

**SEVERE ASTHMA:
CHARACTERIZATION
FOR INDIVIDUALIZED
THERAPY**

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**Anti-IL-5 Therapy and Other
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Severe Asthma Phenotypes

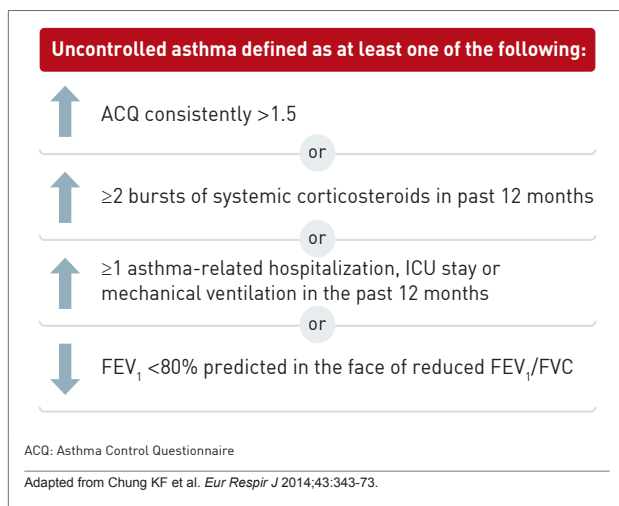
It is now well accepted that the characteristic airway inflammation of asthma develops from multiple and distinct molecular processes. This heterogeneity is captured in the description of phenotypes, which are categorizations based on empirical observations. Differences in apparent triggers, age of onset, response to therapy, and other disease features support the hypothesis that the term asthma encompasses a set of clinical syndromes rather than a single disease entity. As an approach to diagnosis and treatment of severe asthma, phenotyping represents a fundamental reorientation to the presumption that a stepwise treatment algorithm can be uniformly applied to all asthma cases. In severe asthma poorly responsive to standard therapies, phenotyping has been the basis for understanding disease heterogeneity and to seek options for individualizing treatment. Most recently, phenotyping has been driving efforts to identify differences in immune modulators active in mediating airway inflammation. Progress in this area can be credited with a growing number of targeted therapies for severe disease.

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Severe Asthma: Definition and Epidemiology

By guideline definition, asthma is severe when it is refractory to standard therapies. In the most recent European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, the specific criterion for severe asthma is persistent or recurrent uncontrolled symptoms over the previous year despite high doses of an inhaled corticosteroid (ICS) plus a long-acting beta agonist (LABA) or leukotriene modifier.¹ Uncontrolled asthma without systemic corticosteroids maintained for at least 50% of the previous year is also an ERS/ATS criterion of severe disease. Uncontrolled asthma is defined as frequent exacerbations (≥ 2 bursts of systemic corticosteroids in previous year), serious exacerbations (≥ 1 hospitalization or intensive care unit stay in previous year), or airflow limitation ($FEV_1 < 80\%$ predicted) despite appropriate bronchodilator therapy (Figure 1).

FIGURE 1 | Definition of Severe Asthma

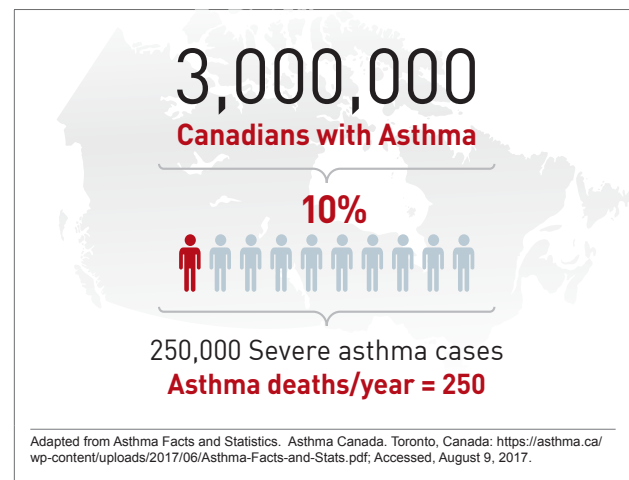


It is estimated that about 10% of patients with asthma have severe disease.² In Canada, which has an estimated asthma prevalence of 7% to 10%,³ as many as 250,000 individuals may have a severe form of asthma, according to data cited by Asthma Canada.⁴ The annual death toll from severe asthma in Canada is approximately 250 individuals (Figure 2). Severe disease also accounts for a disproportionate proportion of asthma care costs. In a U.S. study, the cost of care over a 2-year period was twice as great in those with difficult-to-control than those with controlled asthma.⁵ The correlation between increasing asthma severity and diminishing quality of life is an unsurprising consequence of persistent symptoms and frequent office visits.^{6,7}

A history of recurrent hospitalizations and need for ventilatory assistance represent risk factors for life-threatening episodes of asthma.^{8,9} Catastrophic episodes of asthma, including fatal

events, are considered preventable by intensifying therapy, but severe asthma is not a single disease or itself a useful phenotype.¹⁰ Instead, the goals of grouping patients by phenotype is to gain insight into disease course, response to therapy, and, ultimately, underlying common pathobiology that may prove targetable. Variability in response to asthma therapies, particularly therapies targeted at the characteristic inflammation of asthma, provided the basis for the observation that events driving asthma pathophysiology are not uniform.¹¹

FIGURE 2 | Severe Asthma in Canada



Evolving Concepts of Asthma and Phenotyping

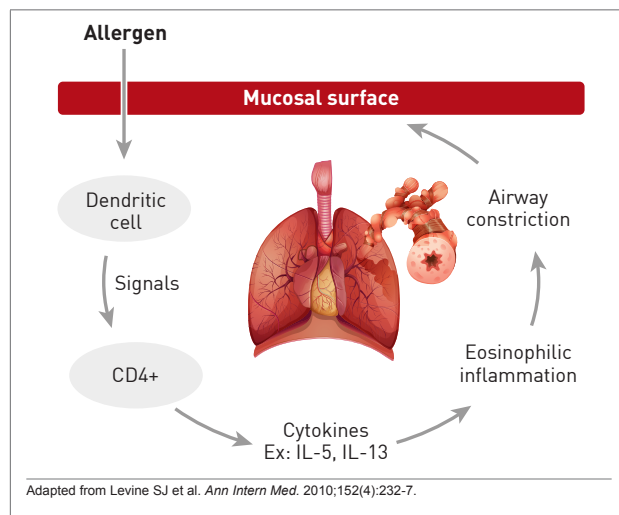
The effort to derive clinical relevance out of the heterogeneity of asthma dates back decades. Asthma subgroups were proposed on the basis of environmental triggers in 1947.¹² In 1958, high and low sputum counts were identified as a potential tool for clinically relevant subtypes based on their association with likelihood of response to corticosteroids.¹³ Examples of subsequent subgroups or phenotypes proposed on observable characteristics included allergic versus non-allergic features,¹⁴ the presence of inflammatory cells based on biopsy,¹⁵ and clinical severity.¹⁶ As the number of features with potential clinical relevance increased, cluster analyses were applied in a data-centered approach to phenotyping. An initiative called the Severe Asthma Research Program (SARP), which compressed 34 variables in to 5 clinical asthma phenotypes, is a prominent example.^{17,18}

Of efforts to phenotype asthma, there has been and continues to be a strong focus on the relative participation of inflammatory cells, particularly CD4+ T-helper 2 (Th2) lymphocytes, and their associated cytokines. While asthma was once considered to be an inflammatory process mediated primarily or exclusively by the Th2 cell pathway (Figure 3), some patients have low expression of the cytokines associated with this type of immune response.¹⁹ Subsequently,

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two distinct molecular phenotypes were recognized. Initially referred to as Th2 high and Th2 low asthma, it is now understood that non-Th2 cells, such as mast cells, are also associated with upregulation of the classic Th2-associated cytokines, which include interleukin (IL)-4, IL-5, and IL-13.¹¹ As a result, the alternative terminologies type 2 high or type 2 low asthma are sometimes employed in place of Th2.

