

How to Assess Effectiveness of Biologics for Asthma and What Steps to Take When There Is Not Benefit



Amber N. Pepper, MD^a, Nicola A. Hanania, MD^b, Marc Humbert, MD, PhD^{c,d}, and Thomas B. Casale, MD^e Tampa, Fla; Houston, Texas; and Le Kremlin-Bicêtre, France

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: March 1, 2021. Credit may be obtained for these courses until February 28, 2021.

Copyright Statement: Copyright © 2021-2023. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*TM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Amber N. Pepper, MD, Nicola A. Hanania, MD, Marc Humbert, MD, PhD, and Thomas B. Casale, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To determine the best initial biologic choice for the treatment of moderate to severe asthma for each patient.
2. To assess response to biologics in patients with asthma.
3. To manage suboptimal responders being treated with biologics for asthma.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: A. N. Pepper and T. B. Casale are and have been investigators in pharmaceutical clinical trials examining biologic agents for the treatment of asthma. N. A. Hanania received honoraria for serving as a consultant or on advisory boards for GlaxoSmithKline, Sanofi, Regeneron, Genentech, Novartis, Boehringer Ingelheim, AstraZeneca, and Mylan pharmaceuticals; and his institution receives research grant support from GlaxoSmithKline, Sanofi, Genentech, Gossamer Bio, Boehringer Ingelheim, Novartis, and AstraZeneca. M. Humbert reports grants, personal fees, and nonfinancial support from GlaxoSmithKline; and personal fees from AstraZeneca, Novartis, Roche, Sanofi, Teva, and Merck, outside the submitted work. T. B. Casale has served as a consultant for GlaxoSmithKline, Novartis, Genentech, Sanofi, Regeneron, and AstraZeneca. M. Schatz declares no relevant conflicts of interest.

Five biologic medications are approved in the United States for the treatment of asthma that is not well controlled with other therapies. All target asthma with elevated type 2 inflammatory markers, such as elevated eosinophils, fractional exhaled nitric

oxide, or total and specific IgE. Asthma severity, phenotype, age, biomarkers, treatment goals/outcomes, comorbid conditions, safety, and cost should all help guide the initial biologic choice. In addition, a shared decision-making process

^aDivision of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, Fla

^bSection of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas

^cFaculty of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France

^dAssistance Publique - Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

^eFood Allergy Research & Education (FARE), University of South Florida, Tampa, Fla

Conflicts of interest: A. N. Pepper and T. B. Casale are and have been investigators in pharmaceutical clinical trials examining biologic agents for the treatment of asthma. N. A. Hanania received honoraria for serving as a consultant or on advisory boards for GlaxoSmithKline, Sanofi, Regeneron, Genentech, Novartis, Boehringer Ingelheim, AstraZeneca, and Mylan pharmaceuticals; and his institution receives research grant support from GlaxoSmithKline, Sanofi, Genentech,

Gossamer Bio, Boehringer Ingelheim, Novartis, and AstraZeneca. M. Humbert reports grants, personal fees, and nonfinancial support from GlaxoSmithKline; and personal fees from AstraZeneca, Novartis, Roche, Sanofi, Teva, and Merck, outside the submitted work. T. B. Casale has served as a consultant for GlaxoSmithKline, Novartis, Genentech, Sanofi, Regeneron, and AstraZeneca.

Received for publication September 24, 2020; revised October 28, 2020; accepted for publication October 29, 2020.

Corresponding author: Thomas B. Casale, MD, Allergy and Immunology, University of South Florida, James A. Haley V.A. Medical Center, 13000 Bruce B. Downs Blvd, 111D, Tampa, FL 33612. E-mail: tbcasale@usf.edu.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.10.048>

Abbreviations used

ADA- Antidrug antibody

FENO- Fractional exhaled nitric oxide

T2- Type 2

with the patient is needed to optimize adherence, with special attention to patient preference regarding outcomes, safety concerns, and medication administration options. After a biologic agent is initiated, sufficient time is needed to monitor efficacy and response. For patients who do not respond favorably, patient-, disease-, and medication-related factors should be considered and remedied, if possible. Persistent suboptimal responders necessitate a reexamination of asthma phenotype, biomarkers, and the suspected immune response pathways. For some patients, a change in biologic therapy or other therapeutic options may be warranted. In this review, we examine the clinical approach for choosing an initial biologic for the treatment of asthma, the assessment of response to biologics, and the process of troubleshooting and adjusting biologic treatment for those patients with suboptimal responses. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:1081-8)

Key words: Severe asthma; Biologics; Omalizumab; Benralizumab; Mepolizumab; Dupilumab; Reslizumab

