REPORT

# Clinical Updates on the Management of Asthma

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## Introduction and Epidemiology

Asthma is a chronic condition of the airways defined by complex interactions of inflammation, airflow obstruction, and bronchial hyperresponsiveness.[1] The disease is characterized by variable and recurring symptoms that differ both within and among patients.[1] Asthma attacks or episodes vary in degree and can range from mild to severe enough to be life threatening. As such, asthma can influence quality of life and cause significant morbidity and mortality. In 1999, the CDC created the National Asthma Control Program. Some of the goals of the program include reducing the number of asthma-related deaths, hospitalizations, emergency department (ED) visits, and school or work days missed, and increasing the number of people receiving guideline-appropriate care. The program has improved asthma treatment and management in the United States.[2]



According to the 2014 National Health Interview Survey published by the CDC, approximately 40 million individuals (12.9%), including 10 million children (13.5%), were diagnosed with asthma.[3] The Global Initiative for Asthma (GINA) estimates that 300 million people in the world suffer from asthma, and an additional 100 million are expected to have asthma by 2025.[4]

Current reports indicate that asthma prevalence among adults and children is approximately 7.4% and 8.6%, respectively.[3] This equates to approximately 1 in 11 adults and 1 in 12 children with asthma.[5] Prevalence is highest among adults aged 18 to 24 years. Prevalence is also higher in black adults and adult females.[2] Black Americans are 2 to 3 times more likely to die from asthma than any other ethnic group.[5] Further, adults who have not completed high school are more likely to have asthma than adults who have graduated high school or college, as are adults with lower annual household incomes compared with adults with higher incomes.[5]

Approximately 11 million individuals (44.7%), including 3 million children (48%), experienced an asthma episode in 2014.[3] In 2011, asthma accounted for 1.8 million ED visits, and in 2014, it accounted for 3651 deaths in the United States.[6] Nonadherence with controller agents increases the risk of deteriorating asthma and asthma episodes. Additionally, suboptimal adherence to prescribed controller medications is often a factor in patients with difficult-to-control asthma.[7]

## ABSTRACT

Asthma is a complex airway disorder that involves multiple inflammatory cells and cellular elements. Genetic and environmental factors result in recurrent episodes of the symptoms of asthma: coughing, wheezing, breathlessness, and chest tightness. Left untreated, these initial symptoms can transform into exacerbations ranging from spontaneous reversible airflow obstruction and airway remodeling to death. As a result, the need for novel therapeutic options for the treatment and long-term management of asthma has become increasingly vital. Some therapies that have been developed in recent years include medications with longer half-lives that can lead to increased adherence, agents biologically altered to decrease side effects, therapies targeting specific pathways within the inflammatory response, the application of radiofrequency, and long-term administration of agents to increase or boost the immune system. Each option represents an individualized treatment approach to managing patients with asthma. Healthcare practitioners need to be educated about these new therapeutic options so they can properly and safely manage their patients' regimens. Mechanisms of action, clinical trial data, and current market availability for each medication are highlighted to provide pharmacists with the fundamental knowledge necessary to effectively and safely treat patients suffering from asthma.

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Pharmacists can help improve patient adherence with controller agents by providing education about medications and ensuring proper device technique.[8,9] Pharmacists are also well positioned within the healthcare team to identify and monitor nonadherence to controller medications or overreliance on quick-acting reliever agents.

Although these statistics demonstrate that asthma is associated with a high disease burden, it remains important for healthcare practitioners to realize that many patients with asthma suffer from comorbid conditions. Comorbidities can greatly affect the severity of asthma that patients experience. In one study, 54% of patients with a diagnosis of asthma had 1 or more comorbid conditions.[10] Having asthma was associated with a greater prevalence of arthritis, heart disease, cancer, diabetes, and hypertension.[10] For every additional comorbid condition, there was a reported increase in the prevalence of asthma symptom episodes, activity limitation, sleep disturbances, and asthma-related ED visits.[10] Quality of life is also affected in patients with asthma. A disability-adjusted life year (DALY) can be thought of as a year lost due to disability, or 1 lost year of "healthy" life.[11] Worldwide, it is estimated that the number of DALYs lost due to asthma is approximately 15 million per year and that asthma accounts for 1% of all DALYs lost.[4] Interestingly, the number of lost DALYs due to asthma is similar to that of diabetes, cirrhosis, or schizophrenia.[4]