FIGURE 3 | Type 2 Asthma Pathway



The key characteristics of type 2-high asthma include increased blood and airway eosinophilia, airway hyperresponsiveness, a thickened subepithelial basement membrane (SBM) and elevated IgE levels.²⁰ The increase in eosinophils is attributed to type 2 mediated expression of IL-5 and IL-13 expression.²¹ Although type 2 high asthma is traditionally considered to be responsive to corticosteroids, severe asthma with eosinophilia is by definition poorly responsive to corticosteroids.²²

Type 2 low asthma remains less well characterized. Although more closely associated with neutrophilic inflammation,¹⁰ type 2 low asthma does not exclude the expression of eosinophils. In a SARP program analysis, for example, four phenotypic clusters based on sputum neutrophils were identified including one with concurrent eosinophilia.²³ Animal models have supported a role of IL-17 in neutrophilic inflammation,²⁴ but it has also been hypothesized that neutrophilic inflammation in at least some patients with asthma is induced by extensive exposure to corticosteroids.¹¹ Overall, a recent review concluded that no biomarkers for the type 2 low phenotype are yet considered to be clinically valid.²⁵

Within type 2 high and type 2 low classifications, a large array of phenotypes can be derived from

specific disease features, such as severity, age of onset, or association with environmental triggers, but not all asthma may fit within either of these immune response pathways. High IL-17 expression, for example, may represent a distinct pathway that is non-type 2 high or low but a product of upregulation of Th17 cells.²⁶ Obesity, a risk factor for asthma, is another example. Factors such as chest wall biomechanics and airway compliance may contribute to the pathobiology of asthma in obese patients independent of immune response.²⁷ For some patients, the key contributor to severe asthma may be corticosteroid resistance by one or more mechanisms, such as impaired glucocorticosteroid receptor binding.²⁸

Phenotyping, Endotyping, and Genetics

Phenotyping has been an empirical tool for capturing the heterogeneity of asthma, but the ultimate goal is to understand and treat the underlying molecular processes. This goal is particularly urgent in severe phenotypes defined by poor response to conventional therapies. As molecular mechanisms are defined, phenotypes have the potential to transform into endotypes, which describe subtypes of disease in which the molecular mechanisms are known. The efficacy of targeted therapies, such as omalizumab, which binds to IgE, and the more recently licensed anti-IL-5 agents have specific molecular targets, but do not yet have well defined asthma endotypes for which efficacy or lack of efficacy is absolutely or even strongly correlated with the presence of absence of the putative molecular targets. In these cases, it appears that putative targets may be necessary but not sufficient to predict response.

In placebo-controlled trials with omalizumab, for example, post-hoc analyses suggest that patients with a history of allergic asthma with IgE levels >75 IU/mL have a lower annualized exacerbation rate than in those with lower IgE levels, but there is no dose response for levels above this threshold, and other features, such as poor previous response to relatively high doses of corticosteroids, are predictors of response independent of the molecular target.²⁹ Omalizumab is effective relative to placebo in patients with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen, but it is typically offered as an adjunct to other asthma treatments to the limited control achieved when this treatment is used alone.³⁰

The targeted anti-IL-5 therapies appear to be more specific. In initial studies with mepolizumab, there was no benefit relative to placebo in unselected patients with asthma inadequately responsive

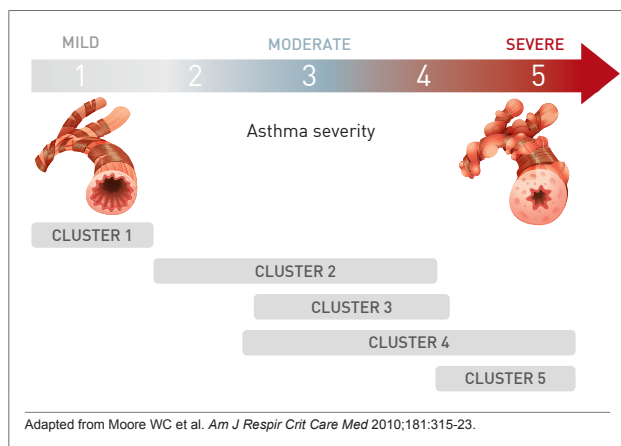
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to corticosteroids.³¹ Subsequent trials with this drug and with two other anti IL-5 therapies, reslizumab and benralizumab, did show significant protection against exacerbations when eosinophilia was a trial entry criterion.³²⁻³⁴ While IL-5 has proven to be an important biomarker in identifying patients most likely to benefit from these targeted agents, not all patients with eosinophilia respond to this medication, suggesting that patients have additional mechanisms participating in disease expression.

One obstacle to defining asthma phenotypes on the path to identification of treatable endotypes is complexity. The large number of attempts to phenotype asthma reveals overlapping clinical and molecular features suggesting that asthma in many or most patients is the product of several mechanisms.³⁵ In a study of over 500 adults and children, more than half of patients fell into two or more phenotypes defined by atopic, eosinophilic, and type 2 asthma criteria.³⁶ The rates of overlap depended on how these phenotypes were defined. For example 31% to 78% of children and 21% to 69% of adults fell into the eosinophilic phenotype depending on whether eosinophil cutoffs of ≥ 150 , ≥ 300 , or ≥ 450 eosinophils/ μL were employed.

Numerous other studies have reported on the frequency of phenotype overlaps (Figure 4).^{37,38}

FIGURE 4 | Phenotype Overlap for Severe Asthma



Phenotype overlap has been further supported by a gene set analysis from sputum cell transcriptomics based on samples from 104 patients with moderate to severe asthma.³⁹ Three distinct molecular phenotypes were derived from the hierarchical clustering. Eosinophilic asthma was dominant in one of these clusters but it was not exclusive to this cluster. Rather, it was also significantly present in a second cluster, while two clusters that were considered non type 2 phenotypes were associated with expression of interferon and tumor necrosis factor cytokines. Although only a single study in a limited study population, the findings emphasize

the potential complexity of molecular signaling underlying asthma severity.

