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Treatment of severe, uncontrolled eosinophilic asthma: Where we are heading

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ABSTRACT

Objective: We sought to highlight how our understanding of the pathophysiology of severe asthma has evolved over time and discuss the role of biomarkers in treatment advances and emerging new therapies. **Data Sources:** Nonsystematic PubMed literature search. **Study Selection:** Articles were selected based on areas of relevance to the classification of asthma by endotype, with an emphasis on the evolution of current treatment guidelines for severe asthma. **Results:** Unlike older guidelines for the treatment of severe asthma, recent updates now distinguish between asthma severity and control. Moreover, asthma classification is shifting from phenotype to endotype with the development of biomarkers used to determine the mechanism driving a patient's disease. Many cases of severe asthma are associated with type-2 inflammation with elevated eosinophil counts in the airways. In recent studies, patients with severe, uncontrolled asthma and high eosinophil counts respond to biologic therapies targeting the type-2 signaling pathway and eosinophils themselves (eg, anti-IL-5 therapy). New treatments that address the pathophysiology of asthma offer a promising alternative to control severe asthma for patients who do not respond to traditional therapies. **Conclusion:** Understanding and using new treatment guidelines that separate the concepts of asthma severity and control may help clinicians to identify patients with severe, uncontrolled asthma who may benefit from new treatment options, such as anti-IL-5 therapies.

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Introduction

Asthma, a chronic, complex inflammatory syndrome, is characterized by bronchoconstriction, airway remodeling, airway hyperresponsiveness, airway edema, and recurrent, reversible symptoms including cough, shortness of breath, and wheezing [1,2]. According to data from the Centers for Disease Control and Prevention (CDC), 1.6 million emergency department visits in the United States (US) in 2013 were a result of asthma [3], and the prevalence of asthma has been increasing worldwide [4]. Moreover, asthma is understood as a heterogeneous disease with different underlying pathophysiologic processes, rather than a single disorder with a discrete cause or mechanism [1,2,5,6]. Asthma symptoms can vary widely among patients because of differing pathophysiologies, individual genetics, and environmental factors, and this variability presents therapeutic challenges. Similarly, psychosocial or economic factors could negatively impact adherence, which, in turn, can complicate treatment.

Although only 5–10% of patients with asthma have severe asthma, these patients account for a large percentage of asthma-associated health care costs [7,8]. Patients with severe disease will require greater dosages and potentially a greater number of medications to maintain control [1]. In order to maintain control, these patients also need to overcome external factors that may influence asthma, such as viral infections and occupational, allergen, and other exposures [1]. In addition, the high risk for exacerbations associated with severe, uncontrolled asthma can significantly impact patients' quality of life [9]. The key challenge for clinicians is to identify the patient with severe asthma who may benefit from novel therapeutic approaches before that patient is hospitalized with a serious exacerbation. This review highlights how our understanding of the pathophysiology of severe asthma has evolved over time and driven the recent guideline updates, the role of biomarkers in treatment advances, and new therapies becoming available for patients with severe, uncontrolled asthma.

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Methods

We conducted a nonsystematic PubMed search for articles pertaining to the classification of severe, uncontrolled asthma by endotype, with an emphasis on the development of biomarkers to guide therapy. Studies chosen for review were published in 2007 or later, included patients ≥ 12 years of age, and focused on severe asthma, biomarkers, or endotypes. Current global and national asthma treatment guidelines were also reviewed.

Results

Where we were

Traditionally, asthma has been described phenotypically by observable clinical, morphologic, or biochemical characteristics [10,11]. Multiple classifications have been proposed, such as allergic versus non-allergic. In addition, cluster analysis based on retrospectively collected data has been used to define 4–5 standard groups of patient types according to phenotypes [12,13]. Although these phenotypic groupings are clinically relevant for many patients, groupings may not relate to or provide insight into the mechanisms driving disease or provide clear guidance on which treatment might be most effective for a particular patient.

The 2007 United States National Asthma Education and Prevention Program (NAEPP) guidelines suggested that asthma severity be assessed prior to treatment initiation [14]. Under these older guidelines, severity is gauged by the impairment caused by asthma symptoms (eg, activity limitations) and the risk for future exacerbations. The assessment of severity under NAEPP guidelines, however, is unrealistic in practice because it is assumed that the patient is currently untreated. In patients who began treatment prior to evaluation, these guidelines suggest that severity be correlated with the lowest level of treatment required to maintain control, which is determined based on the asthma symptoms observed in a patient on treatment.

Although severity and control are necessarily linked, they are often used interchangeably, and the older 2007 guidelines conflate the two, which may contribute to confusion about how to accurately identify severe, uncontrolled asthma. In fact, the field is evolving to conceptualize severity and control as separate facets of a patient's asthma. Severity is considered intrinsic to the disease state, related to the pathophysiology that drives the observable symptoms of a patient's asthma as well as how aggressive a

patient's treatment regimen must be in order to ameliorate his or her symptoms. In contrast, control is considered extrinsic to the disease and is related to the frequency and impact of symptoms. Severity depends on the molecular mechanism of disease, while control may be impacted by other factors, such as the patient's inhaler technique, adherence to treatment regimen, home and work environments, and knowledge of the disease. Because control is independent of disease severity, one patient may have severe asthma that is well-controlled while another patient may have mild asthma that is uncontrolled [1,15]. Efforts to improve control by targeting patient-related factors are ongoing; for example, numerous recent studies have focused on treatment adherence using mobile technologies, such as text messaging, and smart inhaler devices [16,17].

