

Phenotype-Driven Therapeutics in Severe Asthma

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Published online: 23 February 2017
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Abstract Inhaled corticosteroids are the mainstay of asthma treatment using a step-up approach with incremental dosing and additional controller medications in order to achieve symptom control and prevent exacerbations. While most patients respond well to this treatment approach, some patients remain refractory despite high doses of inhaled corticosteroids and a long-acting β -agonist. The problem lies in the heterogeneity of severe asthma, which is further supported by the emergence of severe asthma phenotypes. This heterogeneity contributes to the variability in treatment response. Randomized controlled trials involving add-on therapies in poorly controlled asthma have challenged the idea of a “one size fits all” approach targeting specific phenotypes in their subject selection. This review discusses severe asthma phenotypes from unbiased clustering approaches and the most recent scientific evidence on novel treatments to provide a guide in personalizing severe asthma treatment.

Keywords Severe asthma · Phenotypes · Personalized medicine · Biomarkers · Biologics · Asthma exacerbations

Introduction

Asthma exacerbations are associated with significant burden of disease especially in severe asthma. The dual-premise of asthma treatment is to obtain total control of symptoms and prevent exacerbations. National and international guidelines provide a universalized step-up approach, broadly applied to all asthma severities, which has been the gold standard for treatment [1•, 2•, 3]. While a majority of patients respond well to guideline-based treatment approaches, 5–10% remain refractory despite the recommended maximal therapeutic regimen [4]. More recently, unbiased clustering approaches have led to the identification of severe asthma phenotypes associated with different clinical characteristics, pathophysiology, and pathobiologic mechanisms. These different phenotypes may explain the heterogeneous responses to usual asthma medications observed in severe asthma and guide newer add-on therapies. This article summarizes current knowledge of severe asthma phenotypes, potential biomarkers, and novel therapeutic agents and then suggests a framework to approach add-on disease modifiers in severe asthma unresponsive to usual controller medications.

Severe Asthma Definitions

The recently published consensus statement from the American Thoracic Society/European Respiratory Society defines severe asthma as asthma refractory to treatment at the level of Global Initiative for Asthma (GINA) steps 4–5 [1•]. In the clinic, severe asthma patients are those individuals who are appropriately treated with high doses of inhaled (or oral) corticosteroids and other asthma controller medications but who continue to have significant impairment (daily asthma symptoms requiring short-acting bronchodilators) and high-

This article is part of the Topical Collection on *Asthma*

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risk related to their asthma (exacerbations and progression of chronic airflow obstruction, death). In short, the current guideline approach is inadequate in this group of patients. This is likely due to heterogeneity within the group of “severe asthma” patients and further add-on therapy atop the usual guideline approach requires a deeper understanding of the individual patients within the severe asthma group.

Severe Asthma Phenotypes

In the past 20 years, several asthma cohorts have been recruited and characterized to better understand heterogeneity in severe asthma [5–9]. Unbiased clustering approaches integrating clinical, physiologic, and biologic patient characteristics have lead to the identification of novel severe asthma phenotypes that have advanced our understanding of pathobiologic mechanisms important in severe asthma [6, 10]. The National Institutes of Health-sponsored Severe Asthma Research Program (SARP) identified five distinct clinical clusters amongst adults with mild, moderate, and severe asthma. Most subjects with severe asthma were distributed to three clusters: a late-onset obese cluster of primarily women with moderate reductions in baseline FEV1 disproportionate to their high frequency of symptoms and oral corticosteroid use, an early-onset atopic cluster with reversible airflow obstruction and frequent exacerbations requiring systemic corticosteroids and healthcare use, and a less atopic, older-onset cluster with persistent airflow obstruction despite maximal bronchodilator use with the highest healthcare utilization [10]. A cluster analysis of a refractory asthma cohort from Leicester, UK, identified four severe asthma clusters including two early-onset atopic clusters differing in symptom expression and sputum inflammatory cell characteristics, an obese late-onset non-eosinophilic cluster, and a late-onset cluster with active eosinophilic inflammation [6]. Despite demographic differences between the SARP and Leicester cohorts, there is a considerable amount of overlap in their asthma phenotypes (Fig. 1, comparison of SARP and Leicester severe asthma phenotype characteristics). These severe asthma phenotypes suggest different mechanisms associated with exacerbations and symptom control, which may be explained by the underlying type of inflammatory mechanism.

Inflammatory Biomarkers

Eosinophils, markers of atopy, and exhaled nitric oxide (type-2 inflammatory biomarkers) are currently the best described asthma biomarkers. Sputum eosinophils and neutrophils directly assess airway inflammation and have been associated with exacerbations, healthcare utilization, and disease severity [11–14]. Still, use of sputum biomarkers in the non-specialized primary care setting has been criticized due their impracticality. Peripheral blood eosinophils and exhaled nitric

oxide (FeNO) are considered surrogate markers of sputum eosinophils [15, 16]. However, there has been equivocal evidence in their accuracy in predicting eosinophilic airway inflammation [17–19]. Despite this, peripheral blood eosinophils and FeNO have been associated with increased exacerbation risk, poor symptom control, and healthcare use [20–23].

While biomarkers are helpful in elucidating the inflammatory pathway and risks, studies demonstrate overlap in biomarkers within phenotypes (Fig. 1). The SARP clinical cluster analysis has shown elevated sputum eosinophils in the severe asthma cluster characterized predominantly by atopy. Furthermore, all three severe asthma SARP clinical clusters had similar levels of blood eosinophils and FeNO [10]. In a separate cluster analysis, SARP identified four sub-phenotypes noting four different sputum inflammatory patterns (paucigranulocytic, eosinophil predominant, neutrophil predominant, and mixed granulocytic) present in all clusters [12]. Similarly, sputum neutrophils and eosinophils, although varying in level, were present in all four refractory asthma clusters in the Leicester cohort regardless of their phenotypic expression [6]. These studies emphasize the importance of integrating clinical observations and patient history into the phenotypic evaluation, as biomarkers alone are limited in their ability to phenotypically characterize asthma patients.

