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# Effective Management of Severe Asthma with Biologic Medications in Adult Patients: A Literature Review and International Expert Opinion

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Severe asthma often remains uncontrolled despite effective treatments and evidence-based guidelines. A group of global experts in asthma and biologic medications from 9 countries considered the most relevant clinical variables to manage severe asthma in adult patients and guide treatment choice. The resulting recommendations address the investigation of biomarker levels (blood eosinophil count along with fractional

concentration of exhaled nitric oxide [FeNO]), clinical features (oral corticosteroid [OCS] dependence, specific comorbid disease entities associated with severe type 2 asthma), and safety considerations. Current evidence suggests that biomarkers, including both blood or sputum eosinophil counts as well as FeNO, add prognostic and predictive value and should be measured in all patients with severe asthma. OCS use is an

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#### Abbreviations used

BEC- Blood eosinophil count

BMI- Body mass index

CRSwNP- Chronic rhinosinusitis with nasal polyposis

EGPA- Eosinophilic granulomatosis with polyangiitis

EPX- Eosinophil peroxidase

FeNO- Fractional concentration of exhaled nitric oxide

GINA- Global Initiative for Asthma

ICS- Inhaled corticosteroids

IgE- Immunoglobulin E

IL- Interleukin

IL-5R $\alpha$ - IL-5 receptor alpha

mAb- Monoclonal antibody

OCS- Oral corticosteroid

ppb- Parts per billion

QoL- Quality of life

T2- Type 2

**important factor in biologic selection, especially given the documented ability of some biologics to reduce OCS dependence. Comorbid diseases and relevant safety considerations to each biologic should also be considered. More data are needed to determine whether biomarker profiles identify patients suited to one biologic versus another as limited data support differential predictors of response. Further prospective head-to-head trials and *post hoc* analyses of clinical trial data are warranted. The authors believe that these recommendations have value as they offer expert opinion to assist health care providers in making difficult decisions regarding the quality of care in severe, type 2 asthma with biologic medications. They remain conditional and are based on limited data owing to a lack of head-to-head comparisons.**

**Key words:** Algorithm; Eosinophils; Severe asthma

Asthma is a chronic inflammatory disease estimated to affect 339 million people, with 5% to 10% of these patients reported to have severe asthma.<sup>1-4</sup> Severe asthma causes continuing symptoms that greatly affect quality of life (QoL) and result in severe, life-threatening exacerbations.<sup>5,6</sup> Although only a small percentage of patients in the total asthma population have severe asthma, the care of these patients is associated with substantially greater health care costs and indirect costs, with severe exacerbations in these patients associated with substantial health care costs as well as psychological burden.<sup>7-9</sup>

Asthma is classified as severe when maximal, high-intensity treatment is needed for control or when it remains uncontrolled despite treatment adherence.<sup>3,10,11</sup> Severe asthma requires maintenance treatment with high-dosage inhaled corticosteroids (ICS) plus additional controller medication(s) or systemic corticosteroids to maintain disease control and reduce exacerbations.<sup>3,12</sup> Despite the availability of effective medications to control asthma, severe exacerbations continue to be a major health risk that lead to serious outcomes, such as hospitalization or death, with asthma exacerbations being 3 times more likely to

occur in patients with uncontrolled asthma.<sup>3,9,13</sup> Approximately 25% of patients with severe asthma report 4 or more exacerbations per year.<sup>14</sup>

Severe asthma is associated with different specific phenotypes.<sup>15,16</sup> For this persistent, often uncontrolled disease, identification of a patient's specific asthma phenotype is important not only for research purposes or in clinical trials, but also in clinical practice to guide therapy in the implementation of a successful treatment plan to improve QoL, reduce exacerbations, and limit hospitalizations.<sup>5,17</sup>

The eosinophil granulocyte has been identified as a key mediator of airway inflammation in several asthma phenotypes, including those with both allergic and nonallergic features.<sup>18,19</sup> The biological functions of eosinophils are complex, potentially acting as antigen-presenting cells and releasing type 2 (T2) cytokines, as well as by inducing dendritic cell differentiation through eosinophil-derived neurotoxin release.<sup>20,21</sup> In addition, there is a strong association between nasal and pharyngeal eosinophil peroxidase (EPX) levels and eosinophil percentage of induced sputum, with EPX-generated oxidants found to relate to mucus plug formation and chronic airflow obstruction in severe asthma.<sup>22,23</sup> Furthermore, eosinophils are an important part of immunity, with their cytokines and growth factors contributing to proinflammatory responses.<sup>24,25</sup>

According to the International Severe Asthma Registry, T2 asthma represents approximately 70% of severe asthma cases.<sup>26</sup> T2 asthma includes interleukin (IL)-4, IL-5, and IL-13 pathophysiology, leading to both eosinophilic and allergic disease.<sup>27-29</sup> In eosinophilic asthma, eosinophils increase in the peripheral circulation and accumulate in the airway wall and the airway lumen; eosinophil activation and degranulation contribute to airway inflammation, mucus hypersecretion, mucus plugging, bronchoconstriction, and airway remodeling.<sup>30-32</sup> Elevated blood eosinophil counts (BECs) are associated with more severe disease, increased frequency of exacerbations, and asthma mortality.<sup>33-37</sup> Reducing eosinophil-associated airway inflammation is a therapeutic target for several asthma biologic agents.<sup>38</sup> For patients with severe, eosinophilic asthma, biologic therapies that reduce or deplete eosinophils provide an endotype-specific treatment approach that results in significant reductions in asthma symptoms, reduction in oral corticosteroid (OCS) use, decreased exacerbation frequency, and improved lung function.<sup>11,39-42</sup>

Fraction of exhaled nitric oxide (FeNO) levels have also demonstrated prognostic and predictive value for patients with severe asthma, with a combination of BEC and FeNO providing additive information for biologic medications.<sup>43</sup> These phenotypes may usually be distinguished by identifiable clinical and biomarker profiles that are associated with a typical response to treatment.<sup>27,44</sup> The presence of a specific T2 endotype is assessed in clinical practice using a combination of BEC, FeNO, and total and specific immunoglobulin E (IgE) in an effort to identify the dominant driver (IL-4, IL-5, IL-13, or IgE).<sup>27,44,45</sup> Biologic therapies may have a greater positive clinical impact in particular patient subgroups in asthma,<sup>15</sup> including those with higher FeNO levels and BECs, atopic dermatitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), allergies, and OCS use.