INTRODUCTION

Asthma is a heterogeneous chronic respiratory disease characterized by airway obstruction, inflammation, and hyperresponsiveness. It affects 19.2 million adults and 5.5 million children in the United States.¹ Several unmet needs in asthma management have been identified. Despite optimization of standard therapies, including inhaled corticosteroids and long-acting bronchodilators, approximately 3% to 10% and 17% of patients with asthma have severe and difficult-to-treat disease, respectively.² In addition, varying mechanisms contribute to the development and pathogenesis of asthma and there is a need for a more personalized approach to this disease and to better understand which therapies may benefit individual patients. In 2020, the European Academy of Allergy and Clinical Immunology published guidelines for the treatment of severe asthma using biologics and identified key research needs including comparative trials of different biologics that are thus far lacking.³ In this review, we examine the clinical decision-making process that facilitates the initial choice of a biologic for the treatment of asthma and the assessment of response to biologics. In addition, we will discuss the process of troubleshooting and adjusting biologic treatment for those patients with suboptimal responses.

THE INITIAL CHOICE OF A BIOLOGIC

As of September 2020, in the United States, 5 biologics have been approved for the treatment of uncontrolled moderate to severe asthma (Table I). All these biologics target type 2 (T2) airway inflammation propagated by the T_H2 and T2 innate lymphoid cell response pathways (T2-high asthma).³⁻⁵ Direct head-to-head comparison trials of these biologics are not available, and indirect meta-analyses often give discordant results.¹²⁻¹⁶

The choice of which biologic to initiate should be individualized for each patient on the basis of several factors including asthma severity, phenotype, age, biomarkers, treatment goals/outcomes, comorbid conditions, safety, and cost.³ A shared decision-making process should be used for each patient, including medication administration preferences. Each of these factors will be discussed in more detail below.

Asthma severity and phenotype

All biologics require a diagnosis of asthma that is not well controlled on other controller medications.³ It is imperative that the patient's asthma severity is properly classified and other causes of poor asthma control, such as inadequate inhaler technique and poor adherence, are addressed before adding on biologic therapy (Table II).² Omalizumab and dupilumab are indicated for moderate to severe persistent asthma, whereas benralizumab, mepolizumab, and reslizumab are approved for severe persistent asthma only.⁷⁻¹¹ For patients with allergic asthma (elevated total IgE and sensitization to 1 or more perennial aeroallergens), omalizumab is an approved option.^{10,17,18} Despite conditional recommendations for the use of other biologics in allergic asthma by the European Academy of Allergy and Clinical Immunology guidelines, other currently approved biologics are approved for use in eosinophilic asthma only.³ "Asthma with an eosinophilic phenotype" is difficult to explicitly define because of variations in the pivotal clinical trial inclusion criteria for each biologic. Some trials used a minimum peripheral blood eosinophil count of 150 cells/ μ L, whereas others used 300 or 400.¹⁹⁻²⁵ Still others used fractional exhaled nitric oxide (FENO) as a surrogate for eosinophilic inflammation in the lower airways.²¹ Dupilumab is also separately approved for oral corticosteroid-dependent asthma.⁸

Age

All 5 approved biologics are a treatment option for adults.⁷⁻¹¹ Reslizumab is approved for adults 18 years or older.¹¹ Benralizumab, dupilumab, mepolizumab, and omalizumab are approved for use in adolescents 12 years or older.⁷⁻¹⁰ Only mepolizumab and omalizumab are approved in children age 6 to 11 years.^{9,10} The data are most robust for omalizumab in the 6- to 11-year age group and omalizumab and dupilumab in the adolescent age group.^{3,26}

Biomarkers

Peripheral blood eosinophil count, FENO, and total and allergen-specific IgE are important biomarkers to consider when choosing an initial biologic agent for asthma treatment. Benralizumab, mepolizumab, dupilumab, and reslizumab are all indicated for "eosinophilic" asthma or, from a practical standpoint, asthma with an elevated peripheral blood eosinophil count. Mepolizumab and dupilumab have demonstrated efficacy in patients with eosinophil counts greater than or equal to 150 cells/ μ L.²¹ Reslizumab studies included patients with peripheral eosinophil counts greater than or equal to 400 cells/ μ L and benralizumab in patients with eosinophil counts greater than or equal to 300 cells/ μ L. Because dupilumab targets the IL-13 pathway, it has demonstrated efficacy in patients with elevated FENO (≥ 25 parts per billion) due to the role of IL-13 in the production of nitric oxide from airway epithelial cells.²⁷ As mentioned above, omalizumab has demonstrated efficacy in patients with elevated total IgE (≥ 30 IU/mL) and documentation of sensitization to at least 1 perennial aeroallergen. In general, the efficacy of all the biologics, including omalizumab, is

TABLE I. US Food and Drug Administration—approved biologic agents for the treatment of asthma