Tailoring Therapeutics

Allergic, eosinophilic, and neutrophilic asthma are the three severe asthma phenotypes primarily targeted in randomized controlled trials investigating newer add-on therapies. Currently, the only FDA-approved biologics for phenotype-directed add-on therapy are monoclonal antibodies directed against interleukin-5 (mepolizumab, reslizumab) and IgE (omalizumab). The additional add-on biologics discussed in this review are currently in phases II and III of clinical development.

It is important to understand the inclusion criteria for the pivotal trials on efficacy of these novel immunomodulators because of the phenotype of the patients that were studied. Table 1 describes phenotype-driven, randomized controlled trials that primarily include subjects with severe asthma in three broad categories: (1) allergic asthma with type-2 inflammation, (2) eosinophilic asthma, and (3) neutrophilic asthma. Subjects included in these studies were uncontrolled in their asthma symptoms or were exacerbation-prone despite adherence to pre-specified and optimized doses of ICS. Additionally, when comparing therapies, it is important to understand that the protocol-defined asthma exacerbation outcome was different between clinical trials and thus direct comparison of magnitude of decrease in exacerbations is not always possible.

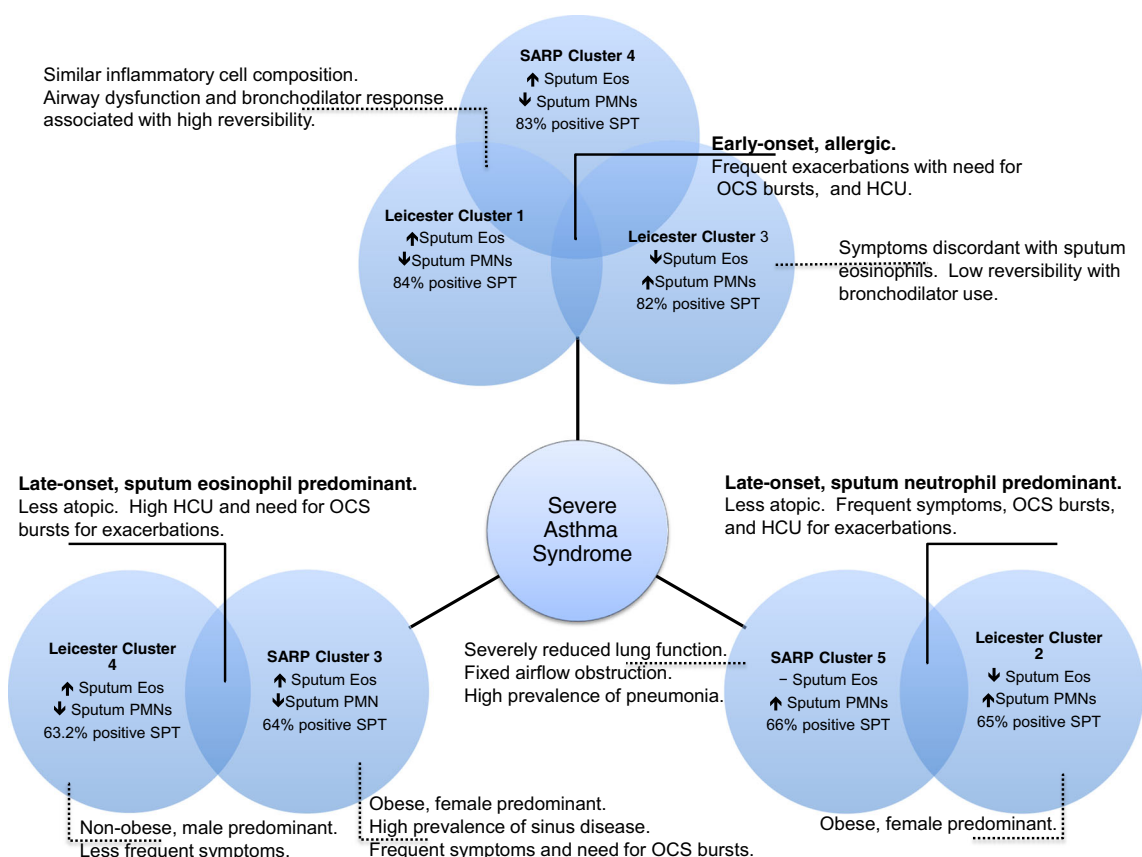


Fig. 1 Clinical phenotypes of severe asthma. Clinical characteristics of the Severe Asthma Research Program (SARP) severe asthma clinical clusters and Leicester refractory asthma clusters have some overlapping clinical characteristics in the 3 severe asthma clusters illustrated above:

early-onset allergic cluster, later-onset cluster, sputum eosinophil predominant cluster, and late-onset sputum neutrophil predominant cluster. *PMN* neutrophils, *SPT* skin prick testing, *OCS* oral corticosteroid, *HCU* health care utilization

1. Severe Asthma with an Allergic Phenotype (Type 2 Inflammatory Phenotype)

Anti-IgE

Omalizumab is a recombinant humanized monoclonal antibody against the Cε3 domain of freely circulating IgE. In the presence of an allergen, the Cε3 domain of IgE binds to the FcεR1 receptor leading to mast cell degranulation, release of histamine, leukotrienes, and upregulation of inflammatory cytokine gene expression. The formation of an omalizumab-IgE complex decreases the binding affinity of the Cε3 domain to the FcεR1 receptor and, in time, leads to marked downregulation of the FcεR1 receptor on mast cells and basophils subsequently halting the allergic cascade in the IgE-mediated part of the Th-2 pathway [24–26].