Where we are

Newer treatment guidelines have begun to more explicitly reflect the distinction between asthma severity and control. The greater emphasis on asthma control in the newer guidelines reflects recognition of the need for ongoing assessment of patients' management of this chronic disease [18,19]. International guidelines such as the 2014 joint recommendations by the European Respiratory Society/American Thoracic Society (ERS/ATS) and the 2017 Global Initiative for Asthma (GINA) guidelines define asthma severity according to the level of treatment required to control asthma symptoms [1,15]. Table 1 summarizes the definitions of severe asthma and uncontrolled asthma according to the three major guidelines. In the 2014 and 2017 guidelines, severe asthma is defined as disease requiring dual therapy with medium- to high-dose inhaled corticosteroids (ICS) plus a second controller such as a long-acting β_2 -agonist (LABA) to maintain symptom control, or alternatively, disease that remains uncontrolled despite these interventions. Both of these new guidelines also stress the assessment of other extrinsic factors that affect asthma control, such as observing a patient's inhaler technique and determining degree of adherence to medication. For example, a patient with poor inhaler technique may not be receiving the correct dose of medication and therefore may still be experiencing symptoms that suggest poor asthma control if the clinician assumes the medication is being taken correctly. One notable difference between the 2014 ERS/ATS and 2017 GINA asthma guidelines is the inclusion of long-acting muscarinic

Table 1. Definitions of severe and uncontrolled asthma in current asthma guidelines.^a

NAEPP ^b (2007) [14]	ERS/ATS (2014) [15]	GINA (2017) [1]
Definition/criteria for severe asthma ^c		
- Symptoms occur throughout the day - Nighttime awakenings due to asthma occur often (7x/week) - SABA use several times per day - Extremely limited activity - FEV₁ <60% predicted, or FEV₁/FVC reduced >5% ≥2 exacerbations requiring OCS per year	"Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy"	"Asthma that requires Step 4 or 5 treatment, eg, high-dose ICS/LABA, to prevent it from becoming 'uncontrolled' or asthma that remains 'uncontrolled' despite this treatment"
Definition/criteria for uncontrolled asthma ^d		
- Symptoms occur throughout the day - Nighttime awakenings due to asthma occur ≥4x/week - Extremely limited activity - SABA use several times per day - FEV₁/peak flow <60% predicted/personal best - ATAQ 3–4, ACT ≤15 ≥2 exacerbations requiring OCS per year	Defined as having ≥1 of the following: - Poor symptom control (defined as ACQ >1.5, ACT <20) - Frequent severe exacerbations (defined as ≥2 bursts of systemic CS >3 days each in previous year) - Serious exacerbations (defined as hospitalization, ICU stay, or mechanical ventilation in the previous year) - Airflow limitation (defined as postbronchodilator FEV₁ <80% predicted)	Defined as having 3–4 of the following in the past 4 weeks: - Daytime asthma symptoms >2x/week - Any nighttime awakenings due to asthma - SABA use >2x/week - Any activity limitation due to asthma

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; ATAQ: Asthma Therapy Assessment Questionnaire; CS: corticosteroids; ER: emergency room; ERS/ATS: European Respiratory Society/American Thoracic Society; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; ICU: intensive care unit; LABA: long-acting β_2 -agonist; NAEPP: National Asthma Education and Prevention Program; OCS: oral corticosteroid; SABA: short-acting β_2 -agonist.

^aFor individuals ≥12 years of age (NAEPP) or ≥6 years of age (ERS/ATS and GINA).

^bFor NAEPP guidelines, meeting any 1 criterion for "severe" or "very poorly controlled" asthma is sufficient to define the asthma as severe or very poorly controlled, respectively.

^cFor NAEPP guidelines, severity assessment is in patients who are not currently using long-term control therapies. For GINA guidelines, severity assessment is in patients who have been using regular control medication for several months.

^dFor NAEPP guidelines, definition/criteria are for "very poorly controlled" asthma (as opposed to "well-controlled" and "not well-controlled" asthma). Meeting any one of the criteria is sufficient to classify as "very poorly controlled" asthma.

antagonists (LAMAs) in the more recent guidance from GINA [1]. Specifically, tiotropium by mist inhaler is included as an add-on therapy for patients who require higher levels of treatment and have a history of exacerbations. The addition of tiotropium to the more recent guidelines reflects accumulating research into a role for tiotropium in asthma management, which has typically been used to treat patients with chronic obstructive pulmonary disease [1,20,21].

For patients with uncontrolled asthma despite adherence to GINA step 5 therapy, treatment options were, until recently, limited to continuing to increase doses of maintenance therapy or prescribing courses of oral corticosteroids to manage exacerbations. Patients with severe asthma that is poorly controlled are at higher risk for serious exacerbations and severely reduced lung function [7]. Fortunately, advances in our understanding of the pathophysiology of severe asthma have led to the development of new cutting-edge treatment options for these patients. As a result, many patients may no longer have to accept life-threatening exacerbations and reduced quality of life because of hospitalizations or multiple rounds of

oral corticosteroids because their disease remains uncontrolled by traditional therapies.

In recent years, tremendous advances have been made in the identification of the underlying mechanistic drivers of asthma [5]. At the same time, recent advances in genomics, molecular immunology, and biotechnology and a focus on translational research have inspired interest in individualized approaches to treatment for a variety of conditions, including asthma [22]. With an accumulating body of knowledge, new asthma classifications based on pathophysiology and defined by genetic and environmental factors have been proposed; these are called endotypes. Examples of proposed endotypes include aspirin-sensitive asthma, eosinophilic atopic asthma, and severe late-onset hypereosinophilic asthma; however, this is an evolving area of research, and there is not yet consensus for a set of standard endotypes (Figure 1) [5,11].