Biologic	Mechanism of action ⁴⁻⁶	Indications and approved ages	Dosing	2020 EAACI strong recommendations ³
Benralizumab ⁷	Binds to IL-5 receptor alpha subunit, blocking IL-5 signaling	Severe eosinophilic asthma* at age ≥ 12 y	30 mg SC every 4 wk for first 3 doses, then every 8 wk	Reduces severe asthma exacerbations in adults
	Enhances ADCC of eosinophils and basophils			Reduces oral steroid use in adults if eosinophil counts ≥ 150 cells/ μ L
Dupilumab ⁸	Binds to IL-4 receptor alpha subunit, blocking IL-4 and IL-13 signaling	Moderate to severe eosinophilic asthma† or oral corticosteroid—dependent asthma at age ≥ 12 y	<i>Asthma:</i> Initial dose of 400 mg SC then 200 mg SC every 2 wk OR Initial dose of 600 mg SC then 300 mg SC every 2 wk	Reduces severe exacerbations in adults and adolescents
		<i>Others:</i> Chronic rhinosinusitis with nasal polyposis (CRSwNP) at age ≥ 18 y	<i>CRSwNP:</i> 300 mg SC every 2 wk	Improves lung function for adults and adolescents with FENO ≥ 50 ppb or eosinophil counts ≥ 300 cells/ μ L
		Moderate to severe atopic dermatitis (AD) at age ≥ 6 y	<i>AD:</i> Adults: Initial dose of 600 mg SC then 300 mg SC every 2 wk	Reduces oral steroid use in adults and adolescents
			Children:	
			≥ 15 kg to <30 kg:	
			Initial dose of 600 mg SC then 300 mg SC every 4 wk	
			≥ 30 kg to <60 kg:	
			Initial dose of 400 mg SC then 200 mg SC every 2 wk	
			≥ 60 kg:	
			Initial dose of 600 mg SC then 300 mg SC every 2 wk	
Mepolizumab ⁹	Binds to and neutralizes IL-5	Severe eosinophilic asthma‡ at age ≥ 6 y	<i>Asthma:</i> Adults and adolescents ≥ 12 y: 100 mg SC every 4 wk	Reduces severe asthma exacerbations in adults
		<i>Others:</i> Eosinophilic granulomatosis with polyangiitis (EGPA) at age ≥ 18 y	Children age 6-11 y: 40 mg SC every 4 wk	Reduces oral steroid use in adults
			<i>EGPA:</i> 300 mg SC every 4 wk	
		Hypereosinophilic syndrome (HES) for ≥ 6 mo without an identifiable nonhematologic secondary cause at age ≥ 12 y	<i>HES:</i> 300 mg SC every 4 wk	
Omalizumab ¹⁰	Binds to and neutralizes IgE	Moderate to severe allergic asthma§ at age ≥ 6 y	<i>Asthma:</i> 75-375 mg SC every 2 or 4 wk based on body weight and total IgE	Reduces severe asthma exacerbations in adolescents and adults with moderate to severe allergic asthma

(continued)

TABLE I. (Continued)

Biologic	Mechanism of action ⁴⁻⁶	Indications and approved ages	Dosing	2020 EAACI strong recommendations ³
	Leads to downregulation of FcεR1 on mast cells, basophils, and dendritic cells	<i>Others:</i> Chronic idiopathic urticaria (CIU) at age ≥12 y	CIU: 150 or 300 mg SC every 4 wk	Reduces severe asthma exacerbations in adults with FENO ≥24 ppb and eosinophil counts ≥260 cells/μL
Reslizumab ¹¹	Binds to and neutralizes IL-5	Severe eosinophilic asthma at age ≥18 y	3 mg/kg IV every 4 wk	Reduces severe asthma exacerbations in adults

ADCC, Antibody-dependent cellular cytotoxicity; EAACI, European Academy of Allergy and Clinical Immunology; FcεR1, high-affinity IgE receptor; IV, intravenous; ppb, parts per billion; SC, subcutaneous.

*Absolute eosinophil count of ≥300 cells/μL at initiation or ≥150 cells/μL for oral corticosteroid-dependent patients.

†Absolute eosinophil count of ≥150 cells/μL or FENO ≥25 ppb.

‡Absolute eosinophil count of ≥150 cells/μL at initiation or ≥300 cells/μL in the past year.

§Total IgE 30-700 IU/mL for adults and adolescents or 30-1300 IU/mL for children 6-11 y and sensitization to 1 or more perennial aeroallergens.

||Absolute eosinophil count of ≥400 cells/μL at initiation.