## Financial Impact

Given the large burden of disease, asthma has a significant financial impact on the healthcare system and patients. This economic impact includes direct and indirect costs. Examples of direct costs include hospital admissions, medications, and diagnostic tests.[4,12] Indirect costs include those secondary to lost productivity due to asthma. These include missed days of school or work (for both patients and caregivers), waiting time, traveling to take care of someone with asthma, or premature death.[4,12,13] A Canadian study discovered that there is a 14% increase in the odds of reporting productivity loss in patients suffering from more comorbidities compared with those suffering from fewer comorbidities.[14] A report by the CDC estimated that in 2013, the number of reported school absences among children 5 to 17 years old with asthma was 13.8 million.[15] The economic costs of asthma are reportedly the highest among chronic health diseases.[13] One review attempting to assess the true financial impact of asthma cited the main drivers for direct costs as medications and hospital admissions.[13] The cost of asthma was also found to strongly correlate to comorbidities, age, and severity of disease.[13]

Due to a multitude of factors affecting the financial impact of asthma, including the significant impact of indirect costs, assessing the true financial impact of asthma can be difficult. However, according to the CDC, asthma costs in the United States approximate to $56 billion each year.[5] Increased provider knowledge about the disease and therapeutic options will help to improve overall treatment goals and may reduce costs. The results of one study showed that patients with controlled asthma who were treated appropriately according to guidelines had fewer costs than those with uncontrolled asthma who may not have been treated according to the guidelines.[16] It is clear that asthma poses a significant financial burden on society. The financial cost of not treating asthma is also significant. Therefore, a clear understanding of the pathophysiology of asthma and the role of novel therapies is crucial in order to provide safe and efficacious management.

## Pathophysiology

The dominant event leading to clinical symptoms in asthma is bronchoconstriction. Many factors, including allergens, medications, or other stimuli, such as exercise or cold air, can contribute to or trigger acute airway obstruction.[1] Currently, there is no definitive answer as to what truly initiates the initial inflammatory process. Innate immunity, genetics, sex, and environmental factors are all thought to play roles. However, once the disease becomes more persistent or chronic, inflammation progresses and edema and mucus hypersecretion can affect airway smooth muscle. If left untreated, structural changes can cause airway remodeling and make responsiveness to usual treatments more challenging.[1]

Although there are many symptoms of asthma, airway inflammation is a hallmark sign. Many cell types and mediators are responsible for the inflammatory features of asthma; the inflammatory reaction is highly complex. **Figure 1**[17-20] and **Figure 2**[17-20] provide visual representations of the inflammatory cascade. In short, inhaled antigens presented to naïve T cells result in T helper 2 (Th2) cell differentiation.[18] Th2 lymphocytes produce interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). These interleukins lead to activation of B lymphocytes, which then secrete immunoglobulin E (IgE). IgE attaches to cell surfaces, and its receptors are found on mast cells, basophils, dendritic cells, and lymphocytes.[1] Mast cell-bound IgE binds allergens and causes degranulation and the release of further chemical mediators, such as histamines, prostaglandins, and leukotrienes.[18] All of these processes result in bronchoconstriction and can further potentiate the immune response.[18] IL-5 eventually leads to further differentiation of eosinophils. Eosinophils migrate to the site of inflammation and attach to the endothelium via binding of adhesion proteins called vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.[1] When eosinophils are activated, leukotrienes and other proteins are released that ultimately damage the airway.[1] As the inflammatory process in the airway has many components and is highly complex, researchers have developed new targets for asthma that focus on this allergic inflammatory component of the disease.

## Advancements in Asthma Therapies

### Asthma Management Guidelines

The assessment, diagnosis, and treatment of asthma is governed by 2 major guidelines: the Expert Panel Report 3 (EPR-3), published by

the National Heart, Lung, and Blood Institute (last updated in 2007), and GINA, which is updated yearly.[1,19] Both guidelines recommend an initial assessment to help characterize the patient's asthma, which includes evaluation of precipitating factors, comorbidities that may aggravate asthma, and a review of asthma control to help classify asthma severity.[1,19]