Asthma: Mechanisms of disease

Recent studies on the pathophysiology of asthma have identified multiple pathways, cells, and mediators that play a role in the chronic inflammation seen

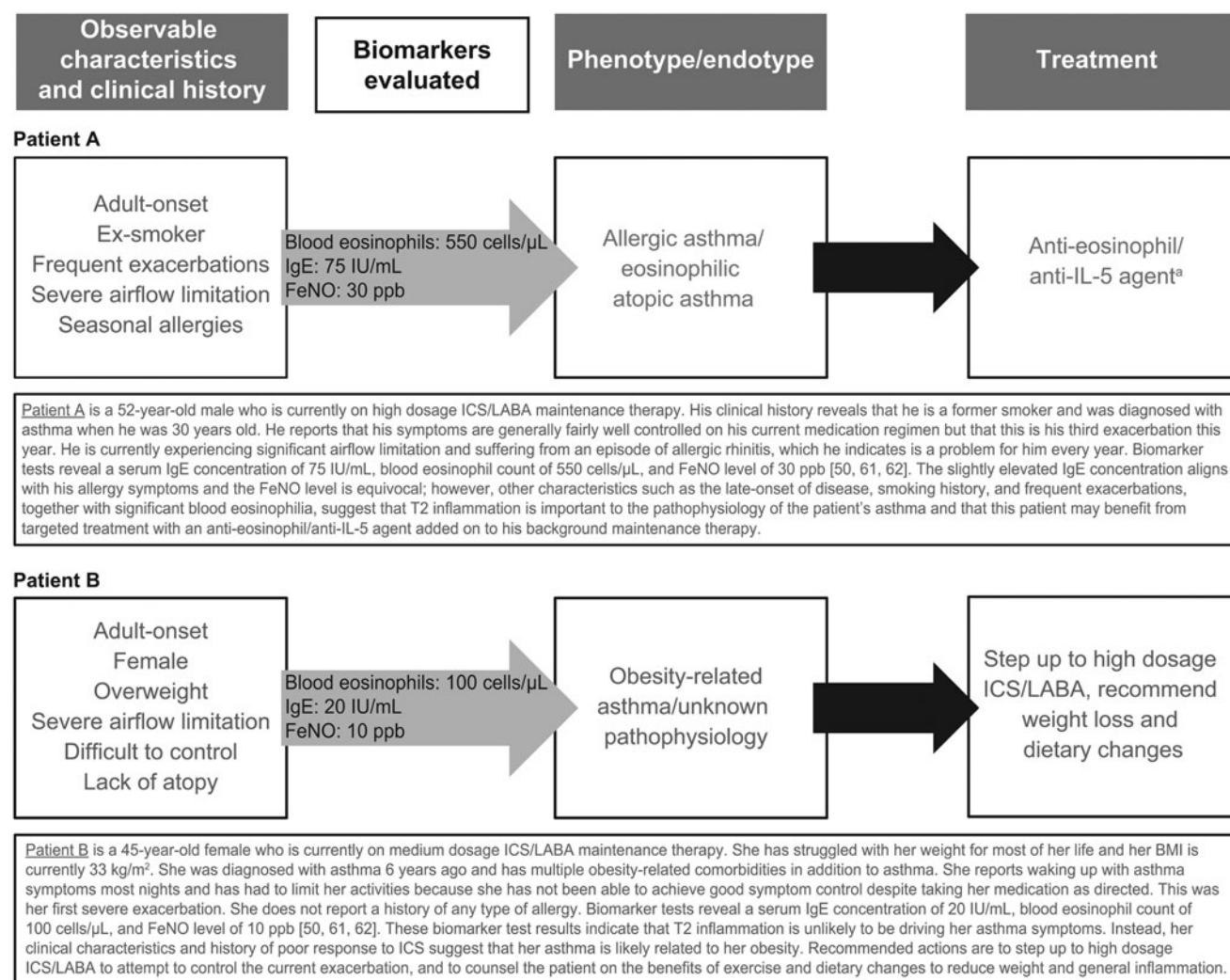


Figure 1. Shifting the focus from observable characteristics to disease mechanisms in asthma: How might a clinician use biomarkers to inform treatment? Currently, asthma diagnosis and treatment are based on clinical history and observable characteristics, which may be caused by a number of different mechanisms. Biomarkers can help to identify the underlying pathophysiology of a patient's asthma, allowing the clinician to address the root cause of disease instead of only the symptoms. Two scenarios describing patients referred from primary care due to a recent exacerbation are shown here to illustrate this process. BMI: body mass index; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; IgE: immunoglobulin E; IL: interleukin; IU: international unit; LABA: long-acting β_2 -agonist; ppb: parts per billion. ^aAdded on to background maintenance therapy.

in this disease [6,10,11,23]. Exposure to triggers such as viruses, allergens, or other irritants stimulates secretion of specific cytokines (interleukin [IL]-25, IL-33, thymic stromal lymphopoietin [TSLP]) by lung epithelial cells, which initiates an inflammatory cascade culminating in the symptoms of asthma [10]. The specific inflammatory pathway initiated can vary depending on the specific trigger, an individual's genetics, the subtype of immune cells activated, and the specific mediators secreted by those cells [10].

Type 2 immune responses are known to play a role in asthma. When a type 2 immune response is induced, T-helper 2 (Th2) cells and type 2 innate lymphoid cells (ILC2) secrete the cytokines IL-4, IL-

5, and IL-13 (Figure 2) [10,24,25]. IL-4 and IL-13 stimulate the production of immunoglobulin E (IgE), implicated in allergic asthma; IL-4, IL-5, and IL-13 are involved in the proliferation, migration, activation, and survival of eosinophils. Because we now know that these effector cytokines are produced by ILC2 cells in addition to Th2 CD4⁺ cells (as well as basophils, mast cells, and eosinophils), the inflammatory pathway marked by high levels of type 2 inflammation is now termed T2-high asthma, rather than Th2-high, to reflect the diverse origin of these cytokines [10]. The presence of high eosinophil counts is a consequence of T2-related inflammation.