Randomized controlled trials have included atopic subjects with at least one positive skin prick test or in vitro response to a perennial allergen and serum IgE level of 30–700 IU/mL whose symptoms remain uncontrolled despite treatment with high-dose ICS plus long-acting β-agonist (LABA). The INvestigation of Omalizumab in SeVere Asthma TrEatment (INNOVATE) study demonstrated a 50% decrease in severe

exacerbation rates associated with clinically significant decreases in peak expiratory flow (PEF) or FEV1 requiring systemic corticosteroids. Significant reductions in cumulative emergency department visits, hospitalizations, and unscheduled physician visits were also seen in subjects with severe allergic, exacerbation-prone asthma receiving subcutaneously administered omalizumab [27]. The EXploring the Effects of Omalizumab in Allergic Asthma (EXTRA) study showed a 25% relative reduction in asthma exacerbations rates associated with worsening asthma symptoms requiring treatment with systemic steroids regardless of changes in PEF or FEV1 and increased time to first exacerbation in subjects phenotypically similar to the INNOVATE cohort [28]. While INNOVATE showed severe exacerbation rates were halved with omalizumab, exacerbations independent of PEF or FEV1, similarly defined in EXTRA, were reduced by 26% [27]. Additionally, observational studies in subjects with moderate-to-severe allergic asthma suggest an oral corticosteroid-sparing effect and reductions in total daily ICS dose with omalizumab [29, 30].

Targeting Optimal Responders to Omalizumab A post hoc analysis EXTRA demonstrated variable treatment effects in

Table 1 Randomized-controlled clinical trials of add-on biologics in subjects with uncontrolled severe asthma

	Subject selection criteria	Clinical effect on measured outcomes				
Drug study*	Phenotype	Exacerbations ^j	FEV1	ACQ	Biomarkers	Reference
INNOVATE ^a (omalizumab)	Allergic asthma, ≥2 exacerbations Biomarkers: ≥1 positive SPT; serum IgE 30–700 IU/mL	↓ 26–50%	↑	↑	N/A	[27]
EXTRA ^a (omalizumab)	Allergic asthma, ≥1 exacerbation Biomarkers: ≥1 positive SPT; serum IgE 30–700 IU/mL	↓ 25%	N/A	N/A	↓ FeNO	[28, 31•]
Dupilumab ^b	Th2-driven asthma with elevated eosinophils, ≥1 exacerbation Biomarkers: blood eos ≥300 cells/μL or sputum eos ≥3%	↓ 87%	↑	↑	↓ FeNO	[15]
MILLY ^c (lebrikizumab)	Th2-driven asthma, with or without exacerbations Biomarkers: IgE >100 IU/mL and blood eos ≥140 cells/μL defined Th2 high	↓ 60%	↑	–	↓ FeNO ↑ blood eos	[35]
DREAM ^a (mepolizumab)	Eosinophilic asthma, ≥2 exacerbations Biomarkers: sputum eos ≥3%, blood eos ≥300 cells/μL, FeNO ≥50 ppb	↓ 39–52%	–	–	↓ sputum eos ↓ blood eos	[16]
SIRIUS ^a (mepolizumab)	Eosinophilic asthma on chronic systemic CS, with or without exacerbations Biomarkers: blood eos ≥150 cells/μL at screening, ≥300 cells/μL past year	↓ 32%	–	↑	↓ blood eos	[43•]
Reslizumab ^d	Eosinophilic asthma, with or without exacerbations Biomarkers: sputum eos ≥3%	–	↑	↑	↓ sputum eos ↓ blood eos	[45]
Reslizumab ^e	Eosinophilic asthma, ≥1 exacerbations Biomarkers: blood eos ≥400 cells/μL	↓ 41–50%	↑	↑	↓ blood eos	[46••]
Benralizumab ^f	Eosinophilic asthma, 2–6 exacerbations Biomarkers: FeNO ≥50 ppb and ELEN index positive defined eosinophilic asthma	↓ 41% ↓ 43–57% ^g	↑	↑	↓ blood eos	[51•]
MK-7123-017 ^h (SCH 527123)	Neutrophilic asthma, <20 pack year smoking, with or without exacerbations Biomarkers: sputum neutrophils >40%	↓ 42% ⁱ	–	–	↓ sputum neutrophils	[53]

All subjects with were non-smokers or had < 10 pack year smoking history unless specified

FEV1 forced expiratory volume in 1 s, ACQ asthma control score, SPT skin prick testing, FeNO fraction of exhaled nitric oxide, eos eosinophils, CS corticosteroids, ELEN eosinophil/lymphocyte and eosinophil/neutrophil index, N/A not attributable/not measured, $\downarrow$ = reduced, $\uparrow$ = increased, – = no effect/not measured, INNOVATE Investigation of Omalizumab in Severe Asthma, EXTRA Exploring the Effects of Omalizumab in Allergic Asthma, MILLY a study of lebrikizumab in adult patients with asthma who are inadequately controlled on inhaled corticosteroids, DREAM Dose Ranging Efficacy and safety with Mepolizumab study, SIRIUS Steroid Reduction with Mepolizumab Study

*Inclusion criteria

^a Severe uncontrolled asthma on high dose inhaled corticosteroids (ICS) plus a long-acting β -agonist (LABA) or other controller medications (leukotriene receptor antagonist (LTRA) or theophylline)

^b Moderate-to-severe asthma uncontrolled on medium to high-dose ICS plus LABA

^c Persistent asthma uncontrolled on low to high-dose ICS with or without LABA

^d Severe asthma uncontrolled on high-dose ICS plus additional medication (short- or long-acting β -agonist, LTRA, cromolyn sodium)