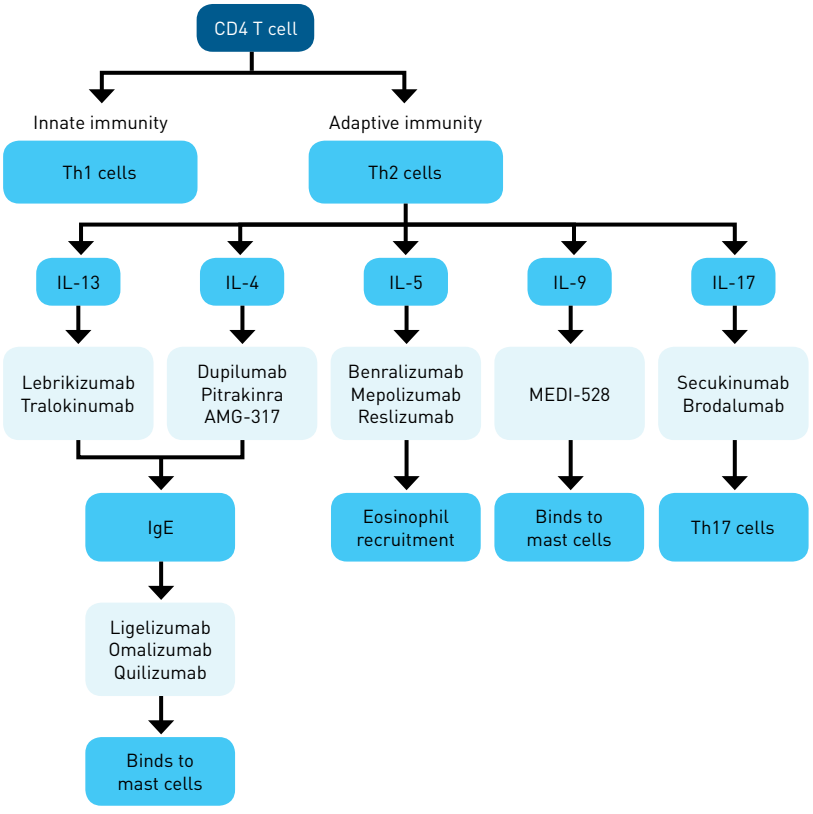
Based on the severity of symptoms, lung function test results, and the level of asthma control, patients are first classified as having intermittent or persistent asthma. Persistent asthma is further stratified as mild, moderate, or severe.[1] Patients should receive quick-relief medication and possibly long-term controller medication, depending on their asthma classification. Based on the pathophysiology, treatment is centered on anti-inflammatory therapy. Periodic assessment of patients facilitates ongoing control of the disease. Patients are classified as being well controlled, not well controlled, or very poorly controlled based on the frequency of symptoms, quick-relief medication use, pulmonary function, and validated questionnaire scores.[1]

Therapy may be stepped up (increased) or stepped down (decreased) within the treatment algorithm. **Table 1**[1,19] provides a summary of the EPR-3 and GINA guidelines. Table 1[1,19] correlates medication therapies with the type of asthma. Medications are classified as being controller (regular maintenance), rescue (breakthrough relief), or add-on therapies (for severe asthma).[19] Recommendations are based on both EPR-3 and GINA guidelines unless otherwise indicated. Of note, this article focuses on the medications that are long acting and used for long-term management. The importance of short-acting quick relief medications cannot be overlooked; however, they are not the highlight of this manuscript.

## Treatment Options and the Need for New Therapies

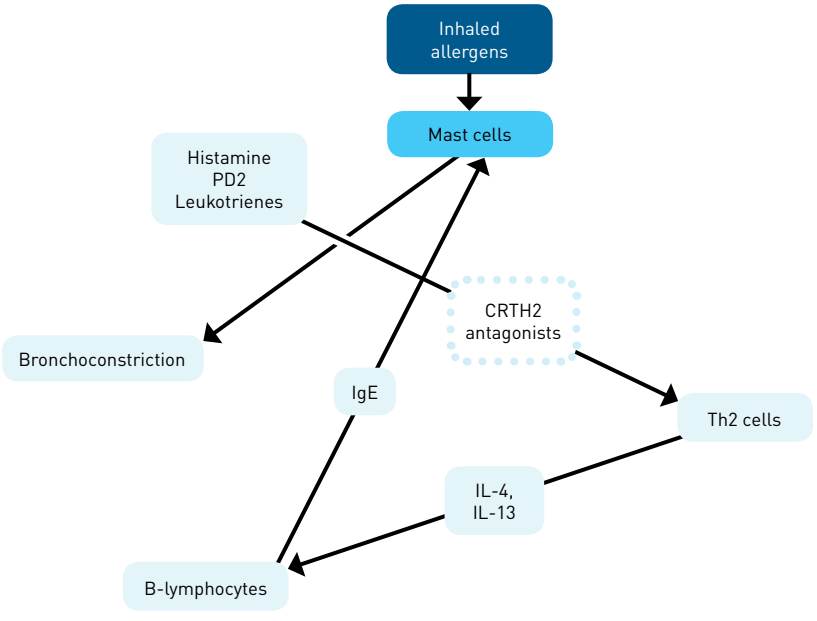
Table 1[1,19] lists the standard regimens for managing patients with asthma. However, not all patients with asthma respond to standard treatment options, such as a high-dose inhaled corticosteroid (ICS) plus a long-acting beta-agonist (LABA). Approximately 5% to 10% of patients with asthma are classified as having severe

**FIGURE 1.** Anti-Interleukin and IgE Agents Within the Inflammatory Cascade[17-20]




IgE indicates immunoglobulin E; IL, interleukin; Th, T helper.

