduction in airway responsiveness in asthma patients.<sup>19-22</sup>

■ **LABAs** are next in line in the step-up, step-down model of symptom management. LABAs should not be prescribed as stand-alone therapy in patients with asthma, as they have received a black box warning from the US Food and Drug Administration (FDA) for an increase in asthma-related death<sup>23</sup>—a concern that has not been demonstrated with the combination of ICS-LABA.

LABAs cause smooth muscle relaxation in the lungs.<sup>24</sup> There are 3 combination products currently available: once-daily fluticasone furoate/vilanterol (Breo), twice-daily fluticasone propionate/salmeterol (Advair), and twice-daily budesonide/formoterol (Symbicort).

Once-daily fluticasone furoate/vilanterol has been shown to improve mean FEV<sub>1</sub>.<sup>25</sup> In a 24-week, open-label, multicenter randomized controlled trial to evaluate the efficacy and safety of all 3 combination ICS-LABAs, preliminary results indicated that—at least in a tightly controlled setting—once-daily fluticasone furoate/vilanterol provides asthma control similar to the twice-daily combinations and is well tolerated.<sup>26</sup>

Two ultra-long-acting (24-hour) LABAs, olodaterol (Striverdi Respimat) and indacaterol (Arcapta Neohaler), are being studied for possible use in asthma treatment. In a phase 2 trial investigating therapy for moderate-to-severe persistent asthma, 24-hour FEV<sub>1</sub> improved with olodaterol when compared to placebo.<sup>27</sup>

Another ongoing clinical trial is studying the effects of ultra-long-acting bronchodilator therapy (olodaterol vs combination olodaterol/tiotropium) in asthma patients who smoke and who are already using ICS (Clini-

➤ **LABAs should not be prescribed as stand-alone therapy in patients with asthma, as they have received an FDA black box warning.**

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Ideal candidates for biological therapy are patients who have exhausted other forms of severe asthma treatment.

**TABLE 2**  
**Step-up therapy for asthma<sup>15</sup>**

Intermittent asthma	<b>Step 1</b> prn SABA
Mild persistent asthma	<b>Step 2</b> Low-dose ICS
Moderate persistent asthma	<b>Step 3</b> Low-dose ICS + LABA
Severe persistent asthma	<b>Step 4</b> Medium-dose ICS + LABA
	<b>Step 5</b> High-dose ICS + LABA
	<b>Step 6</b> Consider adding
	A) Omalizumab (Xolair) for elevated IgE > 30 IU/mL
	B) Anti-IL-5 therapies (Mepolizumab [Nucala], Reslizumab [Cinqair], Benralizumab [Fasenra]) for elevated eosinophils (> 150 cells/mcL)
	C) LAMA
	D) Azithromycin (for neutrophil-predominant phenotype or ACOS)
	E) Bronchial thermoplasty
	F) Oral prednisone

ACOS, asthma-COPD overlap syndrome; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic agonist; PRN, as needed; SABA, short-acting beta-agonist.

calTrials.gov NCT02682862). Indacaterol has been shown to be effective in the treatment of moderate-to-severe asthma in a once-a-day dosing regimen.<sup>28</sup> However, when compared to mometasone alone, a combination of indacaterol and mometasone demonstrated no statistically significant reduction in time to serious exacerbation.<sup>29</sup>

■ **The LAMA tiotropium** is recommended as add-on therapy for patients whose asthma is uncontrolled despite use of low-dose ICS-LABA or as an alternative to high-dose ICS-LABA, per Global Initiative for Asthma (GINA) 2019 guidelines.<sup>15</sup>

Tiotropium induces bronchodilation by selectively inhibiting the action of acetylcholine at muscarinic (M) receptors in bronchial smooth muscles; it has a longer duration of action because of its slower dissociation from receptor types M<sub>1</sub> and M<sub>3</sub>.<sup>30</sup> Tiotropium respimat (Spiriva, Tiova) has been approved for COPD for many years; in 2013, it was shown to prevent worsening of symptomatic asthma and increase time to first severe exacerbation.<sup>13</sup> The FDA subsequently approved tiotropium as an add-on treatment for patients with uncontrolled asthma despite use of ICS-LABA.