^e Moderate-to-severe asthma uncontrolled on medium to high-dose ICS with or without additional controller medication (LABA, oral corticosteroids, LTRA, cromolyn sodium)

^f Moderate-to-severe uncontrolled asthma on medium to high-dose ICS plus LABA

^h Severe asthma on high-dose ICS

^g Subgroup with blood eos ≥ 300 cells/ μ L

ⁱ Reduction seen in mild exacerbations

^j Exacerbations presented as relative risk reduction

biomarker-defined subgroups. Subjects with FeNO ≥ 19.5 ppb demonstrated a 53% reduction in asthma exacerbations compared to 16% in subjects with FeNO < 19.5 ppb. Subjects with blood eosinophils ≥ 260 cells/ μ L demonstrated a 32%

reduction in exacerbations compared to 3% in subjects with lower blood eosinophil levels [31•]. These data suggest that a highly allergic severe asthma phenotype manifested by concurrent increases in total IgE, FeNO, and blood eosinophils

would be the optimal responder phenotype for omalizumab in clinical practice.

Alternative Th-2 Pathway Targeted Immunomodulators

IL-4 and IL-13 are key pro-inflammatory cytokines in type-2 inflammatory pathways. These cytokines bind to the IL-4 receptor α -subunit (IL-4R α) of the IL-4 α or IL-4 α /IL-13 α heterodimer receptor complexes on B-lymphocytes, eosinophils, basophils, bronchial epithelial cells, fibroblasts, and airway smooth muscles. They are associated with immunoglobulin class-switching to IgE, eosinophil recruitment, mucous hypersecretion, bronchoconstriction, and airway remodeling through downstream upregulation of collagen and fibronectin synthesis after allergen induced Th-2 pathway activation [32, 33]. Currently, there are two groups of biologics targeting this pathway.

Dupilumab and AMG 317 are IL-4R α antagonists halting the downstream signaling effects of both IL-4 and IL-13. Dupilumab, administered subcutaneously, was associated with an 87% reduction in exacerbations in moderate-to-severe asthma not well-controlled on medium-to-high dose ICS plus LABA with elevated blood or sputum eosinophils [15]. In contrast, subcutaneously administered AMG 317 did not result in significant decreases in asthma exacerbations [34]. These disparate results may be due to differences in inclusion criteria used between the two studies. The AMG 317 cohort was selected based on atopy while subjects in the dupilumab study were required to have eosinophilic inflammation. These studies suggest that the responder phenotype for IL-4R α antagonists may require evidence of atopy and either systemic and/or airway eosinophilic inflammation.

Subcutaneously administered lebrikizumab and tralokinumb, on the other hand, target freely circulating IL-13 preventing binding to the IL-4 α /IL-13 α receptor complex. Lebrikizumab reduced exacerbations associated with worsening asthma symptoms requiring increased reliever medication use, unscheduled outpatient visits, or 20% decrease in PEF by 60% and improved FEV1 in uncontrolled moderate-to-severe asthma subjects with type-2 inflammation, defined as total IgE ≥ 100 IU/mL and blood eosinophils ≥ 140 cells/ μ L [35]. The study also demonstrated potential benefit in reducing severe exacerbations associated with inpatient stay or systemic corticosteroid use in subjects with concomitantly elevated FeNO. Tralokinumab clinical trials included subjects with moderate-to-severe uncontrolled asthma and did not demonstrate improvements in asthma control, quality of life, or exacerbations [36, 37]. However, these studies suggest that a subgroup with elevated IL-13 activity may benefit the most from tralokinumab with reductions in annual asthma exacerbations by 27% and improvement in FEV1

[37]. Taken together, these studies reinforce the concept that the responder phenotype for anti-IL13 immunomodulators requires evidence of ongoing Th2 inflammation and IL-13 activity.

2. Severe Asthma with an Eosinophilic Phenotype

Anti-IL-5 Immunomodulators

IL-5 is a key mediator in eosinophil differentiation, activation, and survival in asthma. Degranulation of eosinophils leads to the release of cytotoxic and inflammatory mediators that contribute to airway epithelial damage, mucous hypersecretion, hyperresponsiveness, and airway remodeling [38]. Three immunomodulators mediating the effects of IL-5 are mepolizumab, reslizumab, and benralizumab. Mepolizumab and reslizumab are fully humanized anti-IL-5 monoclonal antibodies that selectively bind to circulating IL-5 preventing the association between IL-5 and the α chain of the IL-5 receptor (IL-5R α) on eosinophils. While benralizumab is a recombinant afucosylated antibody directed against IL-5R α . Compared to mepolizumab and reslizumab, benralizumab has been shown to markedly reduce blood and bone marrow eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity leading to direct eosinophil apoptosis [39].

Mepolizumab

Initial randomized controlled trials with mepolizumab did not demonstrate significant clinical effects (FEV1, exacerbations, and quality of life) despite reductions in blood and sputum eosinophils [40, 41]. The paucity of treatment effect in these studies was largely associated with non-specific subject selection, lack of biomarker-based criteria, and inclusion of subjects with non-severe asthma. Randomized controlled trials done subsequent to these were more specific in their inclusion criteria including only subjects with severe or refractory asthma on high-dose ICS plus an additional controller medication and two or more exacerbations requiring systemic corticosteroid treatment. Additionally, eosinophilic biomarkers were used to further define a severe eosinophilic asthma phenotype [16, 42, 43].