TABLE II. Tactics to enhance asthma control before initiating biologic therapy

Patient factors	Teach and train proper inhaler technique Ensure adherence to background asthma therapies
Environmental factors	Assess and treat comorbidities Optimize control of triggers and sensitizers
Disease factors	Ensure correct asthma diagnosis Rule out vocal cord and upper airway disorders, cardiac disorders, etc

Adapted from the Global Initiative for Asthma guidelines.²

more pronounced with increasing levels of peripheral blood eosinophils and, in some cases, other T2-high biomarkers. In placebo-controlled clinical trials, omalizumab most effectively reduced asthma exacerbations in patients with elevated blood eosinophils and FENO, while real-world data indicate that its effectiveness in severe allergic asthma is not dependent on blood eosinophil levels.^{17,18,28}

Outcomes

All approved biologics reduce asthma exacerbations in certain patient populations. Reductions are highest for those with T2-high biomarkers as noted above.³ Dupilumab significantly improves lung function in patients with elevated FENO and eosinophil counts, reaching clinically meaningful values when greater than or equal to 50 parts per billion and greater than or equal to 300 cells/μL, respectively, and in oral corticosteroid-dependent asthma.^{3,21,29} Statistically significant improvements in lung function are also seen in patients with FENO greater than or equal to 25 and less than 50 parts per billion with dupilumab.²¹ Dupilumab, benralizumab, and mepolizumab reduce oral corticosteroid use in patients with asthma with elevated eosinophil counts, and dupilumab carries an indication for oral corticosteroid-dependent asthma.^{8,29-31} All biologics may improve quality of life and asthma control, but the data are less clear for these outcomes because minimal important differences were not consistently met in the pivotal trials.³

Comorbid and coexisting conditions

For patients with asthma who suffer from certain comorbid conditions, choosing a biologic that treats multiple underlying disease processes is practical. Dupilumab is also approved for the

treatment of atopic dermatitis and chronic rhinosinusitis with nasal polyposis.⁸ The utility of benralizumab, mepolizumab, and omalizumab for nasal polyposis is being examined in clinical trials, with omalizumab demonstrating improvement in objective and subjective signs and symptoms of severe chronic rhinosinusitis with nasal polyposis in phase 3 trials.³² Omalizumab is also approved for the treatment of chronic idiopathic urticaria.¹⁰ Mepolizumab is approved, at higher doses, for the treatment of eosinophilic granulomatosis with polyangiitis (EPGA) and some types of hypereosinophilic syndrome.⁹ Reslizumab is dosed on the basis of weight, which may be important in patients with asthma and comorbid obesity.¹¹ Omalizumab is also partially dosed on weight, but dosing data are less robust for patients with higher weights and total IgE.^{3,10} The effectiveness of these biologics for other asthma comorbidities is listed in Table III, based on the authors' assessment of the available published evidence.³³⁻³⁹

Safety

All biologics have the potential to cause hypersensitivity reactions, but this was higher in the pivotal trials for omalizumab and reslizumab, which led the US Food and Drug Administration to impose black box warnings for anaphylaxis risk.^{10,11} Mepolizumab may increase the risk of herpes zoster outbreaks and patients should be immunized before initiation if appropriate.⁹ Dupilumab may cause conjunctivitis and keratitis although these adverse effects are mainly seen in patients with atopic dermatitis.¹³ Dupilumab, and possibly omalizumab, may worsen or trigger hypereosinophilic conditions.^{8,10} A worsening of or increased risk for helminth infections is a hypothetical concern with all biologics. All also warn against discontinuing oral or inhaled corticosteroids abruptly.^{3,6} The above safety profile should be considered in choosing the appropriate biologic agent when applicable.

Cost

All biologic agents approved for the treatment of asthma are costly. In the United States, insurance plans occasionally dictate specific coverage of biologics, which may, in turn, affect the clinicians' choice of which biologic to prescribe to a given patient.⁴⁰ For those patients without insurance or who cannot get coverage for insurance, most pharmaceutical companies offer patient assistance programs. These are unique to the biologic and can change over time.

TABLE III. Biologic effectiveness on asthma comorbidities

Comorbidity	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Atopic dermatitis	+/-	-	No data	No data	Indicated
CRSwNP	+++	+	+	+	Indicated
Food allergy	++	No data	No data	No data	+
Allergic rhinoconjunctivitis/allergic rhinitis	++	No data	No data	No data	+
ABPA	+	+	No data	+/-	No data
EGPA	+	Indicated	No data	No data	No data
ACO	+	No data	No data	No data	No data

+, Favorable data from smaller clinical trials; ++, favorable data from larger trials; +++, favorable data from phase 3 trials; +/-, mixed data or case reports only; -, unfavorable data from clinical trials; *ABPA*, allergic bronchopulmonary aspergillosis; *ACO*, asthma-COPD (chronic obstructive pulmonary disease) overlap; *CRSwNP*, chronic rhinosinusitis with nasal polyposis; *EGPA*, eosinophilic granulomatosis with polyangiitis.