The FDA has approved 5 biologics for the treatment of severe, T2 asthma (including both allergic [total IgE with a predefined range] and eosinophilic asthma), each with distinct mechanisms of action (Table I). Omalizumab is indicated for moderate-to-severe persistent asthma in patients 6 years of age and older with a

**TABLE I.** Biologics for the treatment of severe asthma

Biologic medication	Mechanism of action	Indications	Biomarkers predicting enhanced treatment response
Omalizumab <sup>46-50</sup>	mAb to IgE	Moderate-to-severe asthma for patients aged $\geq 6$ y with symptoms not controlled with ICS	FeNO ( $\geq 20$ ppb), BEC ( $>260$ cells/ $\mu$ L)
Dupilumab <sup>51-56</sup>	mAb to IL-4 receptor alpha	Moderate-to-severe asthma for patients aged $\geq 12$ y, with eosinophilic phenotype or OCS-dependent asthma	FeNO ( $>25$ ppb), BEC ( $>150$ cells/ $\mu$ L)
Mepolizumab <sup>41,57-63</sup>	mAb against IL-5	Add-on maintenance therapy for patients with severe asthma aged $\geq 6$ y, with eosinophilic phenotype	BEC ( $\geq 150$ cells/ $\mu$ L)
Reslizumab <sup>64-67</sup>	mAb against IL-5	Add-on maintenance therapy for patients with severe asthma aged $\geq 18$ y, with eosinophilic phenotype	BEC (400 cells/ $\mu$ L)
Benralizumab <sup>40,42,68-79</sup>	mAb against IL-5 receptor alpha	Add-on maintenance therapy for patients with severe asthma $\geq 12$ y of age, with eosinophilic phenotype	BEC ( $\geq 150$ cells/ $\mu$ L)

BEC, Blood eosinophil count; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; mAb, monoclonal antibody; OCS, oral corticosteroid; ppb, parts per billion.

positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. Omalizumab is a recombinant humanized IgG1 monoclonal antibody (mAb) therapy that targets and binds free IgE, interrupting the IgE-mediated asthma inflammatory cascade at an early stage; thus omalizumab reduces both early and late asthmatic responses and improves exacerbations, lung function, and asthma control, with a greater effect on exacerbations demonstrated for patients with high FeNO levels, BEC, and periostin.<sup>46-50</sup> Mepolizumab, reslizumab, and benralizumab are 3 immunomodulator mAb therapies that act to reduce eosinophilic inflammation and are recommended as add-on therapies for the treatment of patients with severe, uncontrolled asthma who exhibit an eosinophilic phenotype.<sup>12,80,81</sup> Mepolizumab is a fully humanized mAb that binds to IL-5, blocking its action as a key inflammatory cytokine in eosinophil development, activation, and survival; in clinical trials, it reduces exacerbation rates, improves lung function, reduces OCS exposure, and demonstrates clinically significant improvement for patients with a BEC of  $\geq 150$  cells/ $\mu$ L at baseline as well as better outcomes in those patients with adult asthma diagnosis, CRSwNP, lower body mass index (BMI), and lower maintenance prednisolone dosage required at baseline.<sup>41,57-63,81-83</sup> Reslizumab, a humanized anti-human IL-5 mAb, demonstrates clinically significant improvements for patients with poorly controlled asthma, including a significant reduction in the frequency of asthma exacerbations compared with placebo; improvement in lung function is particularly observed in patients with BEC  $\geq 400$  cells/ $\mu$ L.<sup>64-67,81-83</sup> Benralizumab is a humanized IL-5 receptor alpha (IL-5R $\alpha$ )-directed cytolytic mAb that induces rapid and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity, providing clinical benefits for patients with increased BEC, greater exacerbation history, poor lung function, OCS use, CRSwNP, and adult asthma diagnosis.<sup>40,42,68-79</sup> Dupilumab is a fully human mAb directed against the  $\alpha$ -subunit of the IL-4 receptor and blocks both IL-4 and IL-13 signal transduction, which significantly lowers rates of severe asthma exacerbations and OCS use and demonstrates improvement in lung function versus placebo, with the greatest treatment benefits observed for patients with elevated BEC and/or FeNO levels.<sup>51-56</sup>

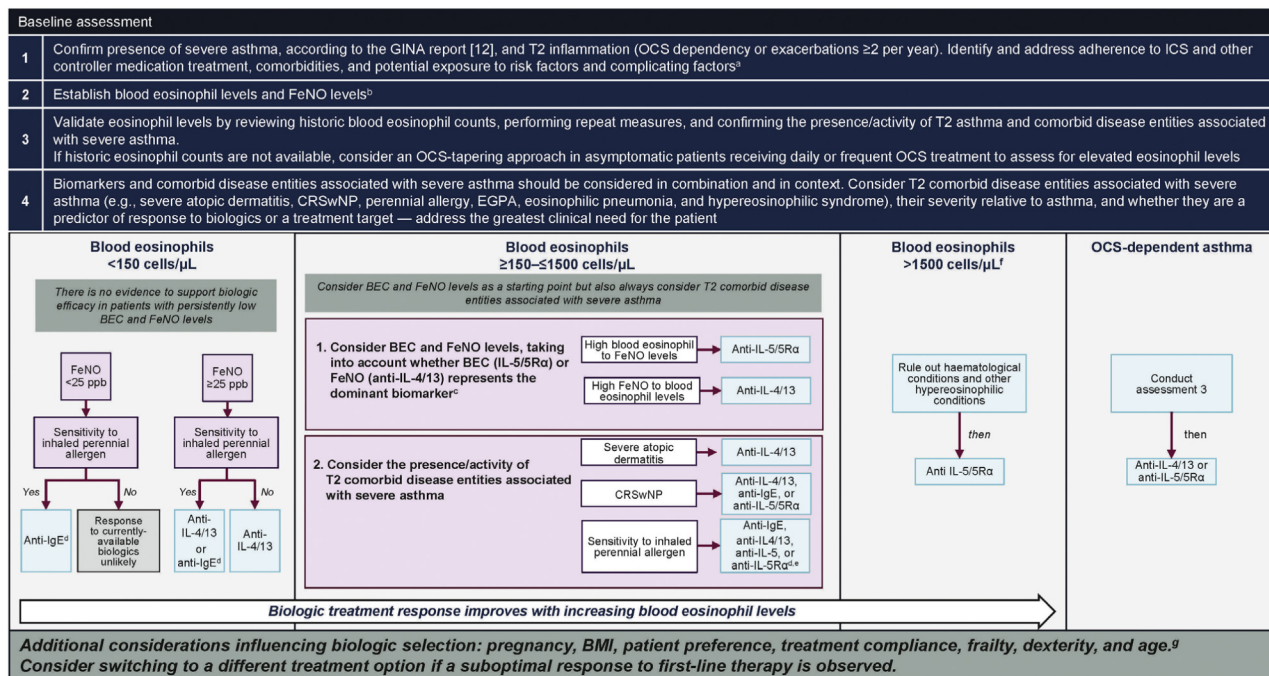
In clinical practice, physicians have a difficult task prioritizing which of these 5 biologics may be an optimal treatment for any given patient; this difficulty results from the significant overlap in

patient characteristics for those who qualify for different biologics. Direct comparisons between biologics do not exist, and meta-analyses and network analyses are inconclusive.<sup>84-89</sup> Various algorithms for the selection of biologics in severe asthma have been published over the past 5 years, with some predating currently available compounds.<sup>5,12,84,90-99</sup> There is a clear need for a planned therapeutic approach in severe asthma that remains uncontrolled.<sup>84</sup> It is important to make a good initial choice in an effort to avoid undesirable switching, spare nonuseful exposure to expensive medications, limit the risk of patient distrust, and decrease the risk of antidrug antibodies.<sup>100</sup>

Some of the treatment algorithms in the current literature are complex and do not fully address the optimal treatment choice between anti-IgE, anti-IL-5, anti-IL-5 receptor, and anti-IL-4 receptor. Individual national reimbursement practices in effect may also guide decisions due to limitations and availability of biologic therapies and the ease of switching between biologic agents. Updated clinical treatment guidelines are needed for optimal, individualized management of this patient population.<sup>6,9</sup> This summary and expert opinion aims to address the investigation of biomarker levels (BEC along with FeNO), clinical features (OCS dependence and specific comorbid disease entities associated with severe T2 asthma [eg, severe atopic dermatitis, CRSwNP, perennial allergy, eosinophilic granulomatosis with polyangiitis (EGPA), and eosinophilic pneumonia]), and safety considerations, some of which are not addressed in previously developed clinical guidelines. All recommendations and opinions provided should be interpreted taking the individual patient, as well as clinical circumstances, perceptions, values, and preferences, into account.