The vast array of phenotypes created by clinical and molecular characteristics, the evidence of considerable phenotype overlap, and the potential for phenotypes to shift as patients progress from mild to severe asthma explain some of the complexity of applying phenotyping in clinical disease management. Although there is a strong consensus that phenotyping or cluster analysis will eventually prove to be a useful tool in personalized care of asthma,¹⁷ the current application has been primarily as a research tool.⁴⁰

Conclusion

Phenotypes provide a framework with which to explore patterns within the heterogeneity of factors that drive severe asthma. These phenotypes, defined variably, provide compelling evidence that asthma is not a single disease but the final expression of multiple pathological processes. For patients with severe airway inflammation, this direction of research has provided a framework for understanding underlying molecular events for disease expression and is leading toward increasingly personalized therapy for disease control. ●

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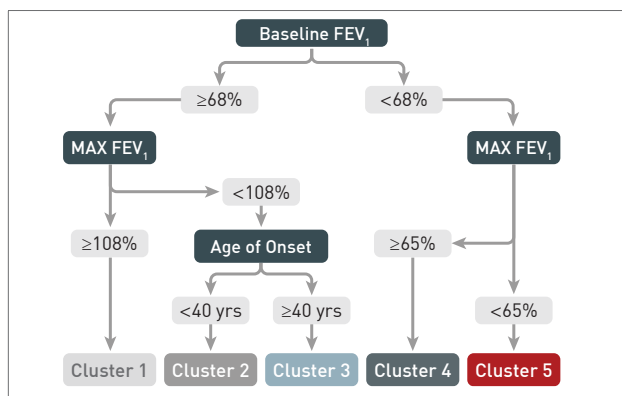
Precision medicine that addresses underlying pathophysiological mechanisms in patients with asthma is dependent on progress in defining endotypes. Unlike the descriptive phenotypes of asthma that have long been used to group patients by observable characteristics, the term endotypes recognizes distinct and potentially targetable pathophysiological mechanisms. In asthma, the identification of meaningful endotypes remains at an early stage, but there has been progress. Biomarkers predicting a greater likelihood of response to currently available targeted therapies provided an initial step toward individualized therapy. As an umbrella term for a complex and heterogeneous set of pathologic processes, asthma, particularly in its severe forms, is unlikely to be distilled into endotypes defined by single molecular mechanisms. Rather, as molecular, genetic, and epigenetic events are employed to distinguish endotypes, the goal will be to identify key processes that can be targeted for precision medicine in those with shared disease features.

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Background

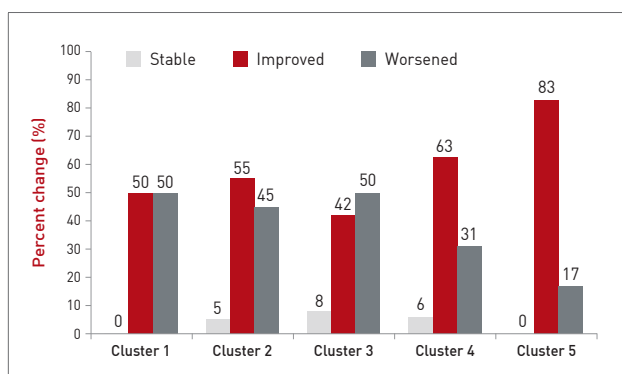
The effort to employ phenotypes as a strategy to address the heterogeneity of asthma has been underway for more than 50 years.¹ As clinical features, such as age of onset, response to therapy, or symptom triggers, proved insufficient for meaningful clinical differentiation, particularly in severe disease, phenotyping has grown in complexity to accommodate multiple disease characteristics. The on-going Severe Asthma Research Program (SARP) is an example. In one early SARP analysis, several hundred clinical variables were distilled into 34 core variables and then evaluated through a statistical-based cluster analysis.² Five distinct clusters were described based on clinical, physiologic, and inflammatory parameters (Figure 1).

FIGURE 1 | Tree Analysis to Assess Classification of Subjects



Adapted from Moore WC et al. *Am J Respir Crit Care Med* 2010; 181:315-323.

FIGURE 2 | Outcomes at 12 Months of Five Severe Phenotype Clusters



Adapted from Bourdin A et al. *J Allergy Clin Immunol* 2014;134:1043-1050.

These and other strategies to improve phenotyping have provided compelling evidence that asthma is a heterogeneous disease likely to involve distinct sets of pathophysiologic mechanisms. However, the specific phenotypes so far described involve overlapping characteristics. In the SARP clusters, the highly significant between-group differences in clinical features, including lung function, median age of asthma

onset, and median body mass index, were not exclusionary but reflected relative differences, limiting their value for characterizing disease in individual patients. In a subsequent longitudinal evaluation that compared SARP clusters by clinical outcomes, there were no differences over a 12-month observation period³ (Figure 2). This included time to first exacerbation and asthma control according to the Asthma Control Questionnaire (ACQ).

Features of Eosinophilic Asthma Phenotype

Phenotyping does correlate modestly with clinical outcome. In one example, five phenotypes were compared for patient-rated asthma control at 12 months.⁴ A frequent exacerbator phenotype was associated with poorer symptom control than an early-onset phenotype. Although the authors concluded that the findings suggest phenotypes may be useful for predicting outcome, their study did not evaluate whether modifications in therapy based on phenotypes could have improved outcomes or evaluate the value of phenotyping in the individual patient as opposed to the between-group differences that were observed. The authors acknowledged that validating studies are needed.

In this study as well as the initial SARP analysis, phenotyping was performed solely on the basis of observable clinical characteristics. Phenotyping that includes biomarkers, sometimes referred to as molecular phenotypes,⁵ have the potential to identify more distinct asthma subtypes. Biomarkers may reflect underlying pathophysiologic events even if they do not necessarily reveal the degree to which these events drive disease. In fact, molecular phenotypes and endotypes are related and not always treated differently. Low and high T-helper cell type 2 (Th2) asthma is based on clinical characteristics and biomarkers reflecting immune system activity (Table 1). Some recent studies have characterized these terms as phenotypes, while others have described them as endotypes.^{6,7}

TABLE 1 | Th2 Low vs. High Asthma

	Th2 Low	Th2 High	Mixed Features
Corticosteroid response	Poor-modest	Good	Modest
Eosinophils in sputum or blood	Low	High	High
Upregulated Th2 associated cytokines (IL-4, IL-5, IL-13)	No	Yes	Yes
Severity without treatment	Low	High	High
Targeted therapy	No	Yes	No

Adapted from Fahy JV et al. *Nat Rev Immunol* 2015;15:57-65.

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Inconsistency in the use of the term endotype is understandable. The Th2 low and high subtypes, proposed nearly 20 years ago,⁸ were based on both clinical characteristics and inflammatory biomarkers at time when it was less clear that asthma was likely to result from more than one pathophysiologic pathway. Endotype has been a term more recently introduced, recognizing that there are distinct mechanisms of disease likely to require distinct treatment strategies.⁹ The description and investigation of Th2 high and low asthma has provided much of the framework for pursuing meaningful endotypes even if these terms are not adequately specific for defining treatment targets.

Biomarkers for Endotyping

The observation that some but not all patients with asthma develop airway eosinophilia was published in 1958.¹⁰ Subsequent studies associated eosinophilia with good response to corticosteroids and low levels of eosinophils in the airway to a poor response.^{11,12} Subsequent studies demonstrated that the presence or absence of eosinophils were related to related events in the inflammatory pathway, such as relative expression of the cytokines interleukin-4 (IL-4) and IL-5.¹³ These observations eventually led to a now widely accepted distinction between Th2 high and low asthma.¹⁴ This stratification is important, because it suggests there are fundamental differences in the immune system activation that drive airway inflammation and bronchial spasm in patients with clinical asthma.

