



Choice of biologics in asthma endotypes

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Purpose of review

The aim of this study was to highlight the phenotypes and endotypes of asthma as a tool for selection of the Food and Drug Administration approved biologic therapies.

Recent findings

An evolving concept of asthma has led to the identification of distinct phenotypes and endotypes in this disease. Asthma endotypes are defined as the biological mechanism and are often categorized as T2-high and T2-low based on the influence of T helper type 2 (T2) cells and type 2 cytokines, including interleukin (IL)-4, IL-5, IL-9 and IL-13. Biomarkers such as peripheral blood absolute eosinophil count, total IgE, specific IgE and fractional exhaled nitric oxide may be used as indicators of asthma endotypes and help predict response to biologic therapies. There are currently five biologic therapies approved as a treatment option for T2-high asthma: omalizumab, benralizumab, mepolizumab, reslizumab and dupilumab.

Summary

Here, we explore the current understandings of asthma endotypes and review their associated phenotypes. We provide practical and evidence-based guidance for clinicians considering a biologic for asthma add-on maintenance therapy.

Keywords

asthma, biologic, endotype, phenotype, T2-high

INTRODUCTION

Asthma is a heterogeneous disease with a prevalence approaching 8% among children and adults within the USA, and there are over 339 million individuals living with asthma globally [1–3]. There is a broad spectrum of disease severity among individuals with asthma, and disease burden may oscillate over a lifetime. Severe asthma affects 3.6–6.1% of patients with this chronic respiratory disease, and increases the risk of healthcare utilization, morbidity and mortality [1,4]. Although definitions of severe asthma vary, the European Respiratory Society (ERS) and American Thoracic Society (ATS) defines it as asthma requiring treatment with high-dose inhaled corticosteroids (ICS) along with an additional controller medication [5]. Annually, thousands of patients die each year from severe and uncontrolled asthma [1]. Novel treatments intended to reduce the burden of disease have emerged in the form of biologic therapies, though identifying the ideal patient for such therapies can often present a challenge for clinicians.

Selecting a biologic therapy for asthma management requires consideration of the phenotypes and endotypes of asthma. An evolving understanding of asthma has led to the identification of several distinct observable characteristics (phenotypes) and

varying pathophysiologic mechanisms (endotypes) in this disease [6[•],7[•],8,9]. Attributes contributing to asthma phenotypes include age of disease onset and lung function (prebronchodilator FEV₁%) [10^{••}]. The phenotypes of asthma have been well characterized in several prominent hierarchical clustering studies [10^{••},11,12], though the endotypes of asthma are less clearly defined.

The first attempts to categorize the distinct inflammatory mechanisms of asthma occurred in 1999, when Wenzel *et al.* [13] stratified asthma into two endotypes: those with high and low levels of type 2 helper T-cells (T2). These endotypes were coined T2-high and T2-low, respectively [13]. T2-high asthma is generally associated with eosinophilic airway inflammation, while T2-low asthma has a neutrophilic, mixed or paucigranulocytic airway inflammation as measured by sputum quantitative cytometry [14,15]. Serum eosinophilia, as

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KEY POINTS

- Asthma is a heterogenous disease that can be distinguished by unique phenotypes and endotypes.
- There are currently five biologic therapies approved for the treatment of asthma.
- Identifying the endotype of asthma may help guide selection of an appropriate biologic therapy for patients with poorly controlled, moderate to severe asthma.

determined by an elevated peripheral blood absolute eosinophil count (AEC) at least 150–300 cells/ μ l, may be used as an imprecise surrogate for sputum cytometry, as it is often positively correlated with airway eosinophilic inflammation [16,17]. Although imperfect biomarkers, the presence of such cells often highlight part of the biologic mechanism driving the disease, and thus, likely contribute to asthma endotypes.