TABLE IV. Asthma biologic therapy administration details

Biologic	Administration locations	Administration devices
Benralizumab ⁷	Health care setting or home	Prefilled syringe or autoinjector
Dupilumab ⁸	Health care setting or home for age ≥12 y	Prefilled syringe or prefilled pen
Mepolizumab ⁹	Health care setting or home for age ≥12 y	Prefilled syringe or autoinjector
Omalizumab ¹⁰	Health care setting only	Prefilled syringe or lyophilized powder in a single-dose vial for reconstitution
Reslizumab ¹¹	Health care setting only	Single-use vial(s)

Dosing and shared decision making

If more than 1 biologic is a reasonable option for asthma treatment, patient preference is also an important consideration, especially regarding the method and frequency of administration. If the patient prioritizes self-administration at home, this is offered for benralizumab, dupilumab, and mepolizumab in the United States.⁷⁻⁹ This may offer a clear advantage during the coronavirus disease 2019 pandemic because some patients are reluctant to have frequent visits to health care facilities. Omalizumab and reslizumab must be administered in a health care setting, and reslizumab is administered intravenously.^{10,11} Different devices for administration are also available. Benralizumab, dupilumab, mepolizumab, and omalizumab all offer prefilled syringes, and benralizumab and mepolizumab offer autoinjectors (Table IV).⁷⁻¹⁰ Dupilumab is dosed the most frequently, every 2 weeks, whereas benralizumab is dosed every 8 weeks after the first 3 doses (Table I).^{7,8} More or less frequent dosing may be desirable for an individual patient. Patients may also be concerned about certain potential side effects or prioritize particular outcomes. Ideally, the initial biologic choice should be guided by as much patient input as possible.

SUBOPTIMAL RESPONDERS: EVALUATION AND MANAGEMENT

Once a biologic is initiated, it is important for clinicians to monitor its effectiveness and safety by closely following the patient's symptoms including asthma control, exacerbation history, lung function, and other metrics (Figure 1).⁴¹ In addition, monitoring for any adverse effects is imperative but rarely is the reason to stop or switch therapy. Patients and physicians should be cognizant that a 4- to 6-month treatment trial period is needed to assess the optimal effect of biologics before contemplating stopping or switching to another agent.³ Patients who show intermediate response may need to be treated for a longer period of 6 to 12 months for optimal response.² The definition of suboptimal response should be based on a composite of outcomes because

reductions in asthma exacerbations may not be apparent for more than 1 year, especially for the patient who has 1 or less exacerbation per year. Indeed, the profile of all the approved biologics indicate a reduction in exacerbations of approximately 50%,³ making it difficult to assess exacerbation reduction in some patients. In those patients who show a suboptimal response, several patient-related, disease-related, and medication-related factors should be considered (Figure 2).

Among the patient-related factors, the most important one remains nonadherence to background controller therapy or to the general management plan proposed to ensure asthma control.³ Many patients fail to realize that the use of a biologic usually does not replace the need for other controllers, especially inhalers. It has been reported that some patients may stop or modify their background controller treatment following the first administration of a biologic without sharing that decision with their treating physicians.⁴² Adherence with the biologic itself is also an issue, especially for those biologics that are self-administered. The incremental cost of biologics may force some patients to prioritize which medication to refill, which may, in turn, influence their use of other controller medicines or lead to less frequent dosing. To mitigate this risk, patient education should be offered to all patients to optimize care. Adherence to asthma therapies (including biologics, especially in the setting of self-administration) should be monitored carefully by evaluation of medication refills or by using smart inhalers with dose counting. To optimize adherence to the overall management plan, the European Academy of Allergy and Clinical Immunology guidelines for the treatment of severe asthma using biologics underscore the importance of a shared decision-making process at the start of the biologic treatment and establishment of common goals following the administration of the drug.³

Other patient-related factors include inadequate inhaler technique and suboptimal management of comorbidities.³ It is therefore important to reassess such issues in the initial assessment of patients who demonstrate suboptimal responses to biologics.