The classical view of asthma as a Th2-mediated disease is based on the premise that some exposure or event, such as a viral respiratory tract infection, activates this subset of T helper cells to release an antibody response of the IgE class along with such cytokines as IL-4, IL-5, and IL-13, thereby triggering eosinophil activation and mobilization. Unlike Th1 mediated immunity, which is associated with release of interferon gamma, IL-2, and tumor necrosis-factor in order to induce cell-mediated immunity,¹⁵ Th2 responses are more closely aligned with allergic responses and have led to the theory that asthma, particularly asthma with a childhood onset, is the result of some trigger of inappropriate Th2 activation.¹⁶

Although this Th2 eosinophilic predominant asthma, described as Th2 high disease, has long been considered the classical form of asthma, only about 50% of cases fit this description.¹⁷ Patients without Th2 high features, or Th2 low asthma, have been identified by a variety of means, starting with a low blood or sputum eosinophil count, which have been defined variably. In one analysis of non-eosinophilic

asthma in the general population, the cut-off was <2% eosinophils in the sputum,¹⁸ but higher counts have been used to identify patients with severe eosinophilic asthma who are candidates biologic therapy for which the presence of eosinophilia is a requirement.¹⁹ Other approaches have included poor response to corticosteroids, low expression of Th2-associated cytokines, such as IL-5, and a gene expression profile linked to non-Th2 high asthma.²⁰

The weakness of defining Th2 low and high asthma as endotypes is that they appear to lack specificity. Biologics targeted at IgE and the IL-5 pathway, which are upregulated in Th2 high asthma, are effective, but response correlates imperfectly with the presence of the target, such as elevated IgE in the case of omalizumab or eosinophils in the case of the IL-5 pathway inhibitors mepolizumab and reslizumab.²¹⁻²³ Omalizumab has shown efficacy in reducing allergic responses without regard to specific allergen,²⁴ but the presence of elevated IgE is not specifically required in current labeling for the treatment of asthma. Labeling for the IL-5 pathway inhibitors do specify the presence of eosinophilia, but the presence of eosinophilia does not guarantee a response.²⁵ In one analysis, sputum eosinophil counts did not predict a treatment response to mepolizumab.²⁶ Lebrikizumab, which targets IL-13, failed to provide consistent benefits in a phase 2 asthma trials even though it is also associated with down regulation of eosinophil activation.²⁷ Dupilumab, an inhibitor of IL-4 and IL-13 signaling, has shown clinical activity in severe asthma independent of eosinophil count²⁸ (Table 2).

TABLE 2 | Targeted Therapies in Asthma

	IgE	IL-5	IL-13	IL-4	IL-17
Approved agents	Omalizumab	Mepolizumab Reslizumab			
On-going investigation		Benralizumab		Dupilumab	
Failed trial			Lebrikizumab		Brodalumab

Adapted from Darveaux J et al. *J Allergy Clin Immunol Pract* 2015;3:152-161.

The evidence supporting Th2 low asthma as an endotype is even less compelling. Although it has been hypothesized that Th2 low inflammation is caused by dysregulation in the innate immune response, resulting in an inflammation predominated by upregulation of neutrophils,²⁹ the precise sequence of events and the potential for targetable events in this sequence remains poorly understood. In animal and human studies, upregulation of IL-17, which is known to induce cytokines and chemokines important to the activation and mobilization of neutrophils, has

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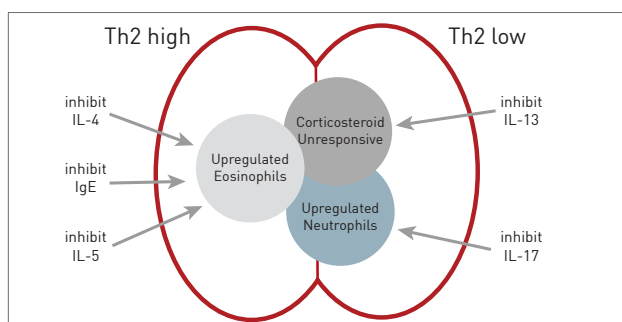
been observed in non-eosinophilic asthma,³⁰ but a clinical study with the anti-IL-17 antibody brodalumab did not demonstrate a treatment effect.³¹ In opposition to a phenotype, endotype requires pathophysiologic mechanisms, and these have yet to be well defined by simple Th2 high and low categories.

Other phenotypes, such as late onset asthma, obesity-associated asthma, or exercise-induced asthma, may be defined by endotypes unrelated or indirectly related to Th2 status. Exercise-induced asthma, for example, is linked to upregulation of inflammatory mediators more closely associated with edema and bronchoconstriction, such as leukotrienes and prostaglandins.³² In these clinical classifications of asthma, like the Th2 low and high phenotypes, clinically useful endotypes may require definitions dependent on multiple characteristics. The complexity of these characteristics may increase with severity. In children with severe asthma, for example, both eosinophils and neutrophils can be elevated, blurring a difference based on characterization by T helper cell inflammation.³³

Clinical Summary

The progress toward endotyping is based on the increasing detail with which the pathophysiology of different phenotypes of asthma is understood. This progress is expected to unravel the mechanisms by which pathologic processes lead to disease expression. Although a detailed understanding of the pathophysiology of asthma may eventually lead to strategies for preventing initial triggers, no immediate goal is more important than reversing drivers of inflammation in severe asthma (Figure 3). Severe asthma, generally defined as poor disease control despite high doses of corticosteroids, only occurs in 10% or fewer of patients, but it is responsible for a high proportion of urgent care visits,³⁴ imposing a measurable toll in asthma-related deaths in Canada as elsewhere.³⁵

FIGURE 3 | Severe Asthma: Precision Medicine



Adapted from Gauthier M et al. *Am Respir Crit Care Med* 2015; 192:660-668.

The introduction of targeted therapies has been an important step toward the definition of endotypes and precision medicine. In particular, the IL-5 pathway inhibitors have been associated with large and clinically significant reductions in exacerbations resulting in emergency department visits or hospitalizations.³⁶⁻³⁸ Elevated eosinophil levels have been a predictor of benefit, thereby establishing the relevance of the target.

It is reasonable to predict that suppression of the IL-5 pathway of eosinophil activation will be one of many steps toward suppressing very specific inflammatory mediators linked to this and the additional endotypes likely to emerge from efforts to trace asthma pathophysiology. There has been enormous progress in identifying the components of the inflammatory cascade. The next steps involve transforming asthma phenotypes into asthma endotypes on the basis of an understanding of which components in the inflammatory cascade drive these asthma subtypes. In turn, these may provide targets of treatment specific to that endotype, expanding the opportunities for precision medicine for a disease or set of diseases that have proven to be remarkably complex.