Glycopyrronium bromide (glycopyrrolate, multiple brand names) and umeclidinium (Incruse Ellipta) are LAMAs that are approved for COPD treatment but have not yet been approved for patients who have asthma only.<sup>31</sup>

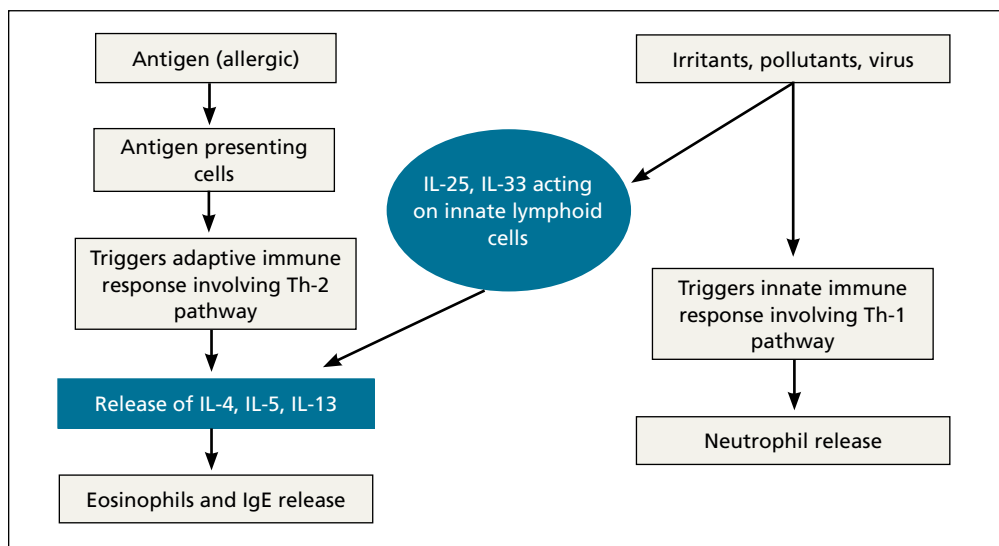
### Biological therapies

In the past few years, improved understanding of asthma's pathophysiology has led to the development of biological therapy for severe asthma. This therapy is directed at Th-2 inflammatory pathways (FIGURE) and targets various inflammatory markers, such as IgE, IL-5, and eosinophils.

Biologicals are not the first-line therapy for the management of severe asthma. Ideal candidates for this therapy are patients who have exhausted other forms of severe asthma treatment, including ICS-LABA, LAMA, leukotriene receptor antagonists, and mucus-clearing agents. Patients with frequent exacerbations who need continuous steroids or need steroids at least twice a year should be considered for biologicals.<sup>32</sup>

All biological therapies must be administered in a clinical setting, as they carry risk for anaphylaxis. TABLE 3<sup>15,33-47</sup> summarizes all

**FIGURE**  
**Pathophysiology of asthma**



IgE, immunoglobulin E; IL, interleukin; Th, T-helper cell.

approved biologicals for the management of severe asthma.

■ **Anti-IgE therapy.** Omalizumab (Xolair) was the first approved biological therapy for severe asthma (in 2003). It is a recombinant humanized IgG1 monoclonal antibody that binds to free IgE and down regulates the inflammatory cascade. It is therefore best suited for patients with early-onset allergic asthma with a high IgE count. The dose and frequency (once or twice per month) of omalizumab are based on IgE levels and patient weight. Omalizumab reduces asthma exacerbation (up to 45%) and hospitalization (up to 85%).<sup>34</sup> Omalizumab also reduces the need for high-dose ICS-LABA therapy and improves quality of life (QoL).<sup>33,34</sup>

Its efficacy and safety have been proven outside the clinical trial setting. Treatment response should be assessed over a 3- to 4-month period, using fractional exhalation of nitric oxide (FeNO); serial measurement of IgE levels is not recommended for this purpose. Once started, treatment should be considered long term, as discontinuation of treatment has been shown to lead to recurrence of symptoms and exacerbation.<sup>35,36</sup> Of note, the GINA guidelines recommend omalizumab over prednisone as add-on therapy for severe persistent asthma.<sup>15</sup>

■ **Anti-IL-5 therapy.** IL-5 is the main cytokine for growth, differentiation, and activation of eosinophils in the Th-2-mediated inflammatory cascade. Mepolizumab, reslizumab, and benralizumab are 3 FDA-approved anti-IL-5 monoclonal antibody therapies for severe eosinophilic asthma. Mepolizumab has been the most commonly studied anti-IL-5 therapy, while benralizumab, the latest of the 3, has a unique property of inducing eosinophilic apoptosis. There has been no direct comparison of the different anti-IL-5 therapies.