**FIGURE 2.** Inflammatory Cascade and CRTH2 Antagonists[17-20]




CRTH2 indicates chemoattractant receptor-homologous molecule expressed on Th2 cells; IgE, immunoglobulin E; IL, interleukin; PD2, prostaglandin D2; Th, T helper.

**TABLE 1.** Guideline Management of Asthma[1,19]

| | Type of Asthma | Quick Relief | | Long-term Controller Options |
|---|---|---|---|---|
| Step 1 | Intermittent | As-needed SABA | As-needed SABA or low-dose ICS/formoterol (not approved for this indication in the United States) | None |
| Step 2 | Persistent | | | Low-dose ICS |
| Step 3 | | | | Low-dose ICS + LABA<br>or<br>medium-dose ICS |
| Step 4 | | | | Medium-dose ICS + LABA<br>High-dose ICS + LABA<br>Add tiotropium |
| Step 5 | | | | High dose ICS + LABA<br>Consider omalizumab<br>Consider mepolizumab<br>Add tiotropium<br>Add low-dose oral steroid |
| Step 6 | | | | High-dose ICS + LABA + oral corticosteroid<br>Consider omalizumab |

ICS indicates inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.

asthma.[20] Currently, there are many unmet needs with respect to the management of severe asthma; thus, many new approaches to treatment are being attempted.[20] Many of the options discussed in the following sections are targeted toward patients suffering from severe asthma who have not gained control of their disease with standard treatment regimens. Of note, many of the medications discussed in the following section are not currently listed in the guidelines, but future options for updated guidelines are discussed.

## FDA-approved Treatments

### *Bronchodilators*

#### ULTRA–LONG-ACTING BETA$_2$-AGONISTS

Beta-agonists are one of the cornerstone therapies of asthma management. They act as bronchodilators by stimulating beta$_2$-receptors to relax smooth muscle. In addition to use of a short-acting beta-agonist (SABA) as rescue therapy in all patients, current guideline recommendations include daily use of the LABAs, salmeterol or formoterol, in combination with an ICS, for long-term control in moderate or severe persistent asthma.[1] Results from SMART (Salmeterol Multicenter Asthma Research Trial) showed a significant increase in asthma-related deaths in patients receiving salmeterol alone compared with placebo.[21] This study resulted in labeling changes for LABAs; the use of LABAs without an ICS in asthma is now contraindicated. Additionally, the FDA conducted a meta-analysis of data and concluded that LABAs increased the risk of severe exacerbations of asthma symptoms (driven by the number of asthma-related hospitalizations).[22] Combination therapy should only be employed as long-term therapy and only if the patient's asthma is not well controlled.

Traditionally, LABAs last more than 12 hours, providing for twice-daily dosing. Newly approved ultra–long-acting beta$_2$-agonists have entered the market and provide for once-daily dosing, with higher selectivity for beta$_2$-receptors. Currently, the only FDA-approved ultra–long-acting beta-agonist for use in asthma is a combination product of vilanterol with fluticasone. However, there are numerous phase 2 and 3 clinical trials that have assessed the use of each of these agents in asthma. **Table 2**[1,19] provides a comparison of the ultra–long-acting beta$_2$-agonists currently approved for use in asthma or chronic obstructive pulmonary disease (COPD).

In clinical trials, fluticasone/vilanterol resulted in significant improvement in pulmonary function and reduced exacerbations compared with placebo or equivalent doses of fluticasone alone.[23,24] This combination has also shown similar efficacy compared with fluticasone/salmeterol in patients with persistent asthma.[25] A clinical trial comparing the combination of fluticasone/vilanterol to the combination of fluticasone/salmeterol or budesonide/formoterol is currently underway (www.clinicaltrials.gov; identifier NCT02446418).