Conclusion

As designation for symptoms that develop from a heterogeneous set of pathophysiologic processes, the term asthma may be as non-specific as the term cancer for defining a disease entity. The importance of recognizing differences in the underlying pathology is reflected in current ERS/ATS guidelines for severe asthma, which repeatedly endorse phenotyping as a strategy to individualize therapy.³⁹ Endotyping relies on a precise understanding of the specific pathophysiologic pathways of asthma. Endotyping remains at an early stage of development, but it is likely to become a tool for substantially improving the treatment of asthma. The contribution of endotyping is particularly promising for its potential to lead to new treatment options for severe disease, which, by definition, has been poorly responsive to traditional therapies. ●

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Severe Eosinophilic Asthma: A Clinical Profile

Eosinophilic asthma has been validated as a clinically relevant phenotype at least in part by the clinical benefit derived from therapies that limit eosinophil activity. Biologics developed for this purpose are currently reserved for patients with severe asthma, a population that by definition is not adequately controlled on standard therapies. As a biomarker for use of biologics in eosinophilic asthma, eosinophilia is a prerequisite, but it is an imperfect predictor of benefit. As asthma is a complex and heterogeneous process, additional biomarkers may further define the patients most likely to respond to agents that downregulate the activity of this pro-inflammatory cell. In the diagnosis and treatment of severe eosinophilic asthma as it is currently defined, treatment with a biologic should be undertaken within a framework of expected benefit, safety and cost. Strategies for patient selection are likely to evolve as additional clinical data become available.

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The Severe Eosinophilic Asthma Phenotype

Asthma is considered severe when symptom control remains poor despite standard therapy that includes high doses of inhaled corticosteroids (ICS) in addition to another controller or when control is lost when high doses of ICS or systemic corticosteroids are tapered¹ (Table 1). This definition excludes patients with symptoms difficult to control for reasons unrelated to treatment efficacy, such as lack of adherence to treatment or poor inhaler technique. Before a patient is characterized as having severe asthma, it is expected that these confounders have already been evaluated and addressed.

TABLE 1 | ERS/ATS Definition of Severe Asthma

Uncontrolled asthma defined as at least one of the following:	
Symptom Control	Asthma Control Test score consistently >1.5
Steroids	≥2 bursts (>3 days each) in prior year
Exacerbations	≥1 hospitalization or mechanical ventilation in prior year
Airflow Limitation	FEV ₁ <80% predicted when FEV ₁ /FVC below normal

Adapted from Chung KF et al. *Eur Respir J* 2014;43:343-373

Among strategies to individualize therapy for patients with severe asthma, phenotyping has practical value as a result of the introduction of biologics that target molecular pathways associated with disease progression in these

phenotypes.² Omalizumab, which targets IgE, was the first of the biologics introduced to target a severe asthma phenotype. The labeling in Canada restricts use of omalizumab to patients with a positive skin test or in vitro reactivity to a perennial aeroallergen, which is characteristic of the allergic asthma phenotype.

Subsequently, the introduction of biologics targeting interleukin-5 (IL-5), an important mediator of eosinophil proliferation, has provided an option for treating severe asthma of the eosinophilic phenotype. Like omalizumab, the two available anti-IL-5 therapies, mepolizumab and reslizumab, have been approved as add-on maintenance in patients with asthma not adequately controlled with standard therapies. For these biologics, the labeling further requires eosinophilia (Table 2).

In severe asthma, these biologics has introduced phenotyping as a strategy for personalizing therapy. Prior to phenotyping in order to consider a biologic therapy, it is appropriate to optimize standard therapies and to evaluate and treat the comorbidities that may be exacerbating symptoms. The lack of eosinophilia is associated with a lack of efficacy of these molecules. Presence of eosinophilia identifies patients with an increased likelihood of benefiting from an anti-IL-5 biologic, but responses remain variable. Biologics have a high acquisition cost. Relative to inhaled or oral therapies, the available products require subcutaneous (SQ) or intravenous (IV)

TABLE 2 | Monoclonal Antibodies in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab
Target	IgE	IL-5	IL-5
Putative mechanism	Inhibits activation of basophils and mast cells	Inhibits activation and migration of eosinophils	Inhibits activation and migration of eosinophils
Indication (in addition to asthma inadequately controlled with inhaled corticosteroids and one additional medication)	Positive skin test or in vitro reactivity to a perennial aeroallergen in patient inadequately controlled with inhaled corticosteroids	Blood eosinophil count of ≥ 150 cells/μL at initiation or ≥ 300 cells/μL in the past 12 months	Blood eosinophil count of ≥400 cells/μL at initiation of the treatment
Recommended dose	3 mg/kg IV every 4 weeks	100 mg subcutaneous injection every 4 weeks	3 mg/kg IV every 4 weeks
Phase 3 Outcome	Reduction in exacerbations and reduced steroid use ¹	Reduction in exacerbations, reduced oral steroid dose and improved quality of life ²	Reduction in exacerbations and improvement of FEV ₁ ³

1. Busse W et al. *J Allergy Clin Immunol* 2001;108:184-190.

2. Bel, EH et al. *N Engl J Med* 2014; 371:1189-1197; Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.

3. Bjermer L et al. *Chest* 2016 Oct;150(4):789-798; Castro M et al. *Lancet Respir Med* 2015;3:355-366.

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administration, which many patients may find inconvenient. As a result, these therapies are not first-line even among those with poorly controlled symptoms and elevated blood or sputum eosinophil counts. Judicious application is appropriate.

Features of Eosinophilic Asthma Phenotype

The eosinophilic asthma phenotype is derived from an even more basic division involving type 2 T-helper (Th2) inflammation. Th2-high asthma describes upregulation of inflammatory cytokines such as IL-4, IL-5, and IL-13, which in turn are associated with immune responses mediated by eosinophils, mast cells, and basophils.³ Th2-low asthma, which is encountered less commonly and is less well described, has been differentiated from Th2-high asthma with several measures, including gene expression,⁴ although there is no standard biomarker for this subtype.⁵ More closely associated with upregulation of neutrophils, Th2-low asthma appears to be less closely associated with inflammation or allergic response. The effort to understand the underlying mediators of this phenotype are on-going.⁶

Further subgrouping of both Th-2-high and Th2-low by phenotype is likely to be relevant to treatment selection, but the eosinophilic phenotype, a subcategory of Th2-high asthma, has gained relevance as a result of biologics that target IL-5. Although other cytokines are associated with eosinophil activity, IL-5 is implicated in differentiation and maturation of eosinophils in the bone marrow, stimulation of eosinophil migration from the blood to tissue sites, and inhibition of eosinophil apoptosis.⁷ Inhibition of IL-5 or the IL-5 receptor alpha, which is highly expressed on the eosinophil,⁸ is associated with a marked decrease in blood and sputum eosinophilia.

The clinical trials with anti-IL-5 biologics validate eosinophils as a target in severe asthma, although they further show that eosinophilia is a necessary but not a sufficient predictor of response. In patients with elevated eosinophils but a modest or no response to anti-IL-5 therapies despite large reductions in eosinophilia, it is likely that other or additional mediators of the airway inflammation are active.