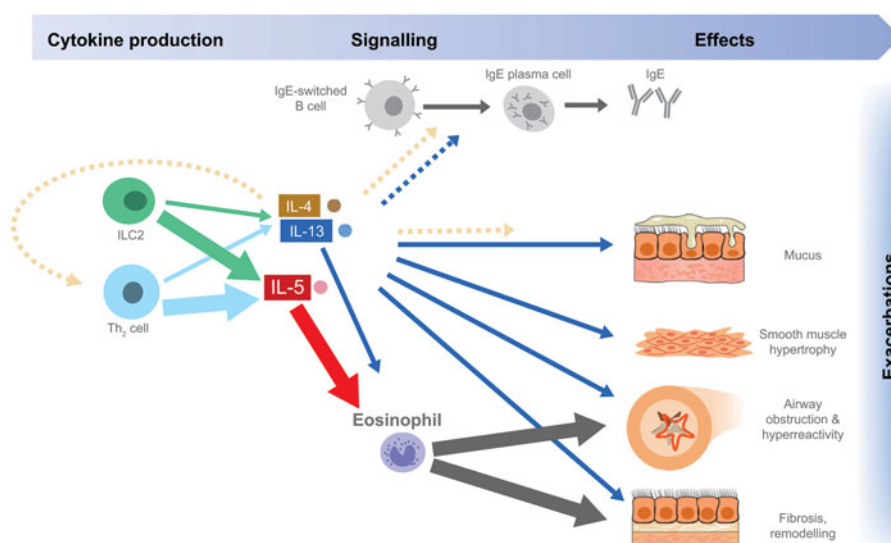


Figure 2. Inflammatory pathways in asthma. ^aType 2 cytokines are responsible for eosinophil recruitment and IgE secretion upon exposure to antigens. These cytokines also play a major role in the observable symptoms of asthma, including airway hyperresponsiveness and remodeling, mucus production, and smooth muscle hypertrophy. Adapted with permission from John Wiley & Sons Ltd from Robinson D, Humbert M, Buhl R, et al. Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy*. 2017;47:161-175. © 2017 The Authors. Clinical & Experimental Allergy; Published by John Wiley & Sons Ltd. [10]. IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; Th₂, T-helper type-2 cell. ^aThickened arrows indicate the pathway that involves IL-5 and eosinophils.

Eosinophils as a potential mechanism of disease in severe asthma

Eosinophils are terminally differentiated granulocytes that function as effectors in the innate immune system, particularly against bacteria and parasitic infection [26,27]. Eosinophils produce and store biologically active molecules, including cytotoxic proteins and cytokines, and new insights are providing a better understanding of their broader role in promoting homeostasis by immunomodulation [26,27]. Among patients with severe asthma, approximately 50% have airway eosinophilia [26]. Eosinophils contribute to airway hyperresponsiveness and remodeling within the lung [27], and high eosinophil counts in the airway are strongly associated with asthma symptom severity, deteriorating lung function, and fatality due to asthma [26]. Thus, quantification of eosinophils can be used as an indicator of disease severity [28]. Quantification of eosinophils directly in the lung via bronchoscopic sampling can be performed but is invasive, time-consuming, and costly, and it requires an experienced clinician [28]. Sputum analysis is a noninvasive alternative, but measurement of blood eosinophils has been the preferred method of quantification due to its simplicity and availability [28]. Blood eosinophil count is considered an acceptable substitute for sputum eosinophils based on studies suggesting their strong correlation. In one study, blood and sputum eosinophil counts had a correlation coefficient of

0.6 ($P < 0.0001$), and, in another study, the correlation coefficient was 0.59 ($P < 0.001$) [29,30].

Fractional exhaled nitric oxide (FeNO) has also been correlated with sputum eosinophilia [29], including one study that demonstrated a correlation coefficient of 0.52 ($P < 0.001$) [30]. Indeed, exposure to type 2 cytokines induces production of nitric oxide in airway epithelial cells [31]. Interestingly, the correlation between FeNO and airway eosinophilia appears to be independent of blood eosinophil counts, suggesting a different mechanism linking each biomarker to the eosinophilic asthma phenotype [29,30].

Biologic Therapies for Eosinophilic Asthma

Currently, three biologics have been approved for use in the US (mepolizumab, reslizumab, and benralizumab) [32,33] whose mechanisms involve interfering with the type 2 inflammatory pathway. Mepolizumab and reslizumab are monoclonal antibodies that bind to the type 2 cytokine IL-5 [34,35]. These two treatments inactivate IL-5 by preventing it from binding to its receptor. Benralizumab is a humanized, afucosylated monoclonal antibody against IL-5 receptor α that produces rapid and near-complete depletion of eosinophils [36]. The afucosylation of the oligosaccharide core segment of the antibody enhances its binding to the Fc γ RIIIa receptor on natural killer cells [37]. Thus, eosinophil depletion occurs via enhanced antibody-dependent cell-mediated cytotoxicity, in

Table 2. Summary of pivotal phase 3 studies of mepolizumab (anti-IL-5 agent).