Compared with placebo, indacaterol resulted in significant improvements in forced expiratory volume in 1 second ($FEV_1$), with good tolerability and safety.[26-28] A study comparing indacaterol versus salmeterol and salbutamol concluded that indacaterol resulted in significant improvements in $FEV_1$ compared with placebo or salbutamol with few adverse events (AEs).[29]

Olodaterol resulted in significant improvements in $FEV_1$ compared with placebo in 2 phase 2 dose-finding studies.[30,31] Doses of up to 20 mcg daily were used compared with placebo, with no significant AEs reported.[30,31]

#### LONG-ACTING MUSCARINIC ANTAGONISTS

Antimuscarinic agents, such as ipratropium, have previously been used for asthma as a quick-relief medication option if patients did not respond to initial SABA therapy. Muscarinic antagonists

**TABLE 2.** Comparison of Ultra–Long-acting Beta$_2$-Agonists[1,19]

| Generic (Brand) | Device Available | Approved for Use in Patients With Asthma | Dose | Frequency |
|---|---|---|---|---|
| Fluticasone furoate/ vilanterol (Breo) | Ellipta | Yes | 100/25 mcg 200/25 mcg | 1 inhalation once daily |
| Indacaterol (Arcapta) | Neohaler | No | 75 mcg | Inhale contents of 1 capsule once daily |
| Olodaterol (Striverdi) | Respimat | No | 2.5 mcg | 2 inhalations once daily |

**TABLE 3.** Comparison of Long-acting Muscarinic Antagonists for Use in Asthma[1,19]

| Generic (Brand) | Device Available | Approved for Use in Patients With Asthma | Dose | Frequency |
|---|---|---|---|---|
| Tiotropium (Spiriva) | Handihaler | No | 18 mcg (capsule) | Inhale contents of 1 capsule once daily |
| | Respimat | Yes | 1.25 mcg/puff, 2 puffs (inhalation) | 2 inhalations once daily |
| Umeclidinium (Incruse) | Ellipta | No | 62.5 mcg | 1 inhalation once daily |
| Aclidinium (Tudorza) | Pressair | No | 400 mcg | 1 inhalation twice daily |
| Glycopyrrolate (Seebri) | Neohaler | No | 15.6 mcg | Inhale contents of 1 capsule once daily |

inhibit muscarinic cholinergic receptors and reduce the intrinsic vagal tone of the airway.[1] Ipratropium bromide is the short-acting antimuscarinic used in combination with a SABA or as an alternative if a patient does not tolerate a SABA. Tiotropium bromide is a once-daily inhaled muscarinic antagonist first utilized in COPD, but it is now approved by the FDA for use in patients with asthma in the Respimat device (**Table 3**[1,19]). It is currently the only long-acting muscarinic antagonist (LAMA) approved for use in asthma.

A systematic review published in *Chest* concluded that tiotropium was noninferior to salmeterol in patients with moderate to severe asthma who were not adequately controlled by an ICS or ICS/salmeterol.[32] Additionally, tiotropium was found to improve lung function and increase the time to severe exacerbations. As such, the GINA 2016 guidelines now recommend it as add-on therapy for step 4 treatment in patients at least 12 years old with a history of asthma exacerbations (Table 1[1,19]).[19]

Beyond tiotropium, other LAMAs are currently available (Table 3[1,19]). Aclidinium has shown promising effects in patients suffering from COPD; study results have shown significant improvements in FEV$_1$ compared with placebo.[33,34] However, there are currently no data to support its use in asthma. Similarly, glycopyrrolate is approved as a bronchodilator in COPD. A phase 2 study of glycopyrrolate as add-on therapy in adults with mild to moderate asthma was recently completed, but results have yet to be published (www.clinicaltrials.gov; identifier NCT02296411).

Umeclidinium is also only currently approved for use in COPD. In a double-blind crossover study in patients with asthma, umeclidinium led to modest improvements in FEV$_1$, which did not appear to be related to the dose. Therefore, the authors were unable to confirm the therapeutic benefit of umeclidinium monotherapy in patients with asthma not requiring ICS treatments.[35] However, in a double-blind crossover study in patients with asthma on an ICS, improvements in FEV$_1$ and both morning and evening peak expiratory flows were observed following combination therapy with fluticasone/umeclidinium.[36] Future long-term clinical trials with all LAMAs, as monotherapy or combination, will provide further insight into their utility in the management of asthma.

### *Combination Products for Long-term Control*

ICSs and beta$_2$-agonists are often used together to increase efficacy outcomes. Glucocorticoids increase the number of beta$_2$-receptors on the cell surface, protecting against the downregulation of beta$_2$-receptors, which can be a consequence of long-term use.[37] Beyond increased efficacy, to try and prevent the unintentional use of a LABA alone, combination inhalers are often developed for use in asthma. GINA guidelines recommend the use of combination therapy as early as step 3.[19] There are combination inhalers currently available that allow for the potential to improve adherence rates, increase efficacy, and even lower costs (due to 1 co-pay vs 2). However, patients can be prescribed individual inhalers.