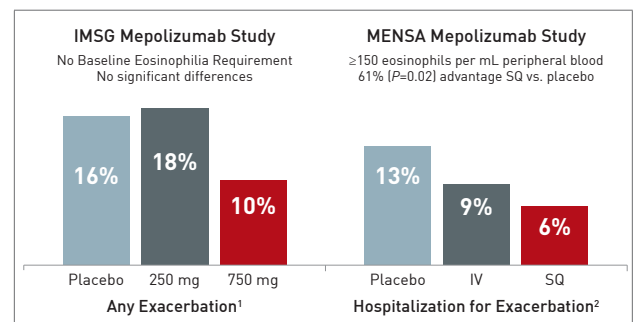
Biologics in Severe Eosinophilic Asthma: Clinical Trials

The initial clinical trials with anti-IL-5 monoclonal antibodies, often conducted in patients with persistent but moderate asthma but who were not required to have eosinophilia at entry, were disappointing. In a double-blind by the International Mepolizumab Study Group (IMSG), mepolizumab was not associated with a significant impact on

any outcome measure, including lung function, despite significant reductions in blood and sputum eosinophils from baseline.⁹ In a study conducted with reslizumab, the dose-dependent reduction in eosinophils was associated with only a trend toward improved lung function and no significant impact on other indices of disease activity.¹⁰

When eosinophilia was required for entry in subsequent trials, benefits became clinically meaningful. In MENSEA, a phase 3 trial with mepolizumab, the rate of exacerbations was reduced by 53% ($P < 0.001$) for the more effective of two tested doses.¹¹ When compared to the earlier IMSG study, MENSEA was largely confirmatory of the importance of baseline eosinophilia (Figure 1). In BREATH, a phase 3 trial with reslizumab, and CALIMA, a phase 3 trial with the experimental IL-5 receptor alpha agent benralizumab, the reductions in the annualized rate of exacerbations on the most effective dose regimens were 59% ($P < 0.001$) and 70% ($P < 0.001$), respectively.^{12,13}

FIGURE 1 | Eosinophilia as Entry Criterion



1. Flood-Page P et al. *Am J Respir Crit Care Med* 2007;176:0162-1071
 2. Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.

These findings provided the basis for the mepolizumab and reslizumab labeling that specifies the presence of blood eosinophilia within the indication for treatment. In theory, sputum eosinophil thresholds could be a more representative indication of the activity of airway eosinophilia, but these are not listed in the labeling. Since clinical trials on anti-IL-5 therapies have not used sputum eosinophil counts prospectively in a large number of subjects, the optimal sputum eosinophil count cut-off for predicting a clinical response to anti-IL5 therapies is unknown. Furthermore, this test is not available in a majority of centres.

As outlined by the authors of ERS/ATS guidelines on severe asthma and others, the availability of biologics has provided an impetus to pursue additional biomarkers with the potential to personalize therapy. Although the accuracy of laboratory and clinical predictors of response to targeted therapies remain limited, more than 100 inflammatory mediators have been implicated in

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asthma pathogenesis,¹⁴ and individual variability in the relative role of these mediators in specific patients may explain the variability of response to specific targeted therapies.

The development of therapies targeted at additional inflammatory mediators may provide new information about how other cytokines, such as IL-4 and IL-13, as well chemokines and growth factors contribute the pathogenesis of asthma at the same time that they provide new opportunities for disease control.

Biologics in Severe Eosinophilic Asthma: Practical Strategies

Asthma is a complex process with a heterogeneous presentation. Comorbidities are common and may affect disease control. In the effort to establish severe disease, it is appropriate to take specific steps to ensure that patients are employing standard therapies appropriately prior to considering a biologic even among those who meet criteria for severe eosinophilic asthma. Comorbidities such as rhinitis, nasal polyposis, sleep apnea, and gastroesophageal reflux disease (GERD) are among treatable conditions that accompany asthma and may exacerbate airway impairment. Some drugs, such as beta blockers, may activate symptoms consistent with asthma, while smoking is a prominent and reversible cause of airway impairment. Environmental triggers of respiratory symptoms should also be evaluated and addressed before declaring that standard therapies are unable to provide adequate symptom control (Table 3).

TABLE 3 | Checklist of Steps to Consider Prior to Biologic Therapy for Severe Asthma

1	Verify patients are adherent and are using standard therapies appropriately.
2	Address all co-morbidities that can impair asthma control including rhinitis, nasal polyposis, sleep apnea, and GERD.
3	Evaluate and assess triggers of asthma specific to the patient, such as drugs, tobacco smoke, and allergens.
4	Optimize alternative controller medications other than inhaled corticosteroids and bronchodilators, such as leukotriene pathway modifiers.
5	Verify presence of prerequisite indications for monoclonal antibodies (e.g. positive skin tests and total IgE between 30 and 700 IU/ml for omalizumab or eosinophilia for IL-5 inhibitors).

In patients with persistence of the severe eosinophilic asthma phenotype despite optimized use of inhaled therapies and leukotriene pathway modifiers, a trial of an anti-IL-5 biologics is reasonable. Choice of agent may be best guided by considerations such as cost or convenience. There are no head-to-head comparisons between mepolizumab and reslizumab or these approved agents and benralizumab, the only other anti-IL-5 therapy to have completed phase 3 trials.

Mepolizumab, which is administered SQ, and reslizumab, which is administered IV, bind to IL-5 to inhibit its activity. Benralizumab binds to the IL-5 receptor alpha. In a recent meta-analysis of randomized trials, there were no significant differences in clinical benefits between agents that inhibit the IL-5 pathway.¹⁵ This analysis did suggest a slight advantage in mean treatment effects for patients with a baseline serum eosinophilia of >300 eosinophils per mm³/L relative to those with fewer eosinophils, but benefit at lower eosinophil counts is well documented.

As recommended in the ERS/ATS guidelines, the treatment of severe eosinophilic asthma may be best relegated at the current time to centers familiar with phenotyping, strategies for evaluating eosinophilia, and the assessment of response. In the absence of reliable methods for predicting benefit, treatment of this phenotype, once eosinophilia is established, remains to a large degree empirical. Anti-IL-5 antibodies are an important option for improving control, including reducing the rate of exacerbations, but these therapies, in part due to their expense, should be reserved for those who cannot be controlled on simpler and less costly strategies. One of the most important contributions of highly targeted therapies is the proof they provide that the underlying drivers of severe asthma are not identical. It is likely that strategies to improve patient selection will emerge from ongoing and future studies.

Agents with highly targeted effect on specific pathways of inflammation raise the possibility of reversing not just controlling asthma. By downregulating the inflammatory component of asthma at an early stage of disease, there may be an opportunity to alter the pathophysiology that underlies asthma chronicity. Although clinical trials exploring this potential have yet to be conducted, progress in identifying important mediators of asthma pathophysiology support the effort to pursue treatments that may address the underlying pathways of disease, shifting a focus that has been largely directed to managing symptoms.

Conclusion

In patients with severe asthma, phenotyping has been rendered relevant by the introduction of biologics. Although the eosinophilia characteristic of the eosinophilic phenotype is necessary but not sufficient for considering biologic therapies, anti-IL-5 therapies can improve control in a group of patients who have traditionally had limited treatment options. A trial of these agents is appropriate as an adjunct to standard therapies after standard therapies have been optimized. Due to variability in response, benefit should be monitored. ●

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Anti-IL-5 Therapy and Other Biologics in Severe Asthma

Monoclonal antibodies targeted at the interleukin-5 (IL-5) pathway have been associated with benefit in severe eosinophilic asthma suboptimally responsive to optimized inhaled therapy, such as corticosteroids plus a long-acting beta agonist. The inhibition of IL-5 has helped establish eosinophils, which mature and proliferate in response to the IL-5 cytokine, as a targetable mediator of airway inflammation. An evaluation of the rationale, design, and outcomes of the clinical trials with IL-5 inhibitors informs current indications, but their role may evolve on the basis of studies designed to address unanswered questions, such as the relative importance of eosinophil depletion. Differences in anti-IL-5 therapies, including their mechanism, may be clinically relevant and contribute to a more thorough understanding of how these therapies control airway inflammation. Although biologics have been relatively well tolerated even when administered over extended periods, patient selection and individualized care are essential to their application in cost-effective treatment.