	Pavord 2012 DREAM [39]	Bel 2014 SIRIUS [40]	Ortega 2014 MENSA [41]
Registration number	NCT 01000506	NCT 01691508	NCT 01691521
Study design			
Dose(s)	75/250/750 mg Q4W	100 mg Q4W	75 mg (IV)/100 mg (SC) Q4W
Administration form	IV	SC	IV/SC
Key inclusion criteria	• 12–74 y • High-dose ICS (≥ 880 $\mu\text{g/d}$ FP or equivalent) and additional controller • NA • ≥ 1 of 4 criteria for eosinophilic inflammation (at study entry or in past 1 y): sputum eosinophils $\geq 3\%$ or blood eosinophils ≥ 300 cells/μL or FeNO ≥ 50 ppb or worsening of asthma control following $\leq 25\%$ reduction in maintenance ICS/OCS • ≥ 2 (requiring OCS treatment) • NA	• ≥ 12 y • High-dose ICS (≥ 880 $\mu\text{g/d}$ FP or equivalent for subjects ≥ 18 y of age; ≥ 4400 $\mu\text{g/d}$ FP or equivalent for subjects 12–17 y of age) in past 6 mo and additional controller for ≥ 3 mo • 6 mo OCS use • Blood eosinophils ≥ 300 cells/μL in past 1 y or ≥ 150 cells/μL during optimization phase • NA • NA	• 12–82 y • High-dose ICS (≥ 880 $\mu\text{g/d}$ FP or equivalent for subjects ≥ 18 y of age) and additional controller for ≥ 3 mo • NA • Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in past 1 y • ≥ 2 (requiring OCS treatment) • FEV₁ $< 80\%$ predicted (subjects ≥ 18 y of age); FEV₁ $< 90\%$ predicted or FEV₁/FVC < 0.8 (subjects < 18 y of age)
Treatment duration	48 weeks	20 weeks	32 weeks
Primary efficacy analysis population	All subjects who received ≥ 1 dose of study drug	All randomized subjects	All subjects who received ≥ 1 dose of study drug
Primary endpoint	Annualized exacerbation rate	Percentage reduction in OCS dose ^b	Annualized exacerbation rate
Key results			
Number of subjects randomized	621	135	580
Number of subjects in primary endpoint analysis	616	135	576
Asthma exacerbations ^c	Percentage difference in mean annualized exacerbation rate as compared with placebo for mepo 75 mg: –48% mepo 250 mg: –39% mepo 750 mg: –52% ($P < 0.0001/0.0005/0.0001$)	Percentage difference in annualized exacerbation rate as compared with placebo for mepo: –32% ($P = 0.04$)	Percentage difference in mean annualized exacerbation rate as compared with placebo for IV mepo: –47% SC mepo: –53% ($P < 0.001$ [both])
Lung function (FEV ₁) ^{a,c}	Mean change from baseline as compared with placebo for mepo 75 mg: +61 mL mepo 250 mg: +81 mL mepo 750 mg: +56 mL	Mean change from baseline as compared with placebo for mepo: +114 mL ($P = 0.15$)	Mean change from baseline as compared with placebo for IV mepo: +100 SC mepo: +98 mL ($P = 0.02/0.03$)
Eosinophil counts ^c	Blood eosinophil counts (adjusted ratio of geometric mean to baseline) as compared with placebo for mepo 75 mg: –0.22 mepo 250 mg: –0.14 mepo 750 mg: –0.12 ($P < 0.0001$ [all])	Blood eosinophil counts (adjusted ratio to baseline) lower for mepo vs. placebo ($P < 0.001$)	Blood eosinophil counts (adjusted ratio to baseline) difference vs. placebo at Wk 12 (and maintained during study) for IV mepo: –83% SC mepo: –86% ($P < 0.001$)
HRQOL (SGRQ/AQLQ) ^{c,d}	Mean change from baseline in AQLQ score as compared with placebo for mepo 75 mg: +0.08 points mepo 250 mg: +0.05 points mepo 750 mg: +0.22 points	Mean change from baseline in SGRQ score as compared with placebo for mepo: –5.8 points ($P = 0.02$)	Mean change from baseline in SGRQ score as compared with placebo for IV mepo: –6.4 SC mepo: –7.0 points ($P < 0.001$ [both])
Safety			
Any AE	• NA	• Placebo, 92%; mepo, 83%	• Placebo, 83%; IV mepo, 84%; SC mepo, 78%
Serious AE	• Placebo, 16%; mepo 75 mg, 13%; mepo 250 mg, 16%; mepo 750 mg, 12%	• Placebo, 18%; mepo, 1%	• Placebo, 14%; IV mepo, 7%; SC mepo, 8%
Fatal AE	• Placebo, 0%; mepo 75 mg, 0%; mepo 250 mg, 1%; mepo 750 mg, $< 1\%$	• Placebo, 2%; mepo, 0%	• Placebo, 1%; IV mepo, 0%; SC mepo, 0%
AE leading to discontinuation	• Placebo, 4%; mepo 75 mg, 3%; mepo 250 mg, 5%; mepo 750 mg, 6%	• Placebo, 5%; mepo, 4%	• Placebo, 2%; IV mepo, 0%; SC mepo, 1%

AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in 1 second; FP: fluticasone propionate; HRQOL: health-related quality of life; ICS: inhaled corticosteroid; IV, intravenous; OCS: oral corticosteroid; LABA: long-acting β_2 -agonist; NA: not applicable; SC: subcutaneous; SGRQ: St. George's Respiratory Questionnaire; Q4W: once every 4 weeks.

^aRefers to FEV₁ before bronchodilation.

^bPrimary endpoint results: 23% of subjects treated with mepolizumab had a 90–100% reduction in OCS dose versus 11% of subjects treated with placebo.

^cOutcomes measured at end of study.

^dLower SGRQ scores indicate better HRQOL; higher AQLQ scores indicate better HRQOL.

Table 3. Summary of pivotal phase 3 studies of reslizumab (anti-IL-5 agent).

	Castro 2015 [43]		Bjermer 2016 [44]	Corren 2016 [45]
Registration number	NCT 01287039	Study 1	NCT 01270464	NCT 01508936
Study design				
Dose(s)	3.0 mg/kg Q4W		0.3/3.0 mg/kg Q4W	3.0 mg/kg Q4W
Administration form	IV		IV	IV
Key inclusion criteria				
• Age	12–75 y		12–75 y	18–65 y
• Current ICS/LABA use	Medium-dose ICS (≥ 440 $\mu\text{g}/\text{d}$ FP or equivalent)		Medium-dose ICS (≥ 440 $\mu\text{g}/\text{d}$ FP or equivalent)	Medium-dose ICS (≥ 440 $\mu\text{g}/\text{d}$ FP or equivalent)
• Current OCS use	NA		+/- additional controller	+/- additional controller
• Eosinophil count	Blood eosinophils ≥ 400 cells/ μL during screening period		Not permitted	Not permitted
• Number of exacerbations	≥ 1 (requiring OCS treatment)		Blood eosinophils ≥ 400 cells/ μL during screening period	NA
• in previous year	NA		NA	NA
• Lung function (FEV_1) ^a	NA		NA	NA
Treatment duration	52 weeks		16 weeks	16 weeks
Primary efficacy analysis population	All randomized subjects		All randomized subjects who received ≥ 1 dose of study drug	All subjects who received ≥ 1 dose of study drug
Primary endpoint	Frequency of asthma exacerbations per subject during the 52-wk treatment period		Change in FEV_1 with resli vs. placebo after Wk 16 of treatment	Change in FEV_1 from baseline to Wk 16
Key results				
Number of subjects randomized	489	464	315	496
Number of subjects in primary endpoint analysis	489	464	311	492
Asthma exacerbations ^b	Percentage difference in exacerbation frequency as compared with placebo for resli: -50% ($P < 0.0001$)	Percentage difference in exacerbation frequency as compared with placebo for resli: -59% ($P < 0.0001$)	NA	NA
Lung function (FEV_1) ^{a,b}	Mean change from baseline as compared with placebo for resli: $+126$ mL ($P < 0.0001$)	Mean change from baseline as compared with placebo for resli: $+90$ mL ($P = 0.0057$)	Mean change from baseline as compared with placebo for resli 0.3 mg/kg: $+115$ mL resli 3 mg/kg: $+160$ mL ($P = 0.0237/0.0018$)	Mean change from baseline as compared with placebo for resli: $+68$ mL ($P = 0.1719$)
Eosinophil counts ^b	Mean change from baseline in blood eosinophil count as compared with placebo for resli: -455 cells/ μL ($P < 0.0001$)	Mean change in blood eosinophil count as compared with placebo for resli: -489 cells/ μL ($P < 0.0001$)	Mean change from baseline in blood eosinophil count as compared with placebo for resli 0.3 mg/kg: -323 cells/ μL resli 3 mg/kg: -494 pt cells/ μL ($P = 0.0000/0.0000$)	Mean change in blood eosinophil count as compared with placebo for resli: -260 cells/ μL ($P < 0.0001$)
HRQOL (SGRQ/AQLQ) ^{b,c}	Mean change from baseline in AQLQ score as compared	Mean change from baseline in AQLQ score as compared	Mean AQLQ score at Wk 16 compared with placebo for	NA