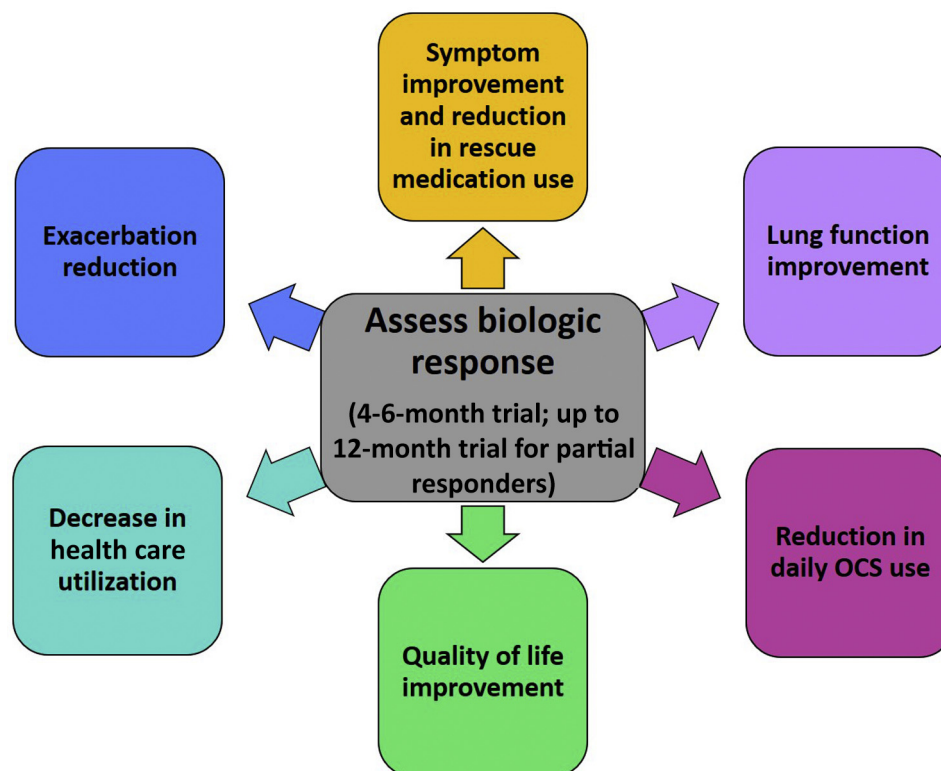


FIGURE 1. Assessment of response to biologic asthma therapy. *OCS*, Oral corticosteroid.

Disease-related factors include the possibility that the patient's disease is driven by different mechanisms than those targeted by the biologic being used, especially if airway eosinophilia and/or T2 airway inflammation persist.³ In such cases, it is appropriate to carefully phenotype the patient and consider switching to biologics targeting another pathway involved in the persistence of T2 airway inflammation.⁴³ Reassessment of the biomarker profile, including examining blood, sputum, and exhaled inflammatory markers, is advised.³ In addition, a holistic approach, considering other treatable or nontreatable factors contributing to the patient's morbidity and exacerbations, is recommended. Such factors may include obesity, deconditioning and dysfunctional breathing, and recurrent lower airway infection.⁴⁴

Medication-related factors include inadequate dosing of an otherwise efficacious agent and neutralizing antidrug antibodies (ADAs). Inadequate dosing may be due to the selection of a fixed dose with some, but not all, marketed biologics. Alternatively, using a different route of administration (intravenous vs subcutaneous) may be an option. Indeed, switching to an agent allowing weight-adjusted therapy administered by a different route may provide added benefits, as demonstrated by Mukherjee et al.⁴⁵ It has also been widely described that unwanted immunogenicity of biologics may lead to the development of neutralizing ADAs, which might in turn alter responses to biologics.⁴⁶ In the COLUMBA open-label long-term extension safety study of mepolizumab (NCT01691859), the percentage of ADAs to mepolizumab was 8%, a proportion that was consistent with previous studies.⁴⁷ Humanized and fully human mAbs can indeed induce endogenous ADA formation, potentially producing inactive immune complexes (mAb-ADA complex). Formation of

complexes accelerates mAbs' clearance because binding of the mAb to ADAs triggers lysosomal degradation.⁴⁸ Nevertheless, the exact clinical consequences of ADAs remain unclear in patients with type 2 asthma treated with biologics. If careful evaluation of biologic failure suggests that ADAs may be the cause, one should consider switching to biologics targeting a different pathway or to a biologic targeting the same pathway but with different mechanism of action or route of administration. Rarely, other causes could explain treatment failure, including immune dysfunctions (T2 innate lymphoid cell activation, autoimmune mechanisms, or IL-5-anti-IL-5 complement activating immune complexes).³ These uncommon cases require referral to a specialized center with multidisciplinary teams after all other causes have been excluded.

In addition, no airway inflammation or neutrophil-rich inflammation may be detected at reevaluation for suboptimal response to a biologic. In that case, T2 inflammation is no longer regarded as the dominant pathomechanism causing asthma (T2-low asthma), the biologic should be interrupted, and measures such as macrolides or bronchial thermoplasty may be proposed in select cases.³

CONCLUSIONS

Biologic therapies are a promising addition to the repertoire of treatment options for patients with moderate to severe asthma. The initial choice of a biologic agent should be personalized for each patient as much as possible. Factors guiding this initial choice include asthma severity, phenotype, age, biomarkers, treatment goals/outcomes, comorbid conditions, safety, and cost. A shared