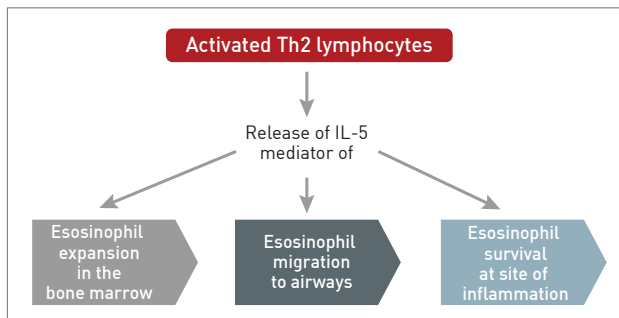
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Background

The association between eosinophilia and asthma has been recognized for more than a century.¹ The potential for eosinophilia to be a modifiable factor in asthma pathogenesis is suggested by the correlation between greater asthma severity and greater numbers of eosinophils in the blood and sputum.¹ Even in advance of therapies designed to specifically downregulate or inhibit activation of eosinophils, reductions in sputum eosinophils achieved by adjusting inhaled corticosteroids (ICS) were associated with a reduction in asthma exacerbations.^{2,3}

Eosinophils, like other leukocytes, are formed in the bone marrow, emerging fully differentiated into the bloodstream.⁴ They typically populate peripheral mucosal tissues, including lymphoid tissue, during their relatively short half-life. Although eosinophils have a number of progenitors in the bone marrow, the IL-5 cytokine has a central role in inducing eosinophil expansion.⁴ Other type 2 helper (Th2) T cell cytokines, such as IL-4 and IL-13, participate in proliferation and migration in an inflammatory response, but IL-5, is implicated in all stages of eosinophil development, including expansion in the bone marrow, migration, and survival at the site of inflammation. IL-5 is widely considered the most important driver of eosinophil activity⁵ (Figure 1).

FIGURE 1 | IL-5 in Eosinophil-Associated Asthma



Adapted from Durham AL et al. *Transl Res* 2016;67:192-203.

Anti-IL-5 Phase 3 Trials

Three anti-IL-5 monoclonal antibodies (MAbs) have been evaluated for severe asthma in phase 3 trials. Two of these agents, mepolizumab and reslizumab, have received regulatory approval in Canada. Both bind to IL-5 to prevent its activity. A third agent, benralizumab, was recently approved by the U.S. FDA and appears to be on track for regulatory approval in Canada based on completed studies. Unlike mepolizumab and reslizumab, benralizumab binds to the IL-5 receptor alpha (IL5R α). Mepolizumab and benralizumab have been developed for subcutaneous (SQ) administration. Reslizumab is available for delivery by the intravenous (IV) route. As a result of the phase 3

trials, the labeling of mepolizumab and reslizumab differ modestly.

The importance of patient selection has been a recurrent lesson from initial negative studies with both mepolizumab and reslizumab. These early trials did not require eosinophilia for entry. Subsequent studies have suggested that eosinophil counts <150 cells/ μ L are a predictor of reduced efficacy with incremental increases in both eosinophil count and prior number of exacerbations being associated with a greater response.⁶

Mepolizumab

In the first of several phase 3 trials with mepolizumab, called DREAM, 621 patients were randomized to one of three doses of IV mepolizumab or placebo.⁷ For this study, elevated eosinophil counts in the sputum (>3%) or blood (\geq 300 cells/ μ L) were listed among selection criteria but alternative signs of severe asthma, such as a fractional exhaled nitric oxide (FeNO) concentration of \geq 50 ppb, were permitted. Relative to placebo, the highest and most effective dose of mepolizumab was associated with a more than 50% reduction in the annualized rate of exacerbations (1.15 vs. 2.4; $P<0.0001$). The efficacy of lower doses relative to placebo was also significant, but the higher dose provided greater efficacy, and all doses were associated with a placebo-like safety profile.

Two subsequent phase 3 studies, called MENSA and SIRIUS, were published simultaneously. In MENSA, the primary outcome was change in the rate of exacerbations.⁶ In SIRIUS, the primary outcome was degree of reduction in glucocorticoid dose.⁸ Both studies required eosinophilia, defined as a blood eosinophil count \geq 300 cells/mcL within the past year or \geq 150 cells/mcL at the time of screening, for entry. Other entry criteria included positive results on a methacholine or mannitol challenge during the previous year. In SIRIUS, the two study arms were 100 mg mepolizumab or placebo administered SQ every 4 weeks. In MENSA, a third arm of 75 mg mepolizumab IV was included.

In MENSA, the rate of exacerbations was reduced 47% on the 75 mg IV dose and 53% by the 100 mg SQ dose (both $P<0.001$) relative to placebo over 32 weeks of follow-up. Several measures of lung function, such as the mean increase in FEV₁ from baseline were also significant relative to placebo. Active therapy was also associated with improvement from baseline in validated symptom questionnaires, such as the 5-item Asthma Control Questionnaire (ACQ-5).

In SIRIUS, there was a median 50% reduction in glucocorticoid dose in patients treated with SQ

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mepolizumab but no change on placebo ($P=0.007$). There was also a significant reduction in the annualized rate of exacerbations for mepolizumab relative to placebo (1.44 vs. 2.12; $P=0.04$). Symptom improvement on the ACQ-5 that was similar to that seen in the MENSA study. Mepolizumab was also associated with significant improvement with the St. George's Respiratory Questionnaire (SGRQ).

Based largely on these trial data, mepolizumab has been licensed in Canada in a SQ 100 mg formulation for administration every 4 weeks. The indication is for add-on maintenance treatment in adults with eosinophilic asthma, defined as a blood eosinophil count ≥ 150 cells/mcL at the time of treatment initiation or ≥ 300 cells/mcL within the past year. In addition, patients should be inadequately controlled with high-dose ICS plus an additional controller, such as a long-acting beta agonist (LABA).

Reslizumab

The clinical development trajectory of reslizumab was similar to that of mepolizumab. An initial placebo-controlled pilot study that did not require eosinophilia for entry was negative.⁹ A subsequent study that did include a minimal level of eosinophils was associated with clinical benefits, providing the rationale for the phase 3 trials that followed.¹⁰

In the duplicate placebo-controlled trials in the phase 3 reslizumab BREATH program published together.¹¹ Entry was restricted to patients with severe inadequately controlled asthma with ≥ 400 eosinophils/mcL. Reslizumab was administered IV in a weight-based dose of 3.0 mg/kg every 4 weeks. The reduction in frequency of annualized rate of exacerbations for reslizumab relative to placebo was 50% in one study and 59% (both $P<0.001$) in the other. This agent, like mepolizumab, was described as having a placebo-like safety profile.

Based largely on these trial data, reslizumab has been licensed in Canada in an IV 100 mg formulation for administration every 4 weeks. Like mepolizumab, the indication is for add-on maintenance treatment in adults with eosinophilic asthma who are inadequately controlled with high-dose ICS plus an additional controller, such as a LABA. Reflecting the phase 3 trials, eosinophilia in the labeling of reslizumab, unlike that of mepolizumab, is defined as ≥ 400 eosinophils/mcL at the time of treatment initiation. The FDA labeling for reslizumab is accompanied by an advisory to monitor patients for hypersensitivity and life-threatening anaphylactic reactions. As yet, there is no evidence of a steroid-sparing effect from reslizumab.