The use of additional biomarkers such as fractional exhaled nitric oxide (FeNO), total immunoglobulin (Ig)E and serum-specific IgE (sIgE)/skin prick testing (SPT) may capture additional endotypes falling under the umbrella of T2-high asthma (Table 1). Such biomarkers also help predict response to available asthma therapies [18[¶]]. Although these biomarkers have clinical utility, their limitations are vast, largely due to a lack of well defined asthma endotypes [18[¶]]. In addition, these biomarkers do not always accurately capture the mechanism of disease, which at times hinders their interpretive value [18[¶]]. Better validated clinical biomarkers are necessary to move toward precision management of asthma.

Biologic therapies may be used as add-on maintenance therapy for uncontrolled moderate-to-severe asthma despite step 4 therapy per the Global

Initiative for Asthma (GINA) 2019 guidelines [19]. Currently, there are five biologics approved by the Food and Drug Administration (FDA) for the treatment of T2-high asthma endotypes: omalizumab, benralizumab, mepolizumab, reslizumab and dupilumab. All of the approved biologics have been shown to decrease the frequency of asthma exacerbations in T2-high asthma. There are other biologics in various stages of clinical trials, such as the thymic stromal lymphopoietin (TSLP) antagonist Tezepelumab [7[¶]]. These mAbs target slightly different inflammatory pathways in T2-high asthma (Table 2). As such, there are no biologics currently FDA approved for T2-low asthma. In this review, we highlight some proposed phenotypes and endotypes of asthma while also exploring how these classifications may guide clinicians when selecting a biologic therapy for this respiratory disease.

T2-HIGH ASTHMA

It is estimated that approximately 50% of asthmatic individuals have a T2-high endotype [20^{¶¶},21]. In T2-high asthma, T2 cells, eosinophils, mast cells and type 2 innate lymphoid cells (ILC2) contribute to chronic airway inflammation. The epithelial derived ‘alarmins’ interleukin (IL)-25, IL-33 and TSLP are released in response to epithelial stimuli such as viruses or allergens, and may activate the T2 immune response. This leads to recruitment of additional cytokines such as IL-4, IL-5, IL-9 and IL-13. Although broadly speaking all T2-high asthma is associated with this inflammatory pathway, there are identifiable differences that result in varying responses to the available biologic therapies.

Allergic eosinophilic asthma

Allergic eosinophilic asthma is perhaps the most widely recognized endotype of asthma. The

Table 1. Tests clinicians may consider obtaining when selecting a biologic therapy for asthma management

Test	Important consideration
Spirometry	FEV1, FVC/FEV1 ratio
CBC with differential (absolute eosinophil count)	On lowest possible OCS dose, repeat up to 3x
Serum-specific IgE and/or SPT to aeroallergens	Off antihistamines if SPT
Serum-specific IgE and/or SPT to <i>Aspergillus fumigatus</i>	Off antihistamines if SPT and if concern for ABPA
Serum IgG to <i>Aspergillus fumigatus</i>	If concern for ABPA
Total IgE	Required for omalizumab or if concern for ABPA
Fractional exhaled nitric oxide (FeNO)	On lowest possible OCS dose, repeat up to 3x.
Nasal examination	Assess for polyposis (CRSwNP, AERD)
Induced sputum	Assess for sputum eosinophilia > 2%. Often challenging to obtain.

ABPA, allergic bronchopulmonary aspergillosis; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; SPT, skin prick testing.

Table 2. Phenotype and endotype factors in the FDA-approved biologic therapies for add-on maintenance treatment of asthma

Biologic	Endotype biomarker				Phenotype		
	AEC (cells/ μ l)	Total IgE (IU/ml)	Specific IgE	FeNO (ppb)	Age	Severity	FEV1 (% predicted)
Anti-IgE							
Omalizumab	NR	6–11 years: 30–1300 ≥ 12 years: 30–700	Positive	NR	≥ 6 years	Moderate to Severe	NR
Anti-IL-5/Anti-IL-5R							
Mepolizumab	≥ 150–300	NR	NR	NR	≥ 6 years	Severe	NR
Reslizumab	≥ 400	NR	NR	NR	≥ 18 years	Severe	<80%
Benralizumab	≥ 300	NR	NR	NR	≥ 12 years	Severe	NR
Anti-IL-4R							
Dupilumab	≥ 150–300 ^a	NR	NR	≥ 25 ^a	≥ 12 years	Moderate to severe or corticosteroid dependent ^b	NR

FEV1, forced expiratory volume in 1 second; NR, not required for this biologic.

