



Editorials

The challenge of choosing the correct biologic for the correct asthma patient



The treatment approach for severe asthma has changed significantly during the past decade. Omalizumab, a monoclonal antibody against immunoglobulin E (IgE), was the first biologic agent approved in the United States and Europe for the treatment of severe asthma. In 2018, 3 additional biologic agents—all targeting interleukin-5 (IL-5) or its receptor, are also available for use.¹ In addition to choosing among various inhalers and other asthma medications, clinicians now face the additional challenge of deciding which biologic agent to use first, if at all, for the treatment of severe asthma. Some patients with poorly controlled severe asthma also have comorbid conditions, such as obesity, atopic dermatitis, allergic rhinitis, and nasal polyps, that can influence the biologic treatment options for asthma.¹

In this issue, Mauka and Wechsler² reviewed the currently approved biologic agents for severe asthma and those that are under investigation in clinical studies. The authors provide insightful approaches to the biologic agent treatment choice and factors involved in the decision making, such as biomarkers and other patient-based factors including body weight, route of administration, and insurance approvals.

All of the currently US Federal Drug Administration (FDA) –approved biologic agents for asthma have shown efficacy in the T2 high asthma phenotype. Despite the improved asthma outcomes, none of the agents have yet demonstrated a true immunomodulation effect. No definitive data show that these monoclonal antibodies can reverse airway remodeling or induce remission of asthma.

Omalizumab is indicated in patients who have moderate to severe asthma and evidence of perennial allergy with a total serum IgE 30 to 700 IU/mL (1,300 in 6- to 11-year-olds). It is the only FDA-approved biologic agent for asthma in pediatric population aged 6–11 years. In Europe, omalizumab is also approved for patients ages 6 years and older with severe asthma and total IgE 30 to 1,300 IU/mL.¹ In recent years, new evidence has suggested that omalizumab also has antiviral effects, especially for reducing the frequency of asthma exacerbations that are triggered by viral infections through a number of mechanisms, including effects on dendritic cells.^{3–5} Although omalizumab has been used for over 15 years, the appropriate treatment duration remains undefined.

Three currently FDA-approved biologic agents target IL-5, mepolizumab, reslizumab, and benralizumab, but no direct comparative data help guide treatment decisions. Indirect meta-analyses comparing 2 or more of these agents have provided some insights into treatment choices.⁶ All 3 have proved effective in treating patients with

asthma who have an eosinophilic phenotype, which is characterized but not defined by specific levels of elevated blood eosinophils. Mepolizumab is also approved for use in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and it is the only IL-5 blocker currently approved for the management of patients as young as 6 years of age in Europe. Benralizumab, the most recently approved IL-5 antagonist, binds to the IL-5 receptor alpha, leading to eosinophil and basophil death. Benralizumab has also been shown in a small study to prevent future asthma exacerbations when given intravenously during asthma exacerbation in an emergency room setting.⁷ We believe that future studies with biologics in the emergency room setting could aid in defining new treatment paradigms for asthma exacerbations.

Other than using antigen-specific IgE and peripheral blood eosinophil counts to help identify asthma phenotypes, the utility of other point-of-care biomarkers is yet to be defined, including periostin, dipeptidyl peptidase 4, and fractional exhaled nitric oxide (FeNO). Because IL-13 is known to induce FeNO production, it might prove to be a good biomarker to predict responsiveness against agents that block IL-13, including dupilumab, a monoclonal antibody against IL-4/IL-13. Dupilumab is currently approved for adults with atopic dermatitis and is being investigated for the treatment of asthma and other atopic conditions. Dupilumab appears to have a faster onset of action than other biologic agents. The phase 3 data on dupilumab for asthma are promising, especially for patients with elevated blood eosinophils.⁸ Whether dupilumab will be approved for the treatment of asthma regardless of phenotype remains to be determined. Interestingly, previous trials with biologic agents directed against either IL-13 alone (lebrikizumab and tralokinumab) or IL-4 alone failed to show improved asthma outcomes regardless of route of administration, suggesting the need to block both IL-4 and IL-13 for clinical effects.

Current data on biologic therapy for T2 low asthma are limited. Unlike the T2 high counterpart, T2 low asthma is generally difficult to define, and the pathophysiology of the disease remains unclear and might be caused by various mechanisms, including defective host defense. Studies on the treatment of T2 low asthma, including IL-17 and IL-6 blocking agents, are ongoing. Brodalumab, an anti-IL-17, did not prove effective for severe asthma, but the population was not enriched for T2 low patients,⁹ and the drug was reported to be associated with a higher incidence of mental health issues, including suicide.

Prostaglandin D2 has a number of effects on eosinophils, lymphocytes, basophils, and type 2 innate lymphoid cells that are effective in treating asthma. *Chemoattractant receptor-homologous molecule expressed on Th2 cells* (CRTH2), the receptor for prostaglandin D2, is another target for asthma treatment. Phase 3 trials on oral CRTH2 antagonists are underway. Although the early data are somewhat

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encouraging,¹⁰ the treatment responses do not appear to be nearly as good as the currently approved anti-IgE and anti-IL-5 therapies. Because of the probable lower cost of CRTH2 blockers compared with other biologics, if approved for use in the future, insurance carriers might require a trial of this medication class before using other costlier biologics.

During the past few years, the treatment approach for severe asthma has increasingly focused on precision care according to individual's phenotype. The use of biologic agents has revolutionized the management of severe asthma, but questions remain regarding this class of agents, including how to select the best treatment for patients with overlapping phenotypes. For example, should patients with severe asthma and elevated blood eosinophils all be treated with an IL-5 blocker, and if so, which one? Would omalizumab be just as effective, because post hoc analyses indicate similar reductions in asthma exacerbations in patients with elevated eosinophils?¹¹ If the patient is obese, is it better to use reslizumab because it has weight-based dosing?¹² Discriminatory biomarkers to better inform selection of the most appropriate biologic for individual patients with T2 high asthma are needed. Because head-to-head trials among biologics are unlikely, efforts should also be made to conduct meta-analyses to measure comparative effects. We still do not know how long to treat patients with a biologic: lifelong; 3 to 5 years; until the patient has a remission (for which we still do not agree on a definition?). Costs aside, whether more than 1 biologic agent can or should be used concurrently in certain patients remains unknown. Other areas that need further investigation include identification of useful biomarkers for T2 low asthma and defining appropriate therapies for these patients.

Until more data are available, we recommend that clinicians select treatment options wisely, based on each patient's characteristics as outlined by Mauka and Wechsler in this issue.² Patients with severe asthma also should be involved in selecting treatment options because adherence will depend on patient preference, including treatment frequency and route of administration, and insurance approval and copayment.

This is an exciting time, in which asthma specialists have new options for the management of severe asthma. We need to embrace biologics and become experts on their use, misuse, and management

of adverse effects. Ultimately, this will result in better care for the patients we serve.

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