Benralizumab

Three phase 3 trials have been conducted with benralizumab, which binds to the IL5R α to produce rapid depletion of eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC).¹² In the phase 1 studies, a single IV dose of benralizumab, which has a mean half-life of more than 2 weeks, produced rapid and near complete depletion of eosinophils.¹³

Favorable efficacy and safety with benralizumab in phase 2 trials of a SQ formulation provided a basis for subsequent phase 3 studies.^{14,15} In two, SIROCCO and CALIMA, patients with severe, poorly controlled asthma defined by numerous clinical criteria, such as ≥ 12 exacerbations in the last year while on high dose ICS and usually at least one additional controller medication, were randomized to 30 mg benralizumab SQ every 4 weeks (Q4), 30 mg benralizumab SQ every 8 weeks (Q8), or placebo. Expressed as a rate ratio, benralizumab in the Q4 and Q8 regimens reduced exacerbation by 45% and 51%, respectively (both $P<0.001$) relative to placebo over 48 weeks of follow-up.¹⁶ In CALIMA, these rate ratios for the Q4 and Q8 regimens relative to placebo corresponded to 36% ($P=0.0018$) and 28% ($P=0.0188$) reductions in exacerbations, respectively.¹⁷

In the more recently completed ZONDA trial, which required a blood eosinophil count of ≥ 150 cells/mcL,¹⁸ patients were again randomized to 30 mg benralizumab in a Q4 or Q8 regimen or placebo. On the primary outcome, benralizumab was associated with a 75% reduction in glucocorticoid dose from baseline to week 28, which was significantly greater ($P<0.001$) than the 25% reduction in the placebo group. The annualized rate of exacerbations was reduced 55% ($P=0.003$) in the Q4 benralizumab group and 70% ($P<0.001$) in the Q8 group relative to placebo. Benralizumab has also been associated with a placebo-like adverse event rate.

There are no large randomized trials comparing mepolizumab to reslizumab, which are the only therapies currently approved for inhibition of the IL-5 pathway in asthma, but these agents and the experimental benralizumab have different characteristics that may be clinically relevant (Table 1). The phase 3 trials have employed variable entry criteria and dosing strategies, but all have been associated with substantial reductions in the annualized rate of exacerbations (Figure 2). In the SIRIUS phase 3 trial with mepolizumab and the ZONDA phase 3 trial with benralizumab, both achieved significant benefit for the primary endpoint was the effect on treatment for glucocorticosteroid sparing (Figure 3).

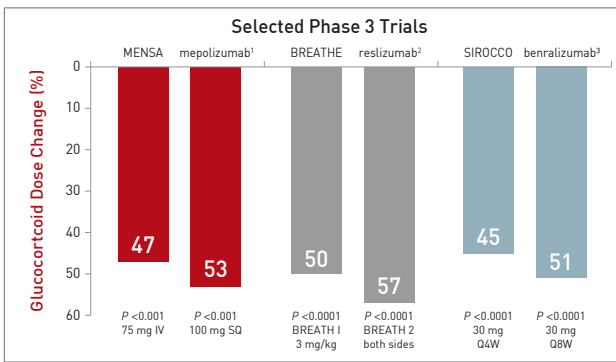
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TABLE 1 | Monoclonal Antibodies Targeting IL-5 Pathway with Completed Phase 3 Trials

	Mepolizumab	Reslizumab	Benralizumab
Route of administration	Subcutaneous	Intravenous	Subcutaneous
Approved dose	100 mg	100 mg/10mL	Not approved
Sputum eosinophil reduction	55%	95%	>95%
Mechanism of action	Binding to IL-5	Binding to IL-5	Binding to IL-5 receptor (IL-5R) and antibody dependent cellular cytotoxicity (ADCC)

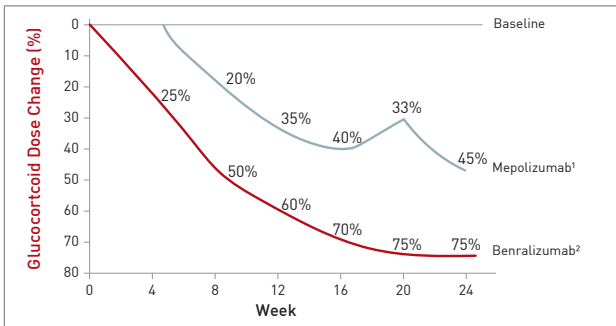
Adapted from Nixon J et al. *Pharmacology & Therapeutics* 2017;169:57-77.

FIGURE 2 | Reductions in Annualized Exacerbation Rate



1. Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.
2. Castro M et al. *Lancet Respir Med* 2015;3:355-366.
3. Bleecker ER et al. *Lancet Respir Med* 2016;388:2115-2127.

FIGURE 3 | SIRIUS and ZONDA Phase 3 Trials: Primary Endpoints



1. Bel EH et al. *N Engl J Med* 2014;371:1189-1197.
2. Nair P et al. *N Engl J Med* 2017;376:2448-2458.

Practical Approach to Anti-IL-5 Therapies

As demonstrated in the phase 3 trials, inhibitors of the IL-5 pathway are associated with clinical benefit as an add-on therapy in adult patients with eosinophilic asthma who are not adequately controlled on ICS plus an additional controller. For the types of patients included in the clinical trials and on which the current indications are based, these therapies can be an important option for improved outcomes. Due to cost and the need for serial IV or SQ administration, it is essential to use these agents judiciously.

Biologics for severe asthma now include the anti-IL-5 MAb as well as omalizumab, a MAb that binds to IgE. Before employing any of these targeted therapies, it is important to first determine that standard therapies are not offering adequate relief. The multiple reasons for an inadequate response include failure to fill or use prescriptions appropriately. For example, inhaler technique, which remains a common cause of treatment failure,¹⁹ should be evaluated routinely. Patients should also be evaluated and treated for comorbidities that mimic or exacerbate symptoms, such as gastroesophageal reflux disease (GERD), sinusitis, and obstructive sleep apnea.²⁰

Fewer than 10% of patients with asthma have a severe form as defined by poor control on appropriately employed standard therapies.²¹ The proportion of those with severe disease in which eosinophils are a targetable factor for disease control appears to be even smaller. According to current labeling, eosinophilia is a prerequisite for initiating anti-IL-5 biologics, but additional criteria designed to ration health resources and maximize cost efficacy of these agents are likely to be required regionally in Canada.

At the present time, patients with asthma who are sufficiently poorly controlled in the primary setting to require biologics are probably best referred to specialists who can consider these treatments in the context of other options for challenging cases. Many aspects of care, including how long patients should remain on biologics once initiated, remain incompletely understood on the basis of available evidence.

Conclusion

Targeted anti-IL-5 therapies are an effective clinical tool in selected patients with severe eosinophilic asthma. The reduced rates of exacerbation associated with these agents in phase 3 trials have addressed an unmet need in a population poorly responsive to traditional therapies. Efforts to further develop targeted agents and expand personalized therapy are likely to further improve care and broaden the understanding of how eosinophils and other inflammatory mediators participate in the expression of asthma phenotypes. ●

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