With this, intravenously administered mepolizumab in subjects with eosinophilic asthma ($\geq 3\%$ sputum eosinophils) refractory to treatment was associated with significantly lower exacerbation rates and improvements in quality of life compared to placebo [42]. The Dose Ranging Efficacy And safety with Mepolizumab (DREAM) study, included a similar cohort of adult severe asthma subjects but expanded their inclusion criteria of eosinophilic inflammation to not only include $\geq 3\%$ sputum eosinophils but also FeNO ≥ 50 ppb, peripheral blood eosinophils ≥ 300 cells/ μ L, or deterioration of asthma control after 25% or less reduction in maintenance inhaled or oral

corticosteroids. DREAM demonstrated a 48, 39, and 52% reduction in asthma exacerbations with intravenous mepolizumab doses of 75, 250, and 750 mg, respectively. A delay in time to the first exacerbation and decrease in emergency department visits was also seen. Additionally, the efficacy of mepolizumab was greatest in subjects with eosinophilic inflammation irrespective of atopic status [16]. Despite a subcutaneous administration of mepolizumab, the Steroid Reduction with Mepolizumab Study (SIRIUS) demonstrated a 32% relative reduction in asthma exacerbations requiring increased systemic corticosteroids dose, emergency department visits, or hospitalizations in corticosteroid-dependent severe eosinophilic asthma subjects with elevated blood eosinophils. SIRIUS also demonstrated a systemic glucocorticoid-sparing effect, reducing corticosteroid doses by 50% with mepolizumab [43•]. A similar steroid-sparing effect was seen in subjects with severe eosinophilic asthma with sputum eosinophils $\geq 3\%$ [44].

Reslizumab

Intravenously administered reslizumab leads to significant improvements in asthma control and baseline lung function but not exacerbations in subjects with poorly controlled eosinophilic asthma defined as sputum eosinophils $\geq 3\%$ despite high-dose ICS plus an additional controller medication [45]. However, two phase 3 studies demonstrated significant reductions in exacerbations, up to 50%, with use of reslizumab. Compared to the prior study, subjects included in the latter studies were exacerbation-prone, poorly controlled asthmatics on at least medium-dose ICS with evidence of systemic eosinophilic inflammation based on blood eosinophils ≥ 400 cells/ μL [46••].

Targeting Optimal Responders to Anti-IL-5 Treatment

Evidence supports the use of mepolizumab in subjects with exacerbation-prone severe eosinophilic asthma, regardless of maintenance corticosteroid use and atopic status. A cluster analysis from DREAM identified a subgroup of less atopic, older, obese women (mean BMI, 33.9 kg/m²) with late-onset asthma with the lowest post-bronchodilator FEV₁, high airway reversibility, and the highest levels of blood eosinophils that had the greatest response to mepolizumab achieving a 67% reduction in exacerbations [47•]. This subgroup is similar to the older-onset, obese, severe asthma phenotype in SARP [10]. Differentiation of biomarker selection in obese individuals is important. Despite high levels of serum eosinophils present in obese individuals with late-onset asthma [48], an inverse relationship between BMI and sputum eosinophils has been shown [49]. Sputum IL-5 and bronchial submucosal eosinophils were greatest in obese subjects with severe asthma, which suggests altered trafficking or function of airway eosinophils in obesity [50•]. These studies suggest that blood

eosinophils may be a more useful biomarker than sputum eosinophils or FeNO in determining eosinophilic inflammation in obese asthmatics.

Compared to mepolizumab, reslizumab studies included subjects with higher blood eosinophil levels and few subjects on maintenance systemic corticosteroids. The efficacy of reslizumab in reducing exacerbations and systemic and inhaled corticosteroid dosage in poorly controlled corticosteroid-dependent asthma subjects is unclear and requires further investigation.

Alternative anti-IL-5 Treatments

In subjects with uncontrolled asthma and 2–6 exacerbations in the past year despite medium-to-high-dose ICS benralizumab, 100 mg administered subcutaneous, was associated with a reduction in the annual exacerbation rate by 41% in eosinophilic asthma compared to 22% in non-eosinophilic asthma. In a subgroup with blood eosinophils ≥ 300 cells/ μL , use of 20 and 100 mg benralizumab was associated with 57 and 43% reductions, respectively, in annual asthma exacerbation rates [51•].

3. Severe Asthma with a Neutrophilic Phenotype

Th1/Th17 Pathway Targeted Immunomodulators

Th1-mediated pathway cytokines bind to CXCR 1 and 2 receptors activating and recruiting neutrophils to sites of inflammation in response to an inciting factor. SCH 527123 is a selective CXCR2 receptor antagonist and may reduce sputum neutrophils and associated tissue damage [52]. Subjects with severe asthma on high-dose ICS and sputum neutrophils $>40\%$ had a 36.4% mean reduction in sputum neutrophils with SCH 527123. Reductions in exacerbations associated with worsening asthma symptoms, decreased PEF, or increased inhaled reliever medication use but not exacerbations requiring systemic corticosteroids have been shown [53].

Brodalumab is a humanized monoclonal antibody against IL-17 receptor found on TH17 lymphocytes and airway epithelial and smooth muscle cells. It prevents the downstream effects of IL-17 associated with neutrophil recruitment [54]. Subjects with moderate-to-severe uncontrolled asthma did not have significant improvements in asthma control or lung function with brodalumab treatment. However, a subset of patients with high bronchodilator reversibility, $\geq 20\%$ change in FEV₁, suggests an improvement in symptom-free days and asthma control [54]. SCH 527123 and brodalumab are promising as immunomodulators in neutrophilic asthma however require further investigation.

Macrolide Antibiotic Therapy

Macrolide antibiotics inhibit bacterial protein synthesis of typical and atypical bacteria through binding to the 50S subunit of bacterial ribosomes. Their role in reducing exacerbations, also in part due to its anti-inflammatory effect, has been shown in cystic fibrosis, non-cystic fibrosis bronchiectasis, and chronic obstructive pulmonary disease (COPD) [55–58]. However, the efficacy of chronic macrolide therapy in severe asthma is unclear.