(Continued)

(Continued)

	Mean change from baseline in AQLQ score as compared with placebo for resli: +0.30 points ($P = 0.0004$)	with placebo for resli: +0.23 points ($P = 0.0052$)	resli 0.3 mg/kg: +0.278 points resli 3 mg/kg: +0.359 points ($P = 0.0822/0.0241$)	
Safety				
• Any AE	• Placebo, 85%; resli, 80%	• Placebo, 87%; resli, 76%	• Placebo, 63%; resli 0.3 mg/kg, 57%; resli 3 mg/kg, 59%	• Placebo, 74%; resli, 55%
• Serious AE	• Placebo, 14%; resli, 10%	• Placebo, 10%; resli, 8%		• Placebo, 4%; resli, 4%
• Fatal AE	• Placebo, <1%; resli, 0%	• Placebo, 0%; resli, 0%		• Placebo, 0%; resli, 0%
• AE leading to discontinuation	• Placebo, 3%; resli, 2%	• Placebo, 4%; resli, 3%	• Placebo, <1%; resli 0.3 mg/kg, 0%; resli 3 mg/kg, 4%	• Placebo, 12%; resli, 8%
			• Placebo, 0%; resli 0.3 mg/kg, 0%; resli 3 mg/kg, 0%	
			• Placebo, 10%; resli 0.3 mg/kg, <1%; resli 3 mg/kg, 6%	

AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; FEV₁: forced expiratory volume in 1 second; FP: fluticasone propionate; HRQOL: health-related quality of life; ICS: inhaled corticosteroid; IV: intravenous; OCS: oral corticosteroid; LABA: long-acting β_2 -agonist; NA: not applicable; SGRQ: St. George's Respiratory Questionnaire; QAW: once every 4 weeks.

^aRefers to FEV₁ before bronchodilation.

^bOutcomes measured at end of study.

^cLower SGRQ scores indicate better HRQOL; higher AQLQ scores indicate better HRQOL.

which natural killer cells trigger apoptosis of eosinophils [37]. This occurs without release of cytotoxic proteins [38].

Tables 2–4 provide a detailed summary of pivotal phase 3 data for these anti-IL-5 (mepolizumab and reslizumab) and anti-eosinophil (benralizumab) agents. The studies were performed in various patient populations and with slightly different inclusion criteria. For mepolizumab, as compared with placebo, annualized exacerbation rate reductions of 32–53% were observed, increases in forced expiratory volume in 1 second (FEV₁) of 56–114 mL were observed, and health-related quality of life (HRQOL), as assessed by the Asthma Quality of Life Questionnaire (AQLQ) and St. George's Respiratory Questionnaire (SGRQ), improved by 0.05 to 0.22 points and 5.8 to 7.0 points, respectively (Table 2) [39–41]. In addition, a secondary analysis of two of the phase 3 studies of mepolizumab showed greater reductions in exacerbation frequency for patients with higher eosinophil counts at baseline and clinically significant improvements in exacerbation frequency for patients with blood eosinophil counts of ≥ 150 cells/ μ L at baseline [42]. For reslizumab, as compared with placebo, reductions in exacerbation frequency of 50–59% were observed, increases in FEV₁ of 68–160 mL were observed, and HRQOL, as assessed by the AQLQ, improved by 0.23 to 0.36 points (Table 3) [43–45]. Notably, in one of the reslizumab studies [45], the improvement in FEV₁ was not statistically significant for the overall population, but was significant for the subgroup of patients with a baseline eosinophil count of ≥ 400 cells/ μ L (mean change from baseline with reslizumab vs placebo of +0.270 mL; $P = 0.0436$). For benralizumab, as compared with placebo, annualized exacerbation rate reductions of 28–70% were observed, increases in FEV₁ of 105–159 mL were observed, and HRQOL, as assessed by the AQLQ, improved by 0.16 to 0.45 points (Table 4) [46–48]. Additional analysis of two of the phase 3 studies of benralizumab demonstrated efficacy in patients with blood eosinophil counts of ≥ 150 cells/ μ L at baseline [49]. In another analysis of these two phase 3 studies, patients with both high blood eosinophils and a history of frequent exacerbations had greater improvements in exacerbation rate with benralizumab treatment compared with placebo [50].

As expected, blood eosinophil counts were drastically reduced for the patients receiving the anti-IL-5/anti-eosinophil agent in the pivotal phase 3 studies (Tables 2–4). Studies have examined eosinophil counts in both blood and tissues after treatment with

Table 4. Summary of pivotal phase 3 studies of benralizumab (anti-eosinophil agent).