## METHODS

New therapeutic options for severe asthma have recently emerged, mostly in the form of biologics targeting relevant inflammatory pathways. Currently, available agents target different aspects of T2 immunity, and their indications often include overlapping patient groups. Because direct head-to-head clinical studies for biologics are lacking, the proposed treatment guidelines for initial choice and potential switch between biologic medications for the management of adult patients with severe asthma are based on current evidence, including clinical trial data and analyses. This guidance also considers the relevant complexities and understanding of the key



**FIGURE 1.** Biologic treatment algorithm for severe asthma. Recommendations for biologic treatment selection for patients with severe asthma. <sup>a</sup>Consider historic adherence to treatment or reassess the inhaler technique first and address non-T2 comorbid disease entities associated with severe asthma. <sup>b</sup>BEC thresholds provided are not absolute, and patient response to biologics should be considered on a continuum of blood eosinophil levels. <sup>c</sup>For patients with high BEC to FeNO levels (high BEC being the predominant signal), treatment with anti-IL-5/5R $\alpha$  is recommended, and for patients with high FeNO to BEC levels (high FeNO being the predominant signal), treatment with anti-IL-4/13 is recommended. BEC and FeNO levels used to indicate a predominant signal are not established and should be based on clinical judgment. <sup>d</sup>Although clinical trial data to support efficacy in these patients are limited, real-world data and clinical experience indicate the effectiveness of treatment with anti-IgE for patients who have sensitivity to allergies (including those patients with high FeNO and BEC levels). <sup>e</sup>Anti-IgE is recommended as a possible choice but not as the only treatment option, especially in patients with high BEC (anti-IL-4/13, anti-IL-5, and anti-IL-5R $\alpha$ ). <sup>f</sup>Dupilumab is to be avoided in these patients because of the risk of hyper-eosinophilia. <sup>g</sup>Although these additional considerations may influence biologic selection, these factors and safety considerations are not essential to be captured as part of the overall biologic treatment choice. BEC, Blood eosinophil count; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional concentration of exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; OCS, oral corticosteroid; ppb, parts per billion; T2, type 2.

characteristics of the different treatment options with predefined targets and experience in clinical practice.<sup>34</sup> Recent research and clinical studies have provided new information regarding severe asthma phenotyping and treatment options.

A PubMed literature search for English-language clinical trial reports, randomized-controlled trials, and meta-analyses on the use of biologic medications to treat patients with severe asthma was conducted. Search terms included “biologic” AND “monoclonal antibody” AND “serious” AND “asthma.” The search yielded 65 results, including literature associated with omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab from 2010 until 2020.

A roundtable meeting, consisting of a group of global experts in asthma management on the use of biologics from 9 countries, was held to review the available data in the medical literature and develop a consensus that may be used to offer expert opinion to assist health care providers in making difficult decisions regarding the quality of care for adult patients with severe asthma in an effort to improve treatment outcomes in this group of patients with asthma that often remains uncontrolled. The roundtable participants considered the

most relevant clinical variables in choosing the optimal treatment for individual adult patients with severe asthma.

The objective of the roundtable was to develop treatment recommendations that address the investigation of biomarker concentrations (BEC along with FeNO levels), clinical features (OCS dependence and comorbid disease entities associated with severe T2 asthma [perennial allergy, CRSwNP, and severe atopic dermatitis]), and safety considerations associated with the biologic medications.

## RESULTS

An expert opinion about treatment recommendations was developed for optimal management of patients with severe asthma with biologic medications (Figure 1). In choosing the optimal biologic medication for patients with severe T2 asthma in clinical practice, BEC and FeNO levels can be used to assist in anti-IL-5, anti-IL-5R $\alpha$ , and anti-IL-4/13 selection. Should a patient have a suboptimal response to first-line therapy, an alternative treatment option that targets a different T2 inflammatory pathway or the possibility of non-T2 disease would be

**TABLE II.** Confirming the presence of asthma<sup>12</sup>

Patient status	Asthma diagnosis confirmation
Variable respiratory symptoms and airflow limitation	Asthma diagnosis confirmed
Variable respiratory symptoms but airflow limitation not variable	Repeat spirometry after withholding BD or during symptoms; check between-visit variability of FEV <sub>1</sub> and BD reversibility; if normal, then asthma diagnosis not confirmed (consider alternative diagnoses)
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Repeat BD reversibility test after withholding BD as above or during symptoms. If normal, then asthma diagnosis not confirmed (consider alternative diagnoses)
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 mo and reassessing symptoms and lung function; if no change, then asthma diagnosis not confirmed (consider additional/alternative diagnoses)

BD, Bronchodilator; FEV<sub>1</sub>, forced expiratory volume in 1 second.

considered. An adequate trial of at least 4 to 6 months is necessary to assess treatment response for biologic medications in patients with severe asthma.<sup>12,97,99</sup> Response to treatment should be assessed by physicians and based on prespecified goals shared with the patient at treatment initiation. A multifaceted approach is generally employed to evaluate treatment, including OCS reduction, symptom control, lung function, and exacerbations.<sup>101</sup> Where improvement in any of the prespecified goals may be considered treatment success, exacerbations are the most important of the outcomes.

### Baseline assessment

A baseline assessment to screen patients who are planned to be treated with mAb is essential to optimize treatment.<sup>92</sup> The current treatment recommendations consist of a 4-part baseline assessment.

**Baseline assessment part 1.** Confirm the presence of severe asthma, according to the Global Initiative for Asthma (GINA) report<sup>12</sup> (Table II), along with OCS dependence or exacerbations  $\geq 2$  per year and T2 inflammation (BEC  $\geq 150$  cells/ $\mu$ L and/or FeNO  $\geq 25$  parts per billion [ppb]) and/or asthma that is clinically allergen driven. Assess adherence to ICS (and maintenance OCS) and other controller medication treatment and reassess the inhaler technique. Identify and address comorbid disease entities associated with severe asthma and potential exposure to risk factors or complicating factors (aspiration, infection). Asthma may not be classified as severe if significant improvement in asthma control occurs when the inhaler technique or adherence is optimized.<sup>12</sup>

**Baseline assessment part 2.** If severe asthma diagnosis is confirmed and treatment has been optimized, establish BEC and FeNO levels. BEC and FeNO levels should ideally be measured in patients who have not used OCS acutely within the past 2 weeks. T2 asthma diagnosis in OCS-dependent patients can be difficult, particularly if excessive systemic steroid is used, and historic values before commencement of OCS should be sought if possible, to avoid these patients being incorrectly labeled as a non-T2 phenotype. Repeat BEC and FeNO level measurements up to 3 times (eg, when asthma worsens acutely or before giving OCS) before assuming that asthma is non-T2.<sup>12</sup> BEC and FeNO levels are both modifiable risk factors for exacerbations.<sup>12</sup> The prognostic and predictive values of biomarkers are related to the intensity, consistency (ie, result always abnormal), and concordance between 2 biomarkers; if both values are abnormal, that is more predictive than only one being abnormal.<sup>43</sup>

**Baseline assessment part 3.** Validate T2 biomarker levels by reviewing historic values and performing repeated measures (especially if the adherence/inhaler technique has been addressed), to confirm the presence/activity of T2 asthma and comorbid disease entities associated with severe asthma. If historic eosinophil counts are not available, consider an OCS-tapering approach in patients receiving daily or frequent OCS treatment who appear T2 low to assess for change in levels.