Currently, the only long-term, once-daily combination product approved by the FDA for asthma is fluticasone furoate/vilanterol. Compared with fluticasone furoate alone, the combination product resulted in significant improvements in FEV$_1$ and more rescue-free and symptom-free days, with similar AEs.[38] **Table 4**[39-47] lists combination products that are currently approved by the FDA and whether or not they are approved for use in asthma. Because tiotropium is the only LAMA approved for use in asthma, and it is only available

**TABLE 4.** Combination Long-term Controller Therapies[39-47]

| Generic (Brand) | Device Available | Approved for Use in Patients With Asthma | Dose | Frequency |
|---|---|---|---|---|
| Fluticasone furoate/vilanterol (Breo) | Ellipta | Yes | 100/25 mcg<br>200/25 mcg | Once daily |
| Fluticasone/salmeterol (Advair) | Diskus | Yes | 100/50 mcg<br>250/50 mcg<br>500/50 mcg | 1 inhalation twice daily |
| Fluticasone/salmeterol (Advair) | HFA | Yes | 45/21 mcg<br>115/21 mcg<br>230/21 mcg | 2 inhalations twice daily |
| Mometasone/formoterol (Dulera) | HFA | Yes | 100/5 mcg<br>200/5 mcg | 2 inhalations twice daily |
| Budesonide/formoterol (Symbicort) | MDI | Yes | 80/4.5 mcg<br>160/4.5 mcg | 2 inhalations twice daily |
| Umeclidinium/vilanterol (Anoro) | Ellipta | No | 62.5/25 mcg | Once daily |
| Tiotropium/olodaterol (Stiolto) | Respimat | No | 2.5/2.5 mcg | 2 inhalations once daily |
| Glycopyrrolate/indacaterol (Utibron) | Neohaler | No | 15.6/27.5 mcg capsule | 1 inhalation twice daily |
| Glycopyrrolate/formoterol (Bevespi) | Aerosphere | No | 9/4.8 mcg | 2 inhalations twice daily |

HFA indicates hydrofluoroalkane; MDI, metered-dose inhaler.

as a single inhaler, combination therapies containing a LAMA are currently not approved for use in asthma. It is anticipated, however, that these products will be utilized in patients with asthma, as GINA guidelines now recommend combining ICS/LABA/LAMA agents.[19]

In clinical trials in patients with COPD, the combination therapies listed in Table 4[39-47] that are currently approved for use in COPD led to greater increases in $FEV_1$ compared with their single components.[48-50] In addition, the combination product glycopyrrolate/indacaterol led to decreases in dyspnea and use of rescue medications.[51] A combination product containing aclidinium/formoterol is currently approved for use in Europe, the United Kingdom, and Canada. There are also ongoing clinical trials in Italy assessing the use of a combination product containing beclomethasone, formoterol, and glycopyrrolate (www.clinicaltrials.gov; identifiers NCT02676076 and NCT02676089). Further clinical trial data are necessary before these combination therapies can be recommended for use in asthma.

### *Immunotherapy*

Allergic rhinitis is often seen in patients with asthma. Asthma symptoms may improve in some patients by controlling their allergies. Allergen immunotherapy creates tolerance to specific antigens (eg, dust mites) by decreasing the immune system's response to them over time.[52] Both subcutaneous and sublingual immunotherapy (in as little as 12 months) can improve asthma symptoms and reduce the need for medications.[53] Patients with uncontrolled symptoms, despite the use of pharmacotherapy, and with evidence of allergic disease (ie, positive skin prick testing, elevated serum IgE) are candidates for immunotherapy.[52]

Eligible patients should consult with their providers to select the best delivery system for them; sublingual tablets require daily dosing and subcutaneous injections require travel to the provider office for administration. As anaphylactic reactions are possible, pharmacists should ensure that patients on either form of immunotherapy are prescribed injectable epinephrine and are educated on its proper use and administration.

### *Bronchial Thermoplasty*

Bronchial thermoplasty (BT) distributes radio frequency energy into the airways via flexible bronchoscopy, which reduces airway smooth muscle mass and bronchoconstriction.[54,55] Electrodes deliver thermal energy to the airway wall. When the energy comes in contact with tissue, it is converted to heat,[55] which disrupts the actin-myosin interaction in airway smooth muscle, rendering it inactive.[56] In a sham-controlled trial (placebo surgery-controlled), BT decreased ED visits, the frequency of severe exacerbations requiring corticosteroids, time lost from work/school after receiving BT and improved quality-of-life scores.[57] BT was approved by the FDA in 2010 for patients older than 18 years who have severe persistent asthma not well controlled with an ICS and LABA.[55] This treatment provided by interventional pulmonologists lends yet another option for patients not well controlled on a high-dose ICS plus LABA therapy.