Registration number Study design	Bleecker 2016 SIROCCO [46]		FitzGerald 2016 CALIMA [47]		Nair 2017 ZONDA [48]	
	NCT 01928771		NCT 01914757		NCT 02075255	
Dose(s)	30 mg Q4W/ 30 mg Q8W (first 3 doses given Q4W)		30 mg Q4W/ 30 mg Q8W (first 3 doses given Q4W)		30 mg Q4W/30 mg Q8W (first 3 doses given Q4W)	
Administration form	SC		SC		SC	
Key inclusion criteria						
• Age	12–75 y		12–75 y		18–75 y (inclusive)	
• Current OCS use	Medium- or high-dose ICS (>250 µg/d fluticasone dry powder for- mulation equivalents) and LABA for ≥1 y		Medium- or high-dose ICS (>250 µg/d or ≥500 µg/d fluticasone dry powder formulation equiva- lents) and LABA for ≥1 y		Medium- or high-dose ICS (>250 µg/d fluticasone dry powder for- mulation equivalents) and LABA for ≥1 y; and high-dose ICS (>500 µg/d fluticasone dry pow- der formulation equivalents) and LABA for ≥6 mo	
• Current OCS use	NA		NA		>6 mo (continuous)	
• Eosinophil count	NA		NA		Blood eosinophils ≥150 cells/µL	
• Number of exacerbations in previous year	≥2 (requiring OCS treatment)		≥2 (requiring OCS treatment)		≥1	
• Lung function (FEV ₁)*	FEV ₁ <80% predicted (<90% for subjects 12–17 y of age)		FEV ₁ <80% predicted (<90% for subjects 12–17 y of age)		Morning FEV ₁ <80% predicted at Wk 8	
Treatment duration	48 weeks		56 weeks		28 weeks	
Primary efficacy analysis population	All randomized subjects who received ≥1 dose of study drug, receiving high-dose ICS/LABA, and with base- line blood eosinophils ≥300 cells/µL		All randomized subjects who received ≥1 dose of study drug, receiving high-dose ICS/LABA, and with base- line blood eosinophils ≥300 cells/µL		All randomized subjects	
Primary endpoint	Annual asthma exacerbation rate ratio vs. placebo		Annual asthma exacerbation rate ratio vs. placebo		Percentage reduction in OCS dose from baseline to Wk 28 while asthma control was maintained ^b	
Key results						
Number of subjects randomized	1205		1306		220	
Number of subjects in primary end- point analysis	809		728		220	
Asthma exacerbations ^c	Percentage difference in annualized exacerbation rate as compared with placebo for benra 30 mg Q4W: –45% benra 30 mg Q8W: –51% (<i>P</i> < 0.0001 for both) ^d		Percentage difference in annualized exacerbation rate as compared with placebo for benra 30 mg Q4W: –36% benra 30 mg Q8W: –28% (<i>P</i> = 0.002/0.019) ^d		Percentage difference in annualized exacerbation rate as compared with placebo for benra 30 mg Q4W: –55% benra 30 mg Q8W: –70% (<i>P</i> = 0.003/< 0.001)	
Lung function (FEV ₁) ^{a,c}	Mean change from baseline as com- pared with placebo for benra 30 mg Q4W: +106 mL benra 30 mg Q8W: +159 mL (<i>P</i> = 0.0215/0.0006) ^d		Mean change from baseline as com- pared with placebo for benra 30 mg Q4W: +125 mL benra 30 mg Q8W: +116 mL (<i>P</i> = 0.0054/0.0102) ^d		Mean change from baseline as com- pared with placebo for benra 30 mg Q4W: +105 mL benra 30 mg Q8W: +112 mL (<i>P</i> = 0.153/0.129)	
Eosinophil counts ^c	Percentage change from baseline in median blood eosinophil count (difference vs. placebo) in the pri- mary analysis population (with baseline blood eosinophil cutoff of ≥300 cells/µL) for benra 30 mg Q4W: –102.2% benra 30 mg Q8W: –99.6% (<i>P</i> < 0.0001 [both]) ^d		Percentage change from baseline in median blood eosinophil count (difference vs. placebo) in the pri- mary analysis population (with baseline blood eosinophil cutoff of ≥300 cells/µL) for benra 30 mg Q4W: –112.3% benra 30 mg Q8W: –106.8% (<i>P</i> < 0.0001 [both]) ^d		Percentage change from baseline in median blood eosinophil count (difference vs. placebo) for benra 30 mg Q4W: –162% benra 30 mg Q8W: –159% (<i>P</i> < 0.001 [both])	

(Continued)

HRQOL (SGRQ/AQLQ) ^{c,e}	Mean change from baseline in AQLQ score as compared with placebo for	Mean change from baseline in AQLQ score as compared with placebo for	Mean change from baseline in AQLQ score as compared with placebo for
Safety	benra 30 mg Q4W: +0.18 points benra 30 mg Q8W: +0.30 points (<i>P</i> = 0.0811/0.0036) ^d	benra 30 mg Q4W: +0.16 points benra 30 mg Q8W: +0.24 points (<i>P</i> = 0.1194/0.0194) ^d	benra 30 mg Q4W: +0.23 points benra 30 mg Q8W: +0.45 points (<i>P</i> = 0.151/0.004)
• Any AE	• Placebo, 76%; benra 30 mg Q4W, 73%; benra 30 mg Q8W, 71%	• Placebo, 78%; benra 30 mg Q4W, 74%; benra 30 mg Q8W, 75%	• Placebo, 83%; benra 30 mg Q4W, 68%; benra 30 mg Q8W, 75%
• Serious AE	• Placebo, 14%; benra 30 mg Q4W, 12%; benra 30 mg Q8W, 13%	• Placebo, 14%; benra 30 mg Q4W, 10%; benra 30 mg Q8W, 9%	• Placebo, 19%; benra 30 mg Q4W, 10%; benra 30 mg Q8W, 10%
• Fatal AE	• Placebo, 1%; benra 30 mg Q4W, <1%; benra 30 mg Q8W, <1%	• Placebo, 0%; benra 30 mg Q4W, <1%; benra 30 mg Q8W, <1%	• Placebo, 0%; benra 30 mg Q4W, 0%; benra 30 mg Q8W, 3%
• AE leading to discontinuation	• Placebo, <1%; benra 30 mg Q4W, 2%; benra 30 mg Q8W, 2%	• Placebo, <1%; benra 30 mg Q4W, 2%; benra 30 mg Q8W, 2%	• Placebo, 3%; benra 30 mg Q4W, 0%; benra 30 mg Q8W, 4%

AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; FEV₁: forced expiratory volume in 1 second; HRQOL: health-related quality of life; ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; NA: not applicable; SC: subcutaneous; SGRQ: St. George's Respiratory Questionnaire; Q4W: once every 4 weeks; Q8W: once every 8 weeks.