**Baseline assessment part 4.** Biomarkers and comorbid disease entities associated with severe asthma should be considered in combination and in context. Although it is important to consider BEC and FeNO levels, always consider comorbid disease entities associated with severe asthma, severity of the comorbid diseases relative to asthma, and whether comorbid disease entities associated with severe asthma are a predictor of response to biologics or a treatment target (eg, CRSwNP, EGPA, eosinophilic pneumonia, severe atopic dermatitis). In considering comorbid disease entities associated with severe asthma, the highest clinical need of the patient should be addressed.

### Biologic treatment choice based on predictors of response

After the 4-part baseline assessment is complete, biologic treatment choice should be made based on the predictors of response, with BEC along with FeNO levels and OCS use being the key factors. Although these factors may influence the choice of a specific biologic, there are additional secondary factors in comparison to BEC, FeNO, OCS, and also IgE. Additional factors and safety considerations that may influence individualized biologic selection that may be considered for certain patients but are not essential to be captured as a part of the overall biologic treatment choice in the treatment recommendations include pregnancy, BMI, patient preference, treatment adherence, frailty, dexterity, and age.

The BEC thresholds determined for these treatment recommendations were BEC  $< 150$  cells/ $\mu$ L, BEC  $\geq 150$  to  $\leq 1500$  cells/ $\mu$ L, and BEC  $> 1500$  cells/ $\mu$ L. These thresholds are not absolute, and patient response to biologics should be considered on a continuum of BEC. Consider switching to a different treatment option if a suboptimal response to first-line therapy is observed.<sup>102</sup>

**Patients with BEC  $< 150$  cells/ $\mu$ L.** For patients who are not on systemic corticosteroids, there is no evidence to support biologic efficacy for patients with persistently low BEC and FeNO levels. In the absence of high BEC (although within the

normal range) and FeNO levels, sensitization to perennial allergens alone does not indicate T2 airway inflammation or potential efficacy of biologic treatment. If there is no evidence of a clear T2 inflammatory signal, physicians should review the patient's clinical history and examination to identify the true cause of the patient's clinical problem.<sup>12</sup>

For patients with FeNO <25 ppb and confirmation of perennial allergy along with a history of confirmed allergy-provoked asthma symptoms, treatment with anti-IgE could be considered. Although clinical trial data to support efficacy in this group are limited, real-world data and clinical experience have demonstrated the effectiveness of treatment with anti-IgE for patients who have sensitivity to allergens (including those patients with high FeNO and BEC levels) and may benefit from anti-IgE therapy.<sup>47,50,103-105</sup> For patients with FeNO ≥25 ppb and confirmation of perennial allergy along with a clear history of confirmed allergy-provoked asthma symptoms, treatment with anti-IL-4/13 or anti-IgE is recommended. If an allergic history is not confirmed, then treatment with anti-IL-4/13 is recommended.<sup>55</sup>

**Patients with BEC ≥150 to ≤1500 cells/μL.** For patients with BEC ≥150 to ≤1500 cells/μL, consider BEC and FeNO levels as the starting point for treatment choice,<sup>43</sup> but also consider T2 comorbid disease entities associated with severe asthma. For patients with high BEC and high FeNO levels, treatment with either anti-IL-5/5Rα or anti-IL-4/13 should be considered. For patients with high BEC to FeNO levels (with high BEC being the predominant signal), treatment with anti-IL-5/5Rα is recommended, with a likelihood of increased treatment response based on expert opinion. Consider either anti-IL-4/13 or IL-5/5Rα, taking into account whether FeNO [anti-IL-4/13] or BEC [IL-5/5Rα] represent a dominant biomarker for the patient. For patients with high FeNO to BEC levels (with high FeNO being the predominant signal), treatment with anti-IL-4/13 is recommended, with a likelihood of increased treatment response based on expert opinion.<sup>43</sup> The BEC and FeNO levels used to determine which is the predominant signal are not established through clinical trials or published literature and, therefore, should be based on clinical judgment. Because of the importance of FeNO and BEC levels in optimizing treatment for patients with severe, eosinophilic asthma, further analysis of clinical trial data to investigate the relationship between the FeNO to BEC ratio and the response to biologic medication is an important priority.

For patients with BEC ≥150 to ≤1500 cells/μL, also consider the presence/activity of comorbid disease entities associated with severe T2 asthma. Comorbid conditions can be both targets and/or predictors of response and the treatment goal must be kept in mind when initiating a specific biologic for severe asthma treatment. For patients with BEC ≥150 to ≤1500 cells/μL and severe atopic dermatitis, anti-IL-4/13 is recommended as the first choice for the treatment of severe asthma<sup>106</sup> because of the increased likelihood of a greater positive clinical impact commonly observed in clinical practice. If a 4- to 6-month trial with anti-IL-4/13 does not lead to satisfactory response, other treatments may be attempted. For patients with BEC ≥150 to ≤1500 cells/μL and severe CRSwNP, treatment with anti-IL-4/13 (approved for treatment of severe CRSwNP) or anti-IgE (approved as add-on maintenance treatment of nasal polyps/CRSwNP in adult patients with inadequate response to nasal

corticosteroids) is recommended as the first choice based on clinical experience, with anti-IL-5/5Rα recommended as an additional treatment option for severe asthma with CRSwNP (as clinical experience and published data demonstrate efficacy in severe asthma for patients with comorbid CRSwNP).<sup>76,107-109</sup> Clinical experience has determined that there is complexity of assessing response in this population due to discordant responses (eg, improvement of the upper airways but not the lower or vice versa). For patients with BEC ≥150 to ≤1500 cells/μL and perennial allergy with a clear history of allergy-provoked asthma symptoms, anti-IgE is recommended as a possible choice in clinical practice, but not as the only treatment option, especially in patients with BEC close to 1500.<sup>110,111</sup> *Post hoc* data clearly demonstrate that anti-IL-5 (mepolizumab), anti-IL-5Rα (benralizumab), and anti-IL-4/13 (dupilumab) treatments are equally effective in patients with high IgE and low IgE.<sup>17,112,113</sup> There is overlap of eligibility in this group, and generally the higher the BEC, even if a perennial allergy is documented, the more likely a positive response to an anti-eosinophil agent. For example, for patients with high BEC and low FeNO anti-IL-5/5Rα, and for patients with lower BEC and high FeNO rather anti-IL-4/13 should be considered.<sup>55</sup> In this treatment setting, BEC should be closely monitored in patients with high BEC treated with IL-4/13.