## Emerging Therapies Currently in Clinical Trials

### Dissociated Corticosteroids

ICSs are the most effective anti-inflammatory therapy available and therefore are often the mainstay of treatment for patients with

asthma.[37] However, the use of ICSs is not devoid of AEs—that include immunosuppression, weight gain, and insomnia—especially with long-term administration. Therefore, efforts are being made to develop dissociated corticosteroids, which have reduced AEs yet retain their anti-inflammatory efficacy.[37]

ICSs bind and activate the glucocorticoid (GC) receptor. The activated receptor then binds in the promoter region of genes and activates transcription (transactivation) or interferes with activation of transcription (transrepression) on transcription factors.[58] Transrepression is believed to be responsible for beneficial anti-inflammatory effects, while transactivation leads to the AEs of GCs.[58] Selective GC receptor agonists (dissociated steroids) are compounds that would dissociate the transactivation function of GCs from the transrepression function, thereby having a larger impact on transactivation, and therefore, may have an improved therapeutic profile with fewer AEs.[58] Many nonsteroidal GC receptor agonists are in development and undergoing clinical trials, but there are currently no approved therapies.

## Biologics and Anti-Interleukin Agents

The understanding of inflammatory mediators and immunologic pathways implicated in asthma and the allergic response continues to increase. As such, a number of monoclonal antibodies targeting interleukins and IgE have been developed with the hopes of providing patients with tailored asthma treatment.[18]

**Table 5**[18-20,59-61] is a summary of biologics currently under investigation for use in asthma. Figure 1[17-20] is a simplified schematic of the inflammatory process highlighting where each anti-interleukin or anti-IgE agents works within the cascade.

### *Anti-IgE Biologics*

Omalizumab was the first biologic therapy approved by the FDA for the treatment of severe asthma. Omalizumab is a humanized anti-IgE antibody that binds unbound IgE, which is central to initiation and propagation of the inflammatory response.[59] It is currently the only FDA-approved anti-IgE therapy. The 2016 GINA guidelines now recommend the use of omalizumab or mepolizumab for patients in step 5 therapy (Table 1[1,19]).[19] Quilizumab and ligelizumab are newer therapies currently undergoing phase 2 clinical trials.[59,61]

In most cases, clinical trials that assess the use of novel monoclonal antibodies compare these agents to placebo. However, ligelizumab was recently compared with omalizumab in a head-to-head trial. Ligelizumab binds IgE with higher affinity than omalizumab, and the study results suggest it may be more efficacious than omalizumab with respect to both inhaled and skin allergen responses in patients with mild allergic asthma.[59]

### *Anti-Interleukin Biologics*

In general, anti-interleukin monoclonal therapies act to decrease airway inflammation and prevent eosinophil activation.[60] IL-5 stimulates eosinophil recruitment. Mepolizumab, reslizumab, and benralizumab are all biologic therapies that target IL-5. Mepolizumab and reslizumab are the only IL-5 antagonist biologics currently approved by the FDA for use in asthma. Benralizumab is slightly different in that it blocks the IL-5 receptor. Importantly, the 2016 GINA guidelines now recommend the use of omalizumab or mepolizumab for patients in step 5 therapy (Table 1[1,19]).[19]

IL-4 stimulates the release of IgE, which ultimately binds and activates mast cells. Dupilumab, pitrakinra, and AMG-317 all target IL-4. Both dupilumab and AMG-317 block the IL-4 receptor. Pitrakinra is unique in that it is an inhaled therapy versus subcutaneous or intravenous. None of the IL-4 agents are currently approved by the FDA for use in asthma.[60]

Interleukin-9 (IL-9) binds to mast cells within the inflammatory cascade. MEDI-528 is currently the only anti IL-9 medication. It is not approved by the FDA for use in asthma, and it is currently in phase 2 clinical trials.[60]

IL-13 stimulates the release of IgE. Lebrikizumab and tralokinumab are the 2 agents that target IL-13. Neither are approved by the FDA for use in asthma, but they are currently undergoing phase 3 clinical trials.[60]