AZithroMycin-Asthma Trial In Community Settings (AZMATICS) is an open-labeled study that demonstrated no significant effect on exacerbation rates or quality of life in subjects randomized to weekly azithromycin 600 mg. Most subjects with severe asthma were included in the open-label arm and reported significant improvements in asthma symptoms, control, and quality of life [59]. However, improvement in the severe asthma group may be confounded by the unblinded nature of the study. The Azithromycin for Prevention of Exacerbations in Severe Asthma (AZISAST) study evaluated the effectiveness of three times a week azithromycin 250 mg as add-on therapy to high-dose ICS plus LABA in severe asthma with ≥ 2 exacerbations and/or lower respiratory tract infections (LRTI) without airway eosinophilia based on FeNO levels below the upper limit of normal. AZISAST did not demonstrate significant reductions in severe exacerbations or LRTI. However, in a subgroup analysis, exacerbation rates in subjects with non-eosinophilic severe asthma and blood eosinophils ≤ 200 cells/ μL were significantly reduced with azithromycin compared to placebo [60].

Targeting Optimal Responders to Macrolide Therapy

Currently, national and international guidelines do not support the chronic use of macrolides in severe asthma [1]. With this, studies have shown that subjects with severe asthma have a greater propensity to have altered lower airway microbiota and impaired macrophage phagocytosis compared to healthy subjects potentially contributing to persistent airway inflammation, poor symptom control, exacerbations, and risk of LRTI [61–63]. Furthermore, subjects with treatment resistant severe asthma and *Moraxella catarrhalis*, *Haemophilus* sp., or *Streptococcus* sp. airway colonization had longer asthma duration, lower FEV1, and higher sputum neutrophil counts [64•]. In SARP, a high-risk severe phenotype with lower lung function and high healthcare use was associated with sputum neutrophils $\geq 40\%$ with or without eosinophils [11, 12•]. These studies support the need for therapies directed at and suggest chronic macrolide therapy may be an alternative add-on approach in severe neutrophilic asthma with bacterial airway colonization, obstructive, or bronchiectatic characteristics.

4. Add-on Therapies for Non-phenotype Specific Severe Asthma Associated with Physiologic Impairment

Airway remodeling characterized by airway smooth muscle (ASM) cell hypertrophy, wall thickening, inflammatory cell infiltration, and mucous gland hyperplasia is often seen in severe asthma and contributes to airflow obstruction and hyperresponsiveness. An inverse correlation between airway remodeling and baseline pre-bronchodilator FEV1 has been shown [65]. In severe asthma, subjects with persistent airflow obstruction (post-bronchodilator FEV1 $< 50\%$ predicted) had increased bronchial wall thickening on high-resolution CT suggestive of airway remodeling compared to subjects with normal lung function [66]. Additionally, the cholinergic parasympathetic system is an important contributor to ASM contraction, mucous secretion, and airway remodeling particularly in obstructive airways disease [67]. These studies suggest that airway remodeling and airflow limitation are prominent characteristics in severe asthma.

As such, an important overlapping characteristic amongst all severe asthma phenotypes is physiologic airflow limitation [10, 68, 69]. In contrast to immunomodulators and macrolide antibiotics, tiotropium, and bronchial thermoplasty are non-phenotype-specific add-on therapies.

Long-Acting Muscarinic Antagonist

Tiotropium is a long-acting muscarinic antagonist inhibiting effects associated with hyperstimulated vagal tone in asthma. It selectively binds to M1 receptors on alveolar walls and parasympathetic airway ganglia and M3 receptors on ASM and submucosal glands mediating muscarinic receptor stimulation by acetylcholine on bronchoconstriction and mucous secretion. Tiotropium in combination with ICS and LABA lead to improvements in baseline FEV1, quality of life, and hospitalizations in COPD [70]. Compared to COPD, clinical trials in severe asthma used lower doses of tiotropium, 5–10 μg daily dose through a soft-mist inhaler. Tiotropium, as an add-on therapy to ICS plus LABA, in subjects with severe uncontrolled asthma with persistent airflow limitation (post-bronchodilator FEV1 $\leq 80\%$ or FVC $\leq 70\%$ predicted) significantly improved FEV1, lengthened time to the first exacerbation and was associated with a 21% overall risk reduction for exacerbations requiring systemic glucocorticoids [71, 72].

Targeting Optimal Responders to Tiotropium An immediate response to short-acting β -agonist has been shown to predict a positive response to tiotropium compared to short-acting anticholinergic. Low FEV1/FVC ratio and high cholinergic tone defined by low resting heart rate were also associated with a positive response to tiotropium but not atopy, asthma duration, BMI, IgE, sputum eosinophils, or FeNO [73•]. These studies suggest that optimal responders to tiotropium

have characteristics of airflow limitation or high cholinergic tone, such as in older adults with asthma.

Bronchial Thermoplasty

Bronchial thermoplasty is a bronchoscopic procedure where controlled radiofrequency-generated heat is sequentially delivered to all lobes of the lung excluding the right middle lobe given theoretical concerns for right middle lobe syndrome and

obstruction [74]. Bronchial thermoplasty is thought to decrease ASM bulk, therefore reducing bronchoconstriction.