**Patients with BEC >1500 cells/μL.** For patients with BEC >1500 cells/μL, first determine potential reasons why BEC is elevated to this level. Hematological conditions and other hypereosinophilic conditions (eg, parasite infection, EGPA, or allergic bronchopulmonary aspergillosis) should be ruled out. If it has been determined that the patient does not have an alternative explanation for the eosinophilia, then treatment with anti-IL-5/5Rα is recommended. (Although outside of the scope of the current expert opinion paper, it should be noted that mepolizumab is approved for hypereosinophilic syndrome at 300 mg rather than the 150 mg for asthma.<sup>114</sup>) Anti-IL-4/13 has not been adequately studied in patients with BEC >1500 cells/μL; for those patients, further blood hypereosinophilia may be observed because of expected blockade of IL-4- and IL-13-mediated trafficking of eosinophils from blood to tissue.<sup>55</sup>

**Patients with OCS-dependent asthma.** Independent of biomarkers, OCS-dependent severe asthma is a suitable phenotype for biologic treatment,<sup>115</sup> and anti-IL-5/5Rα or anti-IL-4/13 treatment is recommended for these patients. For patients with OCS-dependent asthma who are more likely to have an eosinophilic phenotype, conduct Baseline Assessment Part 3 (validate eosinophil levels by reviewing historic BEC, performing repeat measures, and confirming the presence/activity of T2 asthma and comorbid disease entities associated with severe asthma) by using a supervised OCS-taper approach in biomarker-low patients with T2 asthma receiving daily or frequent OCS treatment to assess for elevated BEC, being cautious to avoid the risk of the development of an exacerbation. Treatment with biologic medications has been shown to provide OCS-sparing effects, which improve patient outcomes.<sup>41,42,56,116-118</sup>

## DISCUSSION

It is extremely important to choose the optimal treatment for each individual patient, not only to improve patient outcomes

but also to reduce costs.<sup>100</sup> For optimal treatment choice, predictors of response, including BEC, FeNO levels, and OCS use as the key factors in determining biologic medication choice, should be considered. This expert opinion and recommendation for the management of patients with severe asthma developed by a group of global experts in asthma and biologic medications address the investigation of biomarker levels (BEC along with FeNO) and clinical features (OCS use and specific T2 comorbid disease entities associated with severe asthma), as well as safety considerations (pregnancy, BMI, patient preference, treatment adherence, frailty, dexterity, and age) in an effort to assist in choosing a biologic with a goal of achieving individualized therapy and optimal treatment results.

Before initiating a biologic medication, confirm the diagnosis of severe asthma, exclude possible conditions that can mimic asthma symptoms, and assess for comorbid disease entities associated with severe asthma.<sup>3</sup> A 4-phase baseline assessment is recommended to confirm the presence of severe asthma and T2 inflammation, establish BEC and FeNO levels, validate eosinophil levels, and evaluate comorbid disease entities associated with severe asthma. This is in line with GINA and European Academy of Allergy and Clinical Immunology recommendations, which state that biologic therapy can be used in patients with severe asthma who show typical biomarkers of T2 airway inflammation.<sup>12,97</sup>

Biologic treatment choice should be made by first taking into consideration BEC and FeNO levels. Unfortunately, this decision is commonly driven by BEC only because it is the most easily obtainable biomarker.<sup>100</sup> Of patients with severe asthma, up to 70% have elevated BEC.<sup>26</sup> The BEC thresholds determined for these treatment recommendations were <150 cells/ $\mu$ L, BEC  $\geq$ 150 to  $\leq$ 1500 cells/ $\mu$ L, and BEC >1500 cells/ $\mu$ L, but BEC should be considered on a continuum because the accuracy of BEC measurements is impacted by fluctuations throughout the day.<sup>119</sup> In an international patient population with severe asthma, an equivalent proportion of patients had high, intermediate, and low BEC, yet most patients had a high FeNO level.<sup>14</sup> Per the American Thoracic Society guidelines, FeNO  $\geq$ 50 ppb in adults or  $\geq$ 35 ppb in children is an indicator of T2 inflammation.<sup>120</sup> FeNO  $\geq$ 50 ppb should be considered a high FeNO level compared with  $\geq$ 25 to <50 ppb (medium FeNO level) and <25 ppb (low FeNO level).

Individualized treatment choice for patients with severe asthma should always consider the presence and activity of T2 comorbid diseases and the extent to which the comorbid disease entities associated with severe asthma should be targeted by the selected biologic.<sup>121</sup> T2 inflammation may drive inflammatory diseases of the upper and lower airways.<sup>122-124</sup> Comorbid disease entities associated with severe asthma (eg, EGPA, hyper-eosinophilic syndrome, and eosinophilic pneumonia) with very high eosinophil counts may be the target of anti-IL-5/5R $\alpha$  therapy, as clinical trials and case series demonstrate the benefits of anti-IL-5 therapies in these diseases with positive clinical response.<sup>125-129</sup> Beneficial treatment effects with biologic medications, such as significantly reduced symptoms and increased health-related QoL, have been reported for patients with asthma and CRSwNP.<sup>78,130,131</sup> In addition, CRSwNP has been shown to be associated with enhanced response to biologic treatment for asthma measures.<sup>78</sup> In patients with severe asthma in which severe CRSwNP is particularly troublesome, anti-IL-4/13 and anti-IgE are recommended as first treatment because they are the only biologic medications currently approved for treatment of severe

CRSwNP, although the recent emergence of data for anti-IL-5 and anti-IL-5R $\alpha$  supports the improvement of CRSwNP following treatment and could influence biologic selection for these patients.<sup>53,76,107-109,115,132,133</sup>

OCS use is an important factor in biologic selection. Half of patients with severe asthma report receiving regular or intermittent OCS.<sup>14</sup> Treatment with biologic medications has been shown to provide OCS-sparing effects, which improve patient outcomes and reduce the risk of serious OCS-triggered side effects.<sup>41,42,77,115,116</sup> In a real-world, retrospective study, 62% of patients used continuous OCS before biological therapy, with OCS daily dosage and total number of exacerbations being reduced with the anti-IL-5/5R $\alpha$  group, and the number of annual OCS courses decreasing by twice as much in the anti-IL-5/5R $\alpha$  compared with the anti-IgE groups.<sup>134</sup> Based on real-world data and available clinical data, anti-IL-5/5R $\alpha$  or anti-IL-4/13 are preferred for patients who are OCS-dependent irrespective of atopic status.<sup>41,42,115,116</sup>

Although not of clear clinical relevance, BMI was included in these treatment recommendations as an additional safety consideration because most (70%) patients with severe asthma worldwide are obese.<sup>14</sup> As reslizumab offers a weight-based approach to dosing, one study has shown that it may have greater efficacy than mepolizumab in reducing airway eosinophilia for patients who are overweight;<sup>61,66</sup> however, studies have shown that a higher dosage of mepolizumab is not necessarily associated with greater efficacy. Benralizumab has also shown eosinophil depletion regardless of BMI.<sup>135</sup>

Although there may be a real-world difference in treatment response between anti-IL-5R $\alpha$  and anti-IL-5,<sup>61,77</sup> there are limited clinical data to support differences in efficacy or predictors of response that differentiate between these treatments; further *post hoc* analyses of clinical trial data are warranted, but ideally should be prospectively validated.<sup>88-99</sup> In the absence of head-to-head studies, limited data are available to provide further guidance on anti-IL-5/5R $\alpha$  differentiation, which may derive from the potential effects of anti-IL-5R $\alpha$  on basophils, as well as complete blood eosinophil depletion and reduction in sputum eosinophil concentrations.<sup>75,136</sup> Regarding complete eosinophil depletion associated with benralizumab, the short-term safety profile of anti-IL-5R $\alpha$  is similar to that of anti-IL-5,<sup>137</sup> and complete eosinophil depletion may help eliminate OCS use for patients with uncontrolled severe asthma.<sup>42</sup>