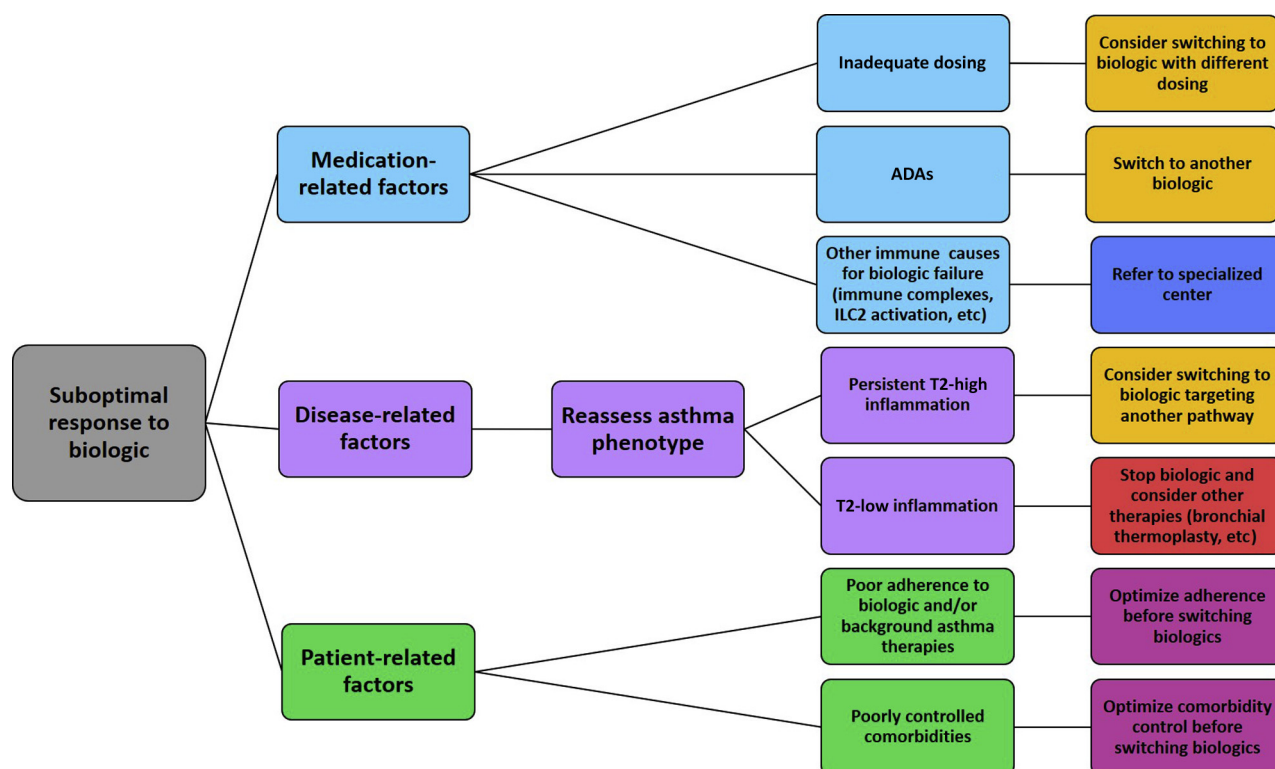


FIGURE 2. Suggested algorithm to assess suboptimal biologic response in asthma. Adapted from the 2020 EAACI guidelines for biologic use in severe asthma.³ EAACI, European Academy of Allergy and Clinical Immunology; ILC2, T2 innate lymphoid cell.

decision-making process is recommended. Patient preferences regarding route, ease, and frequency of medication administration as well as the outcomes and safety concerns prioritized by each patient should be considered when choosing an initial biologic agent. Adequate time is needed to fully assess clinical responses to a biologic. For suboptimal responders despite a sufficient trial with a biologic, patient-, disease-, and medication-related factors should be investigated. Adherence to background asthma therapies and the biologic itself are of utmost importance. Reassessment of biomarkers and the patient's asthma phenotype and endotype may be necessary. Consideration of inadequate dosing or ADAs is also warranted. Ultimately, persistent suboptimal responders may require a change in biologic therapy to an agent targeting another pathway or with a different route of administration. For those patients who develop a T2-low inflammatory asthma profile, other therapeutic options must be considered.