Bronchial thermoplasty in AIR was associated with improvements in mild exacerbations, morning PEF, quality of life, but not severe exacerbations requiring corticosteroid treatment in moderate-to-severe asthma [75]. Compared to AIR, AIR 2 randomized subjects with severe asthma on higher-dose ICS (>1000 versus ≥ 200 $\mu\text{g/day}$ of beclomethasone or equivalent) plus LABA to receive either bronchial thermoplasty or sham treatment. The study

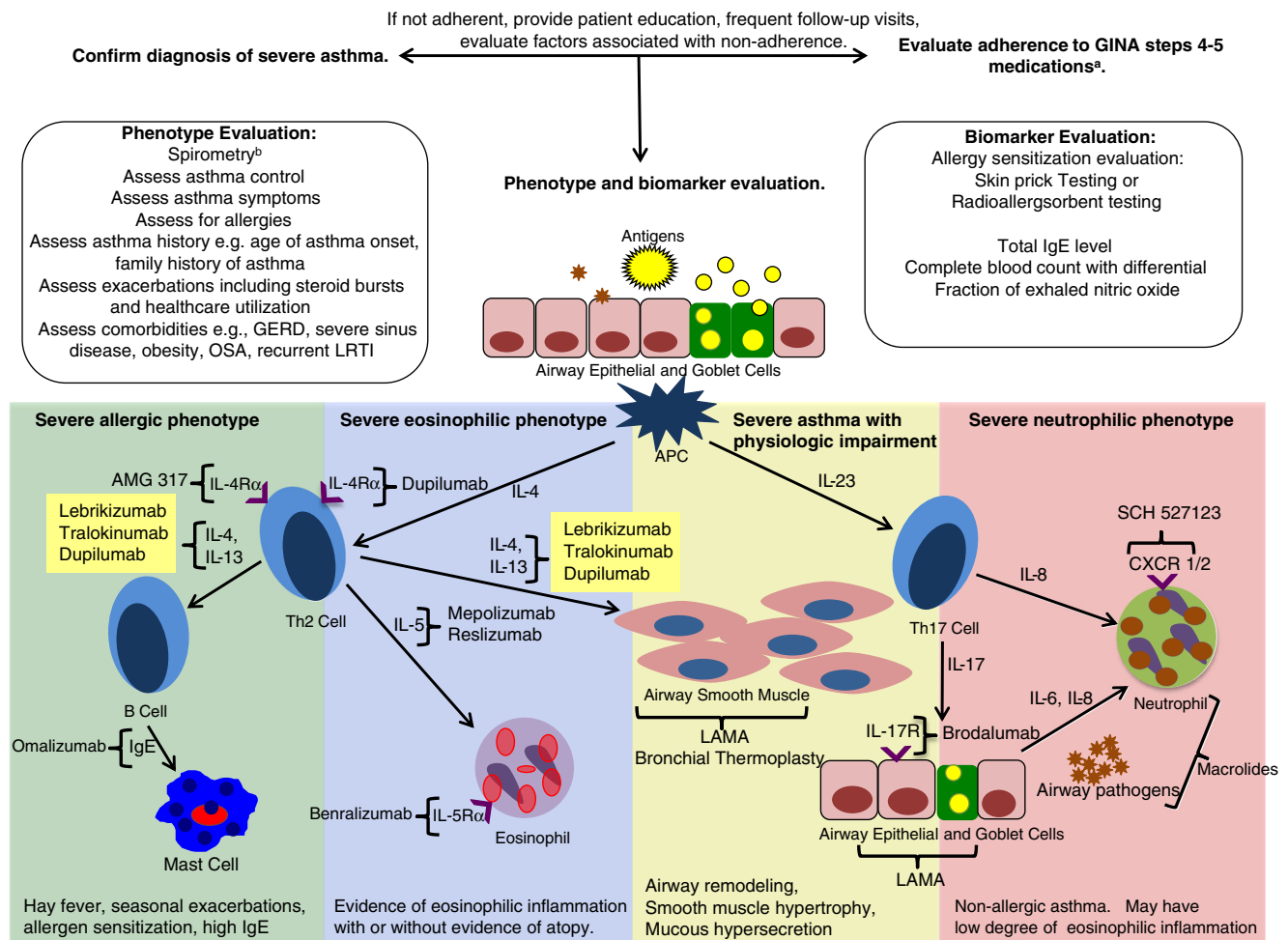


Fig. 2 Approach to add-on therapies in severe asthma. Before the diagnosis of severe asthma can be made, medication use should be assessed including inhaler technique and medication adherence since non-adherence can mask uncontrolled asthma. ^aMedications referred in this step: inhaled corticosteroids, long-acting β -agonists, and leukotriene receptor antagonists. Assessing an individual's phenotype is done through evaluation of demographic, clinical, physiologic, and biologic measures. History obtained should include asthma history (asthma age of onset, family history, medications trialed, symptom triggers) and risk factors for frequent exacerbations. Comorbid conditions should be addressed if there is a significant contribution to ongoing uncontrolled asthma. Physiologic evaluation includes spirometry with before and after maximal bronchodilator inhalation can reveal subjects who have persistent airflow obstruction who may potentially respond to long-acting muscarinic antagonists as add-on therapy. Biomarkers are used to

further differentiate phenotypes and aid in add-on therapy selection. Omalizumab (allergic phenotype) and mepolizumab, reslizumab (eosinophilic phenotype) are biologic agents currently approved for severe asthma. Clinical trials using AMG 317 was trialed in atopic patients. Lebrizumab, tralokinumab, and dupilumab (yellow boxes) are integrated in the Th2 inflammatory pathway. Long-acting muscarinic antagonist may help bronchoconstriction and mucous secretion. Bronchial thermoplasty in subjects with airway remodeling and smooth muscle hypertrophy. Macrolide antibiotics can be used in neutrophil predominant asthma. Both SCH527123 and brodalumab halt neutrophil activation and recruitment. ^bSpirometry before and after maximal bronchodilator inhalation. *SPT* skin prick testing, *RAST* radioallergosorbent test, *GERD* gastroesophageal reflux disease, *OSA* obstructive sleep apnea, *LRTI* lower respiratory tract infections, *FeNO* fraction of exhaled nitric oxide

Table 2 Summary of recommendations for phenotype directed add-on therapies in severe asthma