^aRefers to FEV₁ before bronchodilation.

^bPrimary endpoint results: 75.0% median reduction in OCS dose in both benralizumab treatment groups versus 25.0% median dose reduction with placebo (*P* < 0.001 [both benra groups]).

^cOutcomes measured at end of study.

^dValues reported for primary efficacy analysis population.

^eLower SGRQ scores indicate better HRQOL; higher AQLQ scores indicate better HRQOL.

mepolizumab or benralizumab. After three intravenous (IV) doses of mepolizumab 750 mg or placebo over 20 weeks, median eosinophil counts were reduced from baseline with mepolizumab by 100% in the blood, 55% in the airway, and 52% in bone marrow [51]. Participants in the benralizumab study were treated with a single IV dose of benralizumab 1 mg/kg or placebo; after 3 to 4 weeks, median eosinophil counts were reduced from baseline with benralizumab by 100% in the blood, 61.9% in the airway mucosa, and 18.7% in sputum; no eosinophils were detected in bone marrow after benralizumab treatment [52]. In the same study, another cohort of participants was treated with three monthly subcutaneous doses of benralizumab 100 or 200 mg or placebo; median eosinophil counts were reduced from baseline with benralizumab by 100% in the blood, 95.8% in the airway, and 89.9% in sputum [52].

Discussion

Where we are headed: Biomarkers and precision medicine

Precision medicine takes advantage of these new insights, as well as noninvasive molecular technologies, to predict, diagnose, treat, and prevent disease [22]. Biomarkers are important in this process, as they enable the identification of patients who have asthma subtypes with distinct pathophysiology and underlying mechanisms and who therefore may benefit from targeted, biologic treatment options. For example, certain clinical characteristics have been associated with eosinophilic asthma, such as late onset, no or limited allergies to common allergens, dynamic hyperinflation, and air trapping [53]. For a patient with severe, uncontrolled asthma with these observable characteristics, a simple complete blood count with differential to determine if the patient has an elevated blood eosinophil count (ie, a biomarker) could be used to confirm underlying type 2 inflammation and suggest potential treatments (anti-eosinophil/anti-IL-5 agents) that are reasonably likely to be effective for that patient (Figure 1). Overall, current data strongly support the use of anti-eosinophil/anti-IL-5 therapies for tailored treatment in these patients with severe, uncontrolled asthma with eosinophilia (correspondingly, available data do not support the use of these agents in patients without eosinophilia).

Elevated eosinophil counts are just one example of a biomarker for type 2 inflammation that can be utilized in clinical practice to tailor care to individual patients [54,55]. As previously discussed, FeNO has

been correlated with airway eosinophilia [29–31], and elevated FeNO can be used as an adjunctive tool for asthma diagnosis and to monitor asthma control. Another biomarker is serum IgE, which is associated with an atopic asthma phenotype and could indicate that the patient may be a candidate for the anti-IgE therapy omalizumab [11,56]. Research is ongoing to identify other potential asthma biomarkers. Two currently under investigation are periostin (which has been validated as a type-2 biomarker [54]) and dipeptidyl peptidase-4, both of which are secreted by airway epithelium in response to IL-13 [56–58].

Other asthma endotypes, such as neutrophilic or pauci-immune asthma, are not yet as well characterized as T2-high asthma, but research is ongoing to elucidate the underlying pathobiology of some investigational agents (eg, IL-17 blockers) that are in early development [59]. Patients with a neutrophilic or pauci-immune asthma phenotype are typically insensitive to ICSs, the traditional first line of asthma treatment. Even with increasing ICS doses and, eventually, oral corticosteroids, these patients' asthma may not be controlled [59].

Conclusion

As our understanding of asthma continues to develop, clinicians are becoming better equipped to treat the underlying disease. Asthma guidelines are evolving to reflect this changing understanding of disease mechanisms and are also recommending new treatment options. The latest international guidelines for the treatment of severe asthma now distinguish between asthma severity and control. Although many physicians were originally trained using older guidelines, it is important that they make the shift to the newer frameworks for thinking about asthma diagnosis and management.

There is a movement toward precision medicine and the use of biomarkers to define predicted responses to specific therapies. The recent explosion in the use of monoclonal antibodies targeting eosinophils/IL-5 has driven the push to identify patients who will benefit from these biologic agents. Indeed, the 2014 ERS/ATS and 2017 GINA guidelines specifically identify a contributing role for eosinophil counts in asthma management [1,15]. Moreover, the stronger evidence for the utility of eosinophil counts in the more recent 2017 GINA guidelines illustrates the progress that has been made since the concept of precision medicine in severe asthma was championed by ERS/ATS and points to toward continued

advancement (including the most recent 2018 update to GINA guidelines [60] and the US National Institutes of Health-based guidelines in development).

In order to implement precision medicine in clinical practice, clinicians need to routinely evaluate patients for the presence of biomarkers in addition to assessing the observable clinical characteristics (phenotype) of patients with asthma so they can individualize approaches to therapy. Monitoring of blood eosinophil counts is one step clinicians can take now to identify patients with severe asthma who could benefit from anti-eosinophil/anti-IL-5 therapy. Science advances rapidly, and increased knowledge of underlying pathophysiology of severe asthma will be accompanied by identification of novel diagnostic biomarkers that will reveal potential therapeutic targets to improve outcomes for more patients. That is the promise of precision medicine.

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