Interleukin-17 (IL-17) stimulates the production of Th17 cells, which are another class of T helper cells implicated in the propagation of the immune response. Secukinumab blocks IL-17, and brodalumab blocks the IL-17 receptor. Both of these agents are not currently approved by the FDA for use in asthma, but are undergoing phase 2 clinical trials.[60]

## Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells Antagonists

Levels of prostaglandin D2 (PD2) are elevated in patients with asthma after an allergen challenge.[60] PD2 released by mast cells, Th2

**TABLE 5.** Summary of Biologics and Anti-Interleukin Agents for Use in Asthma[18-20,59-61]

| Target | Drug Name | Development Phase |
|---|---|---|
| IL-5 | IV or SQ mepolizumab | Marketed |
| | IV reslizumab | Marketed |
| | SQ benralizumab (blocks receptor) | 3 |
| IL-4 | SQ dupilumab (blocks receptor) | 3 |
| | INH pitrakinra (recombinant human IL-4 variant) | 2 |
| | SQ AMG-317 (blocks receptor) | 2 |
| IL-9 | SQ MEDI-528 | 2 |
| IL-13 | SQ lebrikizumab | 3 |
| | SQ tralokinumab | 3 |
| IL-17 | IV secukinumab | 2 |
| | SQ brodalumab (blocks receptor) | 2 |
| IgE | SQ omalizumab | Marketed |
| | SQ ligelizumab | 2 |
| | SQ quilizumab | 2 |

Ig indicates immunoglobulin; IL, interleukin; INH, inhalation; IV, intravenous; SQ, subcutaneous.

lymphocytes, and dendritic cells acts on the PD2 receptor, also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). The CRTH2 receptor mediates the activation of T2 lymphocytes, eosinophils, and basophils in response to PD2. This suggests that CRTH2 antagonists may play a role in inhibiting the products of mast cell degranulation, leading to a decrease in the asthma allergic response.[60] Figure 2[17-20] highlights where CRTH2 agents work within the inflammatory cascade.

Fevipiprant is an oral CRTH2 receptor antagonist recently assessed in a phase 3 clinical trial of 61 patients with moderate to severe asthma and an elevated sputum eosinophil count.[62] Patients were randomly assigned to placebo or fevipiprant 225 mg orally twice daily for 12 weeks. The sputum eosinophil count significantly decreased in the fevipiprant group. There were no differences in reported symptoms between groups, and no deaths or serious AEs were reported.[62]

Other agents are currently under investigation and have shown some promise for use in patients with asthma.[63,64] OC000459 is an oral CRTH2 receptor antagonist that demonstrated significant improvement in quality of life and nocturnal symptoms as compared with placebo in a phase 2a clinical trial[65] and significant improvements in $FEV_1$ as compared with placebo in patients with mild to moderate persistent asthma.[63] AZD1981 is an oral CRTH2 receptor antagonist currently being investigated in phase 2 clinical trials. It has demonstrated a favorable safety profile, with potentially favorable results; however, more research is warranted to fully evaluate its use.[64]

### Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PD-4) is the enzyme responsible for metabolizing cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (GMP).[66] GMP and cAMP regulate immune function.[67] Inhibition of PD-4 leads to reductions in pro-inflammatory functions and immune cell activity.[66,67]

Roflumilast is an oral PD-4 inhibitor currently approved for use in COPD, and it is being assessed in phase 2/3 clinical trials for use in asthma. Roflumilast has been shown to be as efficacious as low-dose beclomethasone in improving $FEV_1$ and asthma symptoms in patients with mild to moderate persistent asthma.[68] Treatment with roflumilast significantly improved $FEV_1$ lung function in patients with moderate to severe asthma in combination with montelukast.[69] Roflumilast is considered safe; however, patients often experience gastrointestinal AEs, such as nausea, diarrhea, and weight loss.[66]

## Conclusion

Asthma is a chronic condition of the airways defined by complex interactions of inflammation, airflow obstruction, and bronchial hyperresponsiveness.[1] Despite many therapeutic options, the prevalence of asthma in the United States remains high and is expected to affect 100 million people by 2025.[4] Additionally, not all patients with asthma respond to standard treatment options. As such, novel approaches to asthma management continue to emerge and are vital to the treatment of patients suffering from severe asthma.

Although many of the agents discussed appear promising and provide unique mechanisms of action to target various components of the inflammatory cascade, further work and clinical research is needed to elucidate the long-term efficacy and safety of these agents in patients with asthma. Fortunately, the GINA 2016 asthma guidelines now incorporate a few of the newer therapies and it is highly likely that more agents will be incorporated into the guidelines in the future. ■

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