Although a favorable long-term response is commonly seen with mAbs for patients with severe asthma, some patients show partial or no response, causing physicians to switch between biologic medications.<sup>138</sup> These treatment recommendations are vital because a targeted, optimal choice is essential to improve patient outcomes, avoid undesirable switching, spare nonuseful exposure to expensive medications, limit the risk of patient distrust, and decrease the risk of induction of antidrug antibodies.<sup>100</sup> Lack of clinically meaningful improvement with 1 biologic medication after 4 to 6 months should result in switching to a biologic targeting an alternative mechanism as long as qualification criteria are met.<sup>12,102,139</sup> In a 32-week clinical trial, after switching from omalizumab to mepolizumab, patients with uncontrolled severe, eosinophilic asthma experienced clinically significant improvements in asthma control, health status, and exacerbation rate with no tolerability issues.<sup>102</sup> In addition, preliminary findings also suggest that for patients treated with mepolizumab who had poor asthma symptom control, switching to benralizumab led to



improved QoL scores and reduced OCS maintenance dosages.<sup>138</sup> It should be noted that in patients with poor clinical outcomes, an assessment of adherence to background medications should be conducted.<sup>138</sup> In a study of mepolizumab, patients with good adherence to ICS demonstrated greater reductions in OCS dose and exacerbations than those with poor ICS adherence.<sup>140</sup> One other option for patients who attain incomplete benefit from a biologic is to consider add-on therapy with a second biologic. Unfortunately, add-on studies comparing combination therapy are lacking, and dual therapy may be prohibitively expensive, as they are generally not covered by insurance carriers or health systems.

## CONCLUSIONS

Despite novel treatment options and various treatment guidelines, the management of severe asthma continues to be challenging. Biologic medications have improved treatment options for patients with severe asthma, but treatment recommendations are needed to make an informed treatment choice. The purpose of this expert opinion and subsequent clinical recommendations is to improve the quality of patient care and promote safe and effective treatment with biologic medications for patients with severe asthma. Understanding the patient's phenotypic characteristics and identifying biomarkers assists in classifying the underlying disease endotype and addressing appropriate biologic therapy. Along with BEC and FeNO levels, OCS use is an important factor in biologic selection and should always be taken into consideration. The presence and activity of comorbid diseases and the extent to which the comorbid disease entity associated with severe asthma (eg, EGPA, hyper-eosinophilic syndrome, and eosinophilic pneumonia) should be targeted by the selected biologic should also be considered when choosing treatment options. These opinions and recommendations are conditional and based on limited data (clinical studies and analyses of such studies) and expert opinion. With the lack of head-to-head comparisons of biologic medications in patients with severe asthma, additional data are needed to confirm these treatment recommendations.

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## REFERENCES

- World Health Organization. Asthma. Accessed November 24, 2020. <https://www.who.int/news-room/facts-in-pictures/detail/asthma>
- To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
- Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
- Zervas E, Samitas K, Papaioannou AI, Bakakos P, Loukides S, Gaga M. An algorithmic approach for the treatment of severe uncontrolled asthma. *ERJ Open Res* 2018;4:00125-2017.
- Chippes BE, Corren J, Israel E, Katial R, Lang DM, Panettieri RA Jr, et al. Asthma Yardstick: practical recommendations for a sustained step-up in asthma therapy for poorly controlled asthma. *Ann Allergy Asthma Immunol* 2017;118:133-142.e3.
- Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract* 2016;4: 120-9.e3.
- Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018;73:116-24.
- Bourdin A, Bjermer L, Brightling C, Brusselle GG, Chanez P, Chung KF, et al. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *Eur Respir J* 2019;54:1900900.
- Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;391:783-800.
- Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int* 2019;68:158-66.
- Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed July 13, 2021. <https://ginasthma.org/>
- Haselkorn T, Fish JE, Zeiger RS, Szeffler SJ, Miller DP, Chippes BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124:895-902.
- Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest* 2020;157:790-804.
- Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
- Gaga M, Zervas E, Samitas K, Bel EH. Severe asthma in adults: an orphan disease? *Clin Chest Med* 2012;33:571-83.
- Blaiss MS, Castro M, Chippes BE, Zitt M, Panettieri RA Jr, Foggs MB. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. *Ann Allergy Asthma Immunol* 2017;119:533-40.
- Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: eosinophilic airway inflammation in nonallergic asthma. *Nat Med* 2013;19:977-9.
- Jackson DJ, Humbert M, Hirsch I, Newbold P, Garcia Gil E. Ability of serum IgE concentration to predict exacerbation risk and benralizumab efficacy for patients with severe eosinophilic asthma. *Adv Ther* 2020;37:718-29.
- Berek C. Eosinophils can more than kill. *J Exp Med* 2018;215:1967-9.
- Abdala-Valencia H, Kountz TS, Marchese ME, Cook-Mills JM. VCAM-1 induces signals that stimulate ZO-1 serine phosphorylation and reduces ZO-1 localization at lung endothelial cell junctions. *J Leukoc Biol* 2018;104:215-28.
- Rank MA, Ochkur SI, Lewis TC, Teaford HG 3rd, Wesselius LJ, Helmers RA, et al. Nasal and pharyngeal eosinophil peroxidase levels in adults with poorly controlled asthma correlate with sputum eosinophilia. *Allergy* 2016;71:567-70.
- Duncan EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;128:997-1009.
- Rodrigo-Muñoz JM, Gil-Martínez M, Sastre B, Del Pozo V. Emerging evidence for pleiotropism of eosinophils. *Int J Mol Sci* 2021;22:7075.
- Davoine F, Lacy P. Eosinophil cytokines, chemokines, and growth factors: emerging roles in immunity. *Front Immunol* 2014;5:570.
- Perez-de-Llano L, Tran TN, Al-Ahmad M, Alacqua M, Bulathsinhala L, Busby J, et al. Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes and proportion of patients with these phenotypes in the International Severe Asthma Registry (ISAR). *Am J Respir Crit Care Med* 2020;201:A4525.
- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature Med* 2012;18:716-25.
- Walsh GM. Biologics targeting IL-5, IL-4 or IL-13 for the treatment of asthma—an update. *Expert Rev Clin Immunol* 2017;13:143-9.
- Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Respir Crit Care Med* 2018;197:22-37.
- Johansson MW. Activation states of blood eosinophils in asthma. *Clin Exp Allergy* 2014;44:482-98.

31. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol* 2013;13:9-22.
32. McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. *Front Med* 2017;4:93.
33. Ali Z, Dirks CG, Ulrik CS. Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma. *Chest* 2013;143:1649-55.
34. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
35. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalan G, Li C, et al. Value of peripheral blood eosinophil markers to predict severity of asthma. *BMC Pulm Med* 2016;16:109.
36. Bouquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9.
37. Sur S, Gleich GJ, Swanson MC, Bartemes KR, Broide DH. Eosinophilic inflammation is associated with elevation of interleukin-5 in the airways of patients with spontaneous symptomatic asthma. *J Allergy Clin Immunol* 1995; 96(Pt 1):661-8.
38. Brussino L, Heffler E, Bucca C, Nicola S, Rolla G. Eosinophils target therapy for severe asthma: critical points. *Biomed Res Int* 2018;2018:7582057.
39. Colas L, Hassoun D, Magnan A. Needs for systems approaches to better treat individuals with severe asthma: predicting phenotypes and responses to treatments. *Front Med (Lausanne)* 2020;7:98.
40. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J* 2018;52:1800936.
41. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Kenne ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
42. 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.
43. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. *Am J Respir Crit Care Med* 2019;200:1308-12.
44. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60.
45. Lim HF, Nair P. Airway inflammation and inflammatory biomarkers. *Semin Respir Crit Care Med* 2018;39:56-63.
46. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-34.
47. 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;7:156-64.
48. Hanania NA, Wenzel S, Rosén K, Hsieh H-J, 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.
49. Busse W, Spector S, Rosén K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol* 2013;132:485-486.e11.
50. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szeffler SJ, et al. Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017;139:1431-44.
51. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016;388:31-44.
52. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66.
53. Busse W, Maspero JF, Katelaris CH, Saralaya D, Guillonneau S, Zhang B, et al. Dupilumab improves SNOT-22 scores in asthma patients with chronic rhinosinusitis or nasal polyposis (CRS/NP) in LIBERTY ASTHMA QUEST. *Eur Respir J* 2018;52:PA1125.
54. Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB, et al. Liberty asthma QUEST: phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate dupilumab efficacy/safety in patients with uncontrolled, moderate-to-severe asthma. *Adv Ther* 2018;35:737-48.
55. 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.
56. 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.
57. 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.
58. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549-56.
59. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
60. Khurana S, Brusselle GG, Bel EH, FitzGerald JM, Masoli M, Korn S, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study. *Clin Ther* 2019;41:2041-56.
61. Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Thomson L, et al. Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. *Chest* 2020;158:491-500.
62. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Eftimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
63. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021;9:1141-53.
64. 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.
65. 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.
66. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 2016;150:799-810.
67. 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.
68. Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010;125:1344-53.
69. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med* 2016;111:21-9.
70. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor  $\alpha$  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.
71. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6:51-64.
72. Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. *Curr Med Res Opin* 2017;33:1605-13.
73. 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  $\beta$ 2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
74. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019;7:46-59.
75. O'Quinn S, Xu X, Hirsch I. Daily patient-reported health status assessment improvements with benralizumab for patients with severe, uncontrolled eosinophilic asthma. *J Asthma Allergy* 2019;12:21-33.

76. Moran AM, Ramakrishnan S, Borg CA, Connolly CM, Couillard S, Mwasuku CM, et al. Blood eosinophil depletion with mepolizumab, benralizumab and prednisolone in eosinophilic asthma. *Am J Respir Crit Care Med* 2020;202:1314-6.
77. Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe, eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, Phase 3b trial. *Lancet Respir Med* 2021;9:260-74.
78. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-world effectiveness of benralizumab in severe eosinophilic asthma. *Chest* 2021;159:496-506.
79. Panettieri RA Jr, Welte T, Shenoy KV, Korn S, Jandl M, Kerwin EM, et al. Onset of effect, changes in airflow obstruction and lung volume, and health-related quality of life improvements with benralizumab for patients with severe eosinophilic asthma: phase IIIB randomized, controlled trial (SOLANA). *J Asthma Allergy* 2020;13:115-26.
80. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020;55:1900588.
81. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;9:CD010834.
82. Blanchard C, Rothenberg ME. Biology of the eosinophil. *Adv Immunol* 2009;101:81-121.
83. 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.
84. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, et al. Care pathways for the selection of a biologic in severe asthma. *Eur Respir J* 2017;50:1701782.
85. Matsunaga K, Hirano T, Akamatsu K, Minakata Y. Predictors for identifying the efficacy of systemic steroids on sustained exhaled nitric oxide elevation in severe asthma. *Allergol Int* 2013;62:359-65.
86. Oishi K, Hirano T, Suetake R, Ohata S, Yamaji Y, Ito K, et al. A trial of oral corticosteroids for persistent systemic and airway inflammation in severe asthma. *Immun Inflamm Dis* 2017;5:261-4.
87. Menzella F, Bertolini F, Biava M, Galeone C, Scelfo C, Caminati M. Severe refractory asthma: current treatment options and ongoing research. *Drugs Context* 2018;7:212561.
88. Yan K, Balijepalli C, Sharma R, Barakat S, Sun SX, Falcao S, et al. Reslizumab and mepolizumab for moderate-to-severe poorly controlled asthma: an indirect comparison meta-analysis. *Immunotherapy* 2019;11:1491-505.
89. 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.
90. Cisneros Serrano C, Melero Moreno C, Almonacid Sánchez C, Perpiñá Tordera M, Picado Valles C, Martínez Moragón E, et al. Guidelines for severe uncontrolled asthma. *Arch Bronconeumol* 2015;51:235-46.
91. Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. *Eur Respir J* 2016;47:304-19.
92. Oishi K, Matsunaga K. Three-step algorithm for biological therapy targeted IgE and IL-5 in severe asthma. *Immun Inflamm Dis* 2018;6:374-6.
93. Papaioannou AI, Diamant Z, Bakakos P, Loukides S. Towards precision medicine in severe asthma: treatment algorithms based on treatable traits. *Respir Med* 2018;142:15-22.
94. Papadopoulos NG, Barnes P, Canonica GW, Gaga M, Heaney L, Menzies-Gow A, et al. The evolving algorithm of biological selection in severe asthma. *Allergy* 2020;75:1555-63.
95. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;377:965-76.
96. Dávila I, Quirce S, Olaguibel JM. Selection of biologics in severe asthma: a multifaceted algorithm. *J Investig Allergol Clin Immunol* 2019;29:325-8.
97. Agache I, Rocha C, Pereira A, Song Y, Alonso-Coelle P, Solà I, et al. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: a systematic review for the EAACI Biologicals Guidelines. *Allergy* 2020;76:59-70.
98. Chan R, RuiWen Kuo C, Lipworth B. Pragmatic clinical perspective on biologics for severe refractory type 2 asthma. *J Allergy Clin Immunol Pract* 2020;8:3363-70.
99. American Academy of Allergy Asthma & Immunology. Biologics for the management of severe asthma. Accessed July 13, 2021. <https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Asthma/Biologics-for-the-Management-of-Severe-Asthma>
100. Bakakos A, Loukides S, Usmani OS, Bakakos P. Biologics in severe asthma: the overlap endotype—opportunities and challenges. *Expert Opin Biol Ther* 2020;20:1427-34.
101. Pérez de Llano L, Dávila I, Martínez-Moragón E, Domínguez-Ortega J, Almonacid C, Colás C, et al. Development of a tool to measure the clinical response to biologic therapy in uncontrolled severe asthma: the FEV<sub>1</sub>, Exacerbations, Oral Corticosteroids, Symptoms Score. *J Allergy Clin Immunol Pract* 2021;9:2725-31.
102. Chapman KR, Albers FC, Chipps B, Muñoz X, Devouassoux G, Bergna M, et al. The clinical benefit of mepolizumab replacing omalizumab in uncontrolled severe eosinophilic asthma. *Allergy* 2019;74:1716-26.
103. Soong W, Yoo B, Pazwash H, Holweg CTJ, Casale TB. Omalizumab response in patients with asthma by number and type of allergen. *Ann Allergy Asthma Immunol* 2021;127:223-31.
104. Domingo C, Pomares X, Navarro A, Rudi N, Sogo A, Dávila I, et al. Omalizumab is equally effective in persistent allergic oral corticosteroid-dependent asthma caused by either seasonal or perennial allergens: a pilot study. *Int J Mol Sci* 2017;18:521.
105. Loureiro CC, Amaral L, Ferreira JA, Lima R, Pardal C, Fernandes I, et al. Omalizumab for severe asthma: beyond allergic asthma. *Biomed Res Int* 2018;2018:3254094.
106. Chun PIF, Lehman H. Current and future monoclonal antibodies in the treatment of atopic dermatitis. *Clin Rev Allergy Immunol* 2020;59:208-19.
107. 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.
108. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials [published correction appears in *Lancet* 2019;394(10209): 1618]. *Lancet* 2019;394:1638-50.
109. Jonstam K, Swanson BN, Mannent LP, Cardell L-O, Tian N, Wang Y, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy* 2019;74:743-52.
110. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;124:1210-6.
111. Sheehan WJ, Krouse RZ, Calatroni A, Gergen PJ, Gern JE, Gill MA, et al. Aeroallergen sensitization, serum IgE, and eosinophilia as predictors of response to omalizumab therapy during the fall season among children with persistent asthma. *J Allergy Clin Immunol Pract* 2020;8: 3021-8.e2.
112. Ortega H, Chupp G, Bardin P, Bourdin A, Garcia G, Hartley B, et al. The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. *Eur Respir J* 2014;44:239-41.
113. Corren J, Castro M, O'Riordan T, Hanania NA, Pavord ID, Quirce S, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract* 2020;8:516-26.
114. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;146:1397-405.
115. Yılmaz I, Türk M, Nazik Bahçecioglu S, Tutar N, Gülmez I. Efficacy of mepolizumab treatment in oral corticosteroid-dependent severe eosinophilic asthma patients with chronic rhinosinusitis with nasal polyps: single center, real life study. *Turk J Med Sci* 2020;50:433-41.
116. Bourdin A, Adcock I, Berger P, Bonniaud P, Chanson P, Chenivresse C, et al. How can we minimise the use of regular oral corticosteroids in asthma? [published correction appears in *Eur Respir Rev* 2020;29(155):195085]. *Eur Respir Rev* 2020;29:190085.
117. Cataldo D, Louis R, Michils A, Peché R, Pilette C, Schleich F, et al. Severe asthma: oral corticosteroid alternatives and the need for optimal referral pathways. *Asthma* 2021;58:448-58.
118. Bjerrum AS, Skjold T, Schmid JM. Oral corticosteroid sparing effects of anti-IL5/ anti-IL5 receptor treatment after 2 years of treatment. *Respir Med* 2020;176:106260.
119. Carr TF, Berdnikovs S, Simon HU, Bochner BS, Rosenwasser LJ. Eosinophilic bioactivities in severe asthma. *World Allergy Organ J* 2016;9:21.
120. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.