**Mepolizumab (Nucala)** is a mouse anti-human monoclonal antibody that binds to IL-5 and prevents it from binding to IL-5 receptors on the eosinophil surface. Mepolizumab should be considered in patients with a peripheral eosinophil count > 150 cells/mcL; it has shown a trend of greater benefit in patients with a very high eosinophil count (75% reduction in exacerbation with blood eosinophil count > 500 cells/mcL compared to 56% exacerbation reduction with blood eosinophil count > 150 cells/mcL).<sup>37</sup>

Mepolizumab has consistently been shown to reduce asthma exacerbation (by about 50%) and emergency department (ED) visits and hospitalization (60%), when com-

➤ **Mepolizumab has shown a trend of greater benefit in patients with a very high eosinophil count.**

TABLE 3

## Comparison of FDA-approved biological therapies for severe asthma

Biological therapy	Mechanism of action	Dose	Requirement for the drug approval	Clinical effects	Follow-up	Adverse effects
Omalizumab (Xolair) <sup>15,33-36</sup>	Anti-IgE	Based on weight and IgE levels  Once or twice every 4 weeks  Subcutaneous injection	IgE > 30 IU/mL  Positive aeroallergen skin test or specific aeroallergen IgE  FEV <sub>1</sub> < 80%  Multiple exacerbations	Decrease in hospitalization and need for steroids; improvement in QoL; reduction in ICS dosing	Follow up response clinically at 16 weeks  Reduction in FeNO  No role in following IgE	Headache, tiredness, nausea, anaphylactic reaction (0.2%)  Monitor for helminthic infection
Mepolizumab (Nucala) <sup>15, 37-40</sup>	Anti-IL-5	Fixed dose  100 mg every 4 weeks  Subcutaneous injection	Eosinophil count > 150 cells/mcL  2 or more exacerbations in 12 months or daily prednisone use  2 or more controller therapies including high-dose ICS and additional controller	Decrease in asthma exacerbation and hospitalization; improvement in QoL  Mild improvement in pulmonary function test	Drop in eosinophils by 75% within a month of starting treatment predicts good response	Headache (18%), injection site pain, back pain, hypersensitivity reaction (3%)  Cases of zoster (rare)  Avoid in patients with active helminthic infection
Reslizumab (Cinqair) <sup>15, 41-44</sup>	Anti-IL-5	Based on weight  3 mg/kg every 4 weeks  IV infusion	Eosinophil count > 150 cells/mcL (better response if > 400)	Decrease in asthma exacerbation and hospitalization; improvement in QoL  Mild improvement in pulmonary function test	Sputum eosinophils and peripheral eosinophil count	Oropharyngeal pain, myalgia, elevation in creatinine kinase, anaphylaxis (0.3%)  Avoid in patients with active helminthic infection, acute asthma exacerbation, and malignancy
Benralizumab (Fasenra) <sup>15, 45-47</sup>	Anti-IL-5  Induces eosinophilic apoptosis	Fixed dose  30 mg every 4 weeks for first 3 months (loading) followed by every 8 weeks thereafter  Subcutaneous injection	Eosinophil count > 150 cells/mcL	Decrease in asthma exacerbation; oral corticosteroid dose reduction; improvement in FEV <sub>1</sub>	Eosinophil count	Headache, pharyngitis, hypersensitivity reaction  Avoid in patients with active helminthic infection, acute asthma exacerbation

FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; QoL, quality of life.

pared with placebo in clinical trials.<sup>37,38</sup> It also reduces the need for oral corticosteroids, an effect sustained for up to 52 weeks.<sup>39,40</sup> The Mepolizumab adJunctive therapy in subjects

with Severe eosinophiliC Asthma (MUSCA) study showed that mepolizumab was associated with significant improvement of health-related QoL, lung function, and asthma

symptoms in patients with severe eosinophilic asthma.<sup>38</sup>

GINA guidelines recommend mepolizumab as an add-on therapy for severe asthma. Mepolizumab is given as a fixed dose of 100 mg every 4 weeks. A 300-mg dose has also been approved for eosinophilic granulomatosis with polyangiitis. Monitoring with serial eosinophils might be of value in determining the efficacy of the drug. Mepolizumab is currently in clinical trials for a broad spectrum of diseases, including COPD, hyper-eosinophilic syndrome, and ABPA.