Phenotype	Characteristics	Biomarkers	Add-on therapies	Additional comments
Allergic asthma	Early-onset asthma Symptoms triggered by allergies Seasonal variations in exacerbations and degree of symptoms Associated with strong family history of asthma	• Must demonstrate allergic sensitization to allergens on skin prick or in vitro testing • High IgE • Can have elevated sputum and/or blood eosinophils • +/- FeNO	Omalizumab <i>Other Th2 immunomodulators:</i> Dupilumab, AMG317 Lebrikizumab, tralokinumab <i>Other:</i> Tiotropium ^a Bronchial thermoplasty ^b	Use of novel biologic agents should be reserved for patients with proven severe uncontrolled allergic asthma and ≥ 2 exacerbations despite optimization and adherence to GINA steps 4–5 medications
Eosinophilic asthma	Late-onset asthma Comorbid condition: severe sinus disease, nasal polyps, and aspirin sensitivity Frequent exacerbations requiring healthcare use May require oral corticosteroid maintenance therapy for symptom control	• Must have elevated sputum eosinophils, usually $\geq 2\%$ and/or elevated blood eosinophils as a surrogate marker • Can have allergic sensitization to allergen • +/- FeNO	Mepolizumab <i>Other anti-IL-5 immunomodulators:</i> Reslizumab Benralizumab <i>Other:</i> Tiotropium ^a Bronchial thermoplasty ^b	Use of novel biologic agents should be reserved for patients with proven severe uncontrolled eosinophilic asthma and ≥ 2 exacerbations despite optimization and adherence to GINA steps 4–5 medications Airway and systemic eosinophilia present despite use of high-dose ICS and/or systemic corticosteroids
Neutrophilic asthma	Late-onset asthma Usually seen in older asthmatics Can be associated with recurrent respiratory tract infections May be associated with lower lung function Less responsive to corticosteroid therapy compared to eosinophilic and allergic asthma	• Sputum neutrophilia, usually $\geq 40\%$ • No allergic sensitization • Sputum and blood eosinophils present but does not reach levels equivalent or greater than seen in eosinophilic asthma	Macrolides <i>Th1/Th17 immunomodulators:</i> SCH 527123 Brodalumab <i>Other:</i> Tiotropium ^a Bronchial thermoplasty ^b	Use of novel biologic agents should be reserved for patients with proven severe uncontrolled neutrophilic asthma and ≥ 1 exacerbation despite optimization and adherence to GINA steps 4–5 medications

ICS inhaled corticosteroids, LABA long-acting β -agonist

^a We recommend tiotropium as add-on therapy to ICS and LABA in severe allergic asthma, eosinophilic asthma, and neutrophilic asthma in patients who demonstrate airflow limitation based on FEV1/FVC ratio < 0.70 , post-bronchodilator FEV1 $\leq 80\%$ predicted, or post-bronchodilator FVC $\leq 70\%$ predicted

^b We consider bronchial thermoplasty as both an add-on and a salvage therapeutic intervention. We recommend bronchial thermoplasty in severe allergic asthma, eosinophilic asthma, and neutrophilic asthma who remain uncontrolled despite high dose ICS and LABA with frequent exacerbations and have failed or who do not wish to be on immunomodulator therapy

demonstrated a 32% reduction in severe exacerbation rates and an average risk reduction of 48% over 5 years in subjects who received bronchial thermoplasty [76, 77].

Targeting Optimal Responders of Bronchial Thermoplasty Current guidelines reserve bronchial thermoplasty for adults with severe asthma in the context of an Institutional Review Board-approved independent systematic registry or clinical study [1]. Bronchial thermoplasty may be beneficial in subgroups of patients who remain uncontrolled or frequently exacerbate despite optimized controller medication use and have evidence of airway remodeling. However, the mechanism of action is still not completely understood and characteristics associated with good response to bronchial thermoplasty have yet to be elucidated.

Recommendations for Tailoring Novel Therapeutics to the Individual (a Personalized Phenotype-Driven Approach)

Our approach to personalizing treatment starts with determining a patient's phenotype regardless of the severity of their disease (Fig. 2, an algorithmic approach to phenotypic evaluation and add-on treatment selection). Significant biomarker overlap between all asthma phenotypes must be taken into consideration, as biomarkers are not phenotype-specific. Biomarkers used concomitantly with the patient evaluation strengthen our ability to phenotypically characterize asthma patients. Compared to complex cluster analysis, a three variable approach (baseline pre-bronchodilator FEV1, maximal FEV1 after 6–8 puffs albuterol, and age of asthma onset) assigned subjects into five distinct clinical phenotypes with 80% accuracy in SARP [10]. This approach has been applied in different clinical settings and patient populations and has recreated similar clinical phenotypes to those in SARP [78, 79]. We recommend a similar approach with meticulous asthma history gathering, physical examination, and physiologic and biomarker testing to appropriately phenotype patients and select the optimal responder phenotype to add-on therapy (Fig. 2, Table 2; severe asthma phenotype characteristics and suggested add-on therapies).

Conclusion

The ultimate usefulness of severe asthma phenotypes lies in their ability to direct therapeutic applications. Newer therapeutic modalities should not be universally applied but should follow careful phenotypic and biomarker evaluation. The application of new therapeutic modalities should follow phenotypic cohorts used in clinical trials, which have proven beneficial.

Compliance with Ethical Standards

Conflict of Interests Dr. Opina has no conflict of interest to disclose. Dr. Moore reports grants from NHLBI and has been a subinvestigator on clinical trials sponsored by Aerovance, Amgen, Astrazeneca, Boehringer-Ingelheim, Cephalon, Forest, Genentech, GlaxoSmithKline, Medimmune, Novartis, Pfizer, Sanofi-Aventis, and TEVA.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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