REFERENCES

- Centers for Disease Control and Prevention, National Center for Health Statistics. FastStats: asthma. 2017. Available from: <https://www.cdc.gov/nchs/fastats/asthma.htm>. Accessed July 16, 2020.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2020. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_final_wms.pdf. Accessed July 16, 2020.
- Agache I, Akdis C, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI Biologicals Guidelines—recommendations for severe asthma. *Allergy* 2021;76:14-44.
- Casale TB. Biologics and biomarkers for asthma, urticaria, and nasal polyposis. *J Allergy Clin Immunol* 2017;139:1411-21.
- Pepper AN, Renz H, Casale TB, Garn H. Biologic therapy and novel molecular targets of severe asthma. *J Allergy Clin Immunol Pract* 2017;5:909-16.
- Saco TV, Pepper A, Casale TB. Uses of biologics in allergic diseases: what to choose and when. *Ann Allergy Asthma Immunol* 2018;120:357-66.
- FASENRA (benralizumab) prescribing information. Wilmington, DE: Astra-Zeneca Pharmaceuticals LP; 2019. Available from: <https://www.fasenra.com/>. Accessed July 16, 2020.
- DUPIXENT (dupilumab) prescribing information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2020. Available from: <https://www.dupixent.com/>. Accessed July 16, 2020.
- NUCALA (mepolizumab) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2020. Available from: <http://www.nucala.com/>. Accessed October 19, 2020.
- XOLAIR (omalizumab) prescribing information. South San Francisco, Calif: Genentech, Inc; 2019. Available from: <http://www.xolair.com/>. Accessed July 16, 2020.
- CINQAIR (reslizumab) prescribing information. West Chester, Pa: Teva Respiratory, LLC; 2020. Available from: <http://www.cinqair.com/>. Accessed July 16, 2020.
- Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M. Reslizumab compared with benralizumab in patients with eosinophilic asthma: a systematic literature review and network meta-analysis. *J Allergy Clin Immunol Pract* 2019;7:122-130.e1.
- Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison. *J Allergy Clin Immunol* 2019;143:190-200.e20.
- Ifthikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung* 2018;196:517-30.
- Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res* 2019;20:179.
- He LL, Zhang L, Jiang L, Xu F, Fei DS. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: a pairwise and Bayesian network meta-analysis. *Int Immunopharmacol* 2018;64:223-31.
- Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J* 2018;51:1702523.

18. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract* 2019;7:156-164.e1.
19. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
20. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016;150:789-98.
21. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
22. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
23. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
24. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
25. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
26. Gupta A, Pouliquen I, Austin D, Price RG, Kempford R, Steinfeld J, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. *Pediatr Pulmonol* 2019;54:1957-67.
27. Ingram JL, Kraft M. IL-13 in asthma and allergic disease: asthma phenotypes and targeted therapies. *J Allergy Clin Immunol* 2012;130:829-42. quiz 843-4.
28. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
29. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475-85.
30. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
31. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448-58.
32. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020;146:595-605.
33. Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma-COPD overlap: post hoc analysis of PROSPERO. *J Allergy Clin Immunol* 2019;143:1629-1633.e2.
34. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018;32:850-78.
35. Long A, Borro M, Sampath V, Chinthrajah RS. New developments in non-allergen-specific therapy for the treatment of food allergy. *Curr Allergy Asthma Rep* 2020;20:3.
36. Yu C, Wang K, Cui X, Lu L, Dong J, Wang M, et al. Clinical efficacy and safety of omalizumab in the treatment of allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *Am J Rhinol Allergy* 2020;34:196-208.
37. Celebi Sozener Z, Gorgulu B, Mungan D, Sin BA, Misirligil Z, Aydin O, et al. Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases. *World Allergy Organ J* 2018;11:39.
38. Humbert M, Bousquet J, Bachert C, Palomares O, Pfister P, Kottakis I, et al. IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. *J Allergy Clin Immunol Pract* 2019;7:1418-29.
39. Tolebeyan A, Mohammadi O, Vaezi Z, Amini A. Mepolizumab as possible treatment for allergic bronchopulmonary aspergillosis: a review of eight cases. *Cureus* 2020;12:e9684.
40. Anderson WC III, Szefer SJ. Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: to biologic or not to biologic? *Ann Allergy Asthma Immunol* 2019;122:367-72.
41. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol* 2012;129:S1-8.
42. d'Ancona G, Kavanagh J, Roxas C, Green L, Fernandes M, Thomson L, et al. Adherence to corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. *Eur Respir J* 2020;55:1902259.
43. Albers FC, Hozawa S, Bratton DJ, Yancey SW, Prazma CM, Humbert M, et al. Update: mepolizumab treatment in patients with severe eosinophilic asthma and prior omalizumab use. *Allergy* 2020;75:942-6.
44. Pavord ID, Shrimamker R, Hanania NA. Biologics targeting type 2 inflammation in severe asthma. In: Chung KF, Israel E, Gibson PG, editors. *Severe asthma [ERS Monograph]*. Sheffield, UK: European Respiratory Society; 2019. p. 285-303.
45. Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med* 2018;197:38-46.
46. Rup B, Pallardy M, Sikkema D, Albert T, Allez M, Broet P, et al. Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: recommendations of the Innovative Medicines Initiative ABIRISK consortium. *Clin Exp Immunol* 2015;181:385-400.
47. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019;143:1742-1751.e7.
48. Matera MG, Calzetta L, Rogliani P, Cazzola M. Monoclonal antibodies for severe asthma: pharmacokinetic profiles. *Respir Med* 2019;153:3-13.