**Reslizumab (Cinqair)** is a rat anti-human monoclonal antibody of the IgG4κ subtype that binds to a small region of IL-5 and subsequently blocks IL-5 from binding to the IL-5 receptor complex on the cell surface of eosinophils. It is currently approved for use as a 3-mg/kg IV infusion every 4 weeks. In large clinical trials,<sup>41-43</sup> reslizumab decreased asthma exacerbation and improved QoL, asthma control, and lung function. Most of the study populations had an eosinophil count > 400 cells/mcL. A small study also suggested patients with severe eosinophilic asthma with prednisone dependency (10 mg/d) had better sputum eosinophilia suppression and asthma control with reslizumab when compared with mepolizumab.<sup>44</sup>

**Benralizumab (Fasenra)** is a humanized IgG1 anti-IL-5 receptor α monoclonal antibody derived from mice. It induces apoptosis of eosinophils and, to a lesser extent, of basophils.<sup>45</sup> In clinical trials, it demonstrated a reduction in asthma exacerbation rate and improvement in prebronchodilator FEV<sub>1</sub> and asthma symptoms.<sup>46,47</sup> It does not need reconstitution, as the drug is dispensed as prefilled syringes with fixed non-weight-based dosing. Another potential advantage to benralizumab is that after the loading dose, subsequent doses are given every 8 weeks.

**Bronchial thermoplasty**

Bronchial thermoplasty (BT) is a novel non-pharmacologic intervention that entails the delivery of controlled radiofrequency-generated heat via a catheter inserted into the bronchial tree of the lungs through a flexible bronchoscope. The potential mecha-

nism of action is reduction in airway smooth muscle mass and inflammatory markers.

Evidence for BT started with the Asthma Intervention Research (AIR) and Research in Severe Asthma (RISA) trials.<sup>48,49</sup> In the AIR study, BT was shown to reduce the rate of mild exacerbations and improve morning peak expiratory flow and asthma scores at 12 months.<sup>48</sup> In the RISA trial, BT resulted in improvements in Asthma Quality of Life Questionnaire (AQLQ) score and need for rescue medication at 52 weeks, as well as a trend toward decrease in steroid use.<sup>49</sup>

However, these studies were criticized for not having a placebo group—an issue addressed in the AIR2 trial, which compared bronchial thermoplasty with a sham procedure. AIR2 demonstrated improvements in AQLQ score and a 32% reduction in severe exacerbations and 84% fewer ED visits in the post-treatment period (up to 1 year post treatment).<sup>50</sup>

Both treatment groups experienced an increase in respiratory adverse events: during the treatment period (up to 6 weeks post procedure), 16 subjects (8.4%) in the BT group required 19 hospitalizations for respiratory symptoms and 2 subjects (2%) in the sham group required 2 hospitalizations. A follow-up observational study involving a cohort of AIR2 patients demonstrated long-lasting effects of BT in asthma exacerbation frequency, ED visits, and stabilization of FEV<sub>1</sub> for up to 5 years.<sup>51</sup>

The Post-market Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) showed similar beneficial effects of BT on asthma control despite enrolling subjects who may have had poorer asthma control in the “real world” setting.<sup>52</sup>

In summary, BT results in modest improvements in AQLQ scores and clinically worthwhile reductions in severe exacerbations and ED visits in the year post treatment, which may persist for up to 5 years. BT causes short-term increases in asthma-related morbidity, including hospital admissions. While there is encouraging data and the scope is increasing, BT remains limited to carefully selected (by a specialist) patients with severe asthma that is poorly controlled despite maximal inhaled therapy.



**Bronchial thermoplasty results in clinically worthwhile reductions in severe exacerbations and ED visits in the year post treatment.**

CONTINUED

➤  
**The potential benefits of allergen immunotherapy must be weighed against the risk for adverse effects, including anaphylaxis.**

### Immunotherapy

Immunotherapy for allergic disease is aimed at inducing immune tolerance to an allergen and alleviating allergic symptoms. This is done by administration of the allergen to which the patient is sensitive. There are 2 approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT; a dissolvable tablet under the tongue or an aqueous or liquid extract).

Immunotherapy is generally reserved for patients who have allergic symptoms with exposure to a trigger and evidence (through skin or serum testing) of specific IgE to that trigger, especially if there is poor response to pharmacotherapy and allergen avoidance. Overall, evidence in this field is limited: Most studies have included patients with mild asthma, and few studies have compared immunotherapy with pharmacologic therapy or used standardized outcomes, such as exacerbations.

■ **SCIT.** A 2010 Cochrane review concluded that SCIT reduces asthma symptoms and use of asthma medications and improves bronchial hyperreactivity. Adverse effects include uncommon anaphylactic reactions, which may be life-threatening.<sup>53</sup>

■ **SLIT** has advantages over SCIT as it can be administered by patients or caregivers, does not require injections, and carries a much lower risk for anaphylaxis. Modest benefits have been seen in adults and children, but there is concern about the design of many early studies.