121. Rogliani P, Calzetta L, Matera MG, Laitano R, Ludovica Ritondo B, Hanania NA, et al. Severe asthma and biological therapy: when, which, and for whom. *Pulm Ther* 2020;6:47-66.
122. Wenzel SE. Emergence of biomolecular pathways to define novel asthma phenotypes: type-2 immunity and beyond. *Am J Respir Cell Mol Biol* 2016;55:1-4.
123. Ray A, Raundhal M, Oriss TB, Ray P, Wenzel SE. Current concepts of severe asthma. *J Clin Invest* 2016;126:2394-403.
124. Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2013;131:1350-60.
125. Harish A, Schwartz SA. Targeted anti-IL-5 therapies and future therapeutics for hypereosinophilic syndrome and rare eosinophilic conditions. *Clin Rev Allergy Immunol* 2020;59:231-47.
126. Vultaggio A, Nencini F, Bormioli S, Vivarelli E, Dies L, Rossi O, et al. Low-dose mepolizumab effectiveness in patients suffering from eosinophilic granulomatosis with polyangiitis. *Allergy Asthma Immunol Res* 2020;12:885-93.
127. Hočevcar A, Kopač P, Rotar Ž, Novljan MP, Škrjat S. Eosinophilic granulomatosis with polyangiitis evolution during severe eosinophilic asthma treatment with benralizumab. *J Allergy Clin Immunol Pract* 2020;8:2448-9.
128. Kent BD, d'Ancona G, Fernandes M, Green L, Roxas C, Thomson L, et al. Oral corticosteroid-sparing effects of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. *ERJ Open Res* 2020;6:00311-2019.
129. Nanzer AM, Dhariwal J, Kavanagh J, Hearn A, Fernandes M, Thomson L, et al. Steroid-sparing effects of benralizumab in patients with eosinophilic granulomatosis with polyangiitis. *ERJ Open Res* 2020;6:00451-2020.
130. Ren L, Zhang N, Zhang L, Bachert C. Biologics for the treatment of chronic rhinosinusitis with nasal polyps—state of the art. *World Allergy Organ J* 2019;12:100050.
131. Brown WC, Senior B. A critical look at the efficacy and costs of biologic therapy for chronic rhinosinusitis with nasal polyposis. *Curr Allergy Asthma Rep* 2020;20:16.
132. Bachert C, Hellings PW, Mullol J, Hamilos DI, Gevaert P, Naclerio RM, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy* 2020;75:148-57.
133. Heffler E, Saccheri F, Bartzaghi M, Canonica GW. Effectiveness of omalizumab in patients with severe allergic asthma with and without chronic rhinosinusitis with nasal polyps: a PROXIMA study post hoc analysis. *Clin Transl Allergy* 2020;10:25.
134. Kotisalmi E, Hakulinen A, Mäkelä M, Toppila-Salmi S, Kauppi P. A comparison of biologicals in the treatment of adults with severe asthma—real-life experiences. *Asthma Res Pract* 2020;6:2.
135. Trudo F, Hirsch I, Gopalan G, Martin U. Impact of body mass index on efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma: pooled analysis of the SIROCCO and CALIMA trials. *American Thoracic Society International Conference Abstracts*. Accessed July 13, 2021. [https://www.atsjournals.org/doi/pdf/10.1164/ajrcm-conference.2018.197.1\\_MeetingAbstracts.A2490](https://www.atsjournals.org/doi/pdf/10.1164/ajrcm-conference.2018.197.1_MeetingAbstracts.A2490)
136. Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. *J Allergy Clin Immunol* 2018;141:1529-32.e8.
137. Jackson DJ, Korn S, Mathur SK, Barker P, Meka VG, Martin UJ, et al. Safety of eosinophil-depleting therapy for severe, eosinophilic asthma: focus on benralizumab. *Drug Saf* 2020;43:409-25.
138. Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-term therapy response to anti-interleukin-5 biologics in severe asthma—a real-life evaluation. *J Allergy Clin Immunol Pract* 2021;9:1194-200.
139. Kavanagh JE, Hearn AP, d'Ancona G, Dhariwal J, Roxas C, Green L, et al. Benralizumab after sub-optimal response to mepolizumab in severe eosinophilic asthma. *Allergy* 2021;76:1890-3.
140. 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.