A 2015 Cochrane review of SLIT in asthma recommended further research using validated scales and important outcomes for patients and decision makers so that SLIT can be properly assessed as a clinical treatment for asthma.<sup>54</sup> A subsequently published study of SLIT for house dust mites (HDM) in patients with asthma and HDM allergic rhinitis demonstrated a modest reduction in use of ICS with high-dose SLIT.<sup>55</sup>

In another recent study, among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate-or-severe asthma exacerbation during ICS reduction.<sup>56</sup> Additional studies are needed to assess long-term efficacy and safety. However, for patients who experi-

ence exacerbations despite use of a low-dose or medium-dose ICS-LABA combination, SLIT can now be considered as an add-on therapy.

Per the GINA guidelines, the potential benefits of allergen immunotherapy must be weighed against the risk for adverse effects, including anaphylaxis, and the inconvenience and cost of the prolonged course of therapy.<sup>15</sup>

### ■ Azithromycin

Macrolides have immunomodulatory and anti-inflammatory effects in addition to their antibacterial effects. Maintenance treatment with macrolides such as azithromycin has been proven to be effective in chronic neutrophilic airway diseases (FIGURE). There have been attempts to assess whether this therapy can be useful in asthma management, as well. Some randomized controlled trials and meta-analyses have shown conflicting results, and early studies were limited by lack of data, heterogeneous results, and inadequate study designs.

The AZithromycin Against pLacebo in Exacerbations of Asthma (AZALEA) study was a randomized, multicenter, double-blind, placebo-controlled clinical trial in the United Kingdom among patients requiring emergency care for acute asthma exacerbations. Azithromycin added to standard care for asthma attacks did not result in clinical benefit.<sup>57</sup> While azithromycin in acute exacerbation is not currently recommended, recent trials in outpatient settings have shown promise.

The AZithromycin in Severe ASThma study (AZISAST) was a randomized, double-blind, placebo-controlled trial in subjects with exacerbation-prone severe asthma in Belgium. Low-dose azithromycin (250 mg 3 times a week) as an add-on treatment to combination ICS-LABA therapy for 6 months did not reduce the rate of severe asthma exacerbations or lower respiratory tract infection (LRTI). However, subjects with a non-eosinophilic variant (neutrophilic phenotype) experienced significant reduction in the rate of exacerbation and LRTI.<sup>58</sup>

The recently published Asthma and Macrolides: the AZithromycin Efficacy and



Safety Study (AMAZES) shows promise for chronic azithromycin therapy as an add-on to medium-to-high-dose inhaled steroids and a long-acting bronchodilator in adults with uncontrolled persistent asthma. This was a large multicenter, randomized, double-blind, placebo-controlled, parallel group trial in New Zealand and Australia. Patients were excluded if they had hearing impairment or abnormally prolonged QTc. Azithromycin at a dose of 500 mg 3 times a week for 48 months reduced asthma exacerbations and improved QoL compared to placebo. The effect was sustained between subgroups based on phenotypes (eosinophilic vs noneosinophilic; frequent exacerbators vs nonfrequent exacerbators) and even among those with symptom differences at baseline (eg, cough or sputum positivity). The rate of antibiotic courses for respiratory infectious episodes was significantly reduced in the azithromycin-treated group.<sup>59</sup>

**■ The take-away:** Chronic azithromycin might prove to be a useful agent in the long-term management of asthma patients whose disease is not well controlled on inhaled therapy. Further studies on mechanism and effects of prolonged antibiotic use will shed more light. For more information, see When guideline treatment of asthma fails, consider a macrolide antibiotic; <http://bit.ly/2vDAWc6>.

**A new era**

We have entered an exciting era of asthma management, with the introduction of several novel modalities, such as biological therapy and bronchial thermoplasty, as well as use of known drugs such as macrolides, immunotherapy, and LAMA. This was made possible through a better understanding of the biological pathways of asthma. Asthma management has moved toward more personalized, targeted therapy based on asthma phenotypes.

It's important to remember, however, that pharmacological and nonpharmacological aspects of management—including inhaler techniques, adherence to inhaler therapy, vaccinations, control of asthma triggers, and smoking cessation—remain the foundation of optimal asthma management and need

to be aggressively addressed before embarking on advanced treatment options. Patients whose asthma is not well controlled with inhaled medications or who have frequent exacerbations (requiring use of steroids) should be comanaged by an expert asthma specialist to explore all possible therapies. **JFP**

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**➤ Chronic azithromycin might prove to be a useful agent in the long-term management of asthma patients whose disease is not well controlled on inhaled therapy.**

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