^aApproved for 'eosinophilic phenotype' as determined by AEC and/or FeNO elevation.

^bNo biomarkers required for OCS-dependent asthma.

phenotype is typically early-onset, with lung function ranging from preserved to severe airflow obstruction [10²²,11,12]. Although often associated with eosinophilic airway inflammation and peripheral eosinophilia, the pathognomonic biomarker for this asthma endotype is actually the presence of allergic sensitization to specific aeroallergens identified on SPT or sIGE [10²²]. Other associated biomarkers may include elevated FeNO and total IgE [18²³].

In patients with allergic eosinophilic asthma in whom a biologic therapy is being considered, it is worth noting that all of the currently approved biologics have demonstrated efficacy in this endotype of asthma, and there are no head-to-head comparative studies among biologics. Biomarkers may therefore be used to guide selection of biologic therapy in allergic eosinophilic asthma (Table 2). The degree of serum eosinophilia is one such biomarker (Table 2). Mepolizumab and dupilumab may lead to improved asthma symptoms in patients with an AEC at least 150 cells/ μ l, while benralizumab and reslizumab are suggested for patients with AEC at least 300 and 400 cells/ μ l, respectively [7²⁴]. Anti-IgE therapy in the form of omalizumab does not utilize the AEC as selection criteria, though peripheral eosinophilia and elevated FeNO do appear to predict responsiveness to this biologic [22²⁵]. Instead, the total serum IgE is utilized to identify candidates for omalizumab in individuals with allergic eosinophilic asthma (Table 2).

Nonallergic eosinophilic asthma

In nonallergic eosinophilic asthma, a blood and airway eosinophilic inflammation is observed, though these patients do not demonstrate IgE sensitization to aeroallergens [10²⁶]. The associated phenotype is often late-onset with preserved lung function [10²⁶]. Both eosinophils and ILC2 cells are believed to play a significant role in this endotype of asthma [23²⁷]. The anti-IL-5/anti-IL-5R mAbs mepolizumab, reslizumab and benralizumab and anti IL-4R mAb dupilumab reduce eosinophilic inflammation, and are all candidate biologics for nonallergic eosinophilic asthma. In contrast, data do not support the use of anti-IgE therapy with omalizumab for this endotype [20²⁸]. Benralizumab and dupilumab have demonstrated the largest improvements in prebronchodilator FEV₁% [20²⁸,24–27]. In paediatric patients, age 6–11 years, mepolizumab is the only biologic approved for nonallergic eosinophilic asthma in this age group (Table 2). These factors all may be taken into consideration when selecting a biologic therapy.

Oral corticosteroid dependent asthma

OCS-dependent asthma is unlikely to represent a distinct endotype or phenotype of disease. Instead, it is speculated to include both allergic and nonallergic eosinophilic asthmatics with a more severe phenotype. If a primary goal of therapy is to wean from chronic OCS, dupilumab, benralizumab and mepolizumab have shown the greatest efficacy for this

endpoint, though only dupilumab is FDA approved for OCS-dependent asthmatic individuals [24,28].

Aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD) represents a unique phenotype and endotype of asthma. The AERD phenotype consists of adult-onset asthma, nasal polyposis and respiratory reactions in response to cyclooxygenase (COX)-1 inhibitors such as aspirin. In severe asthma, it is estimated that 15% of these patients have comorbid AERD [29]. A complex T2-high endotype is involved in the immunopathogenesis of this disease. There appears to be dysregulation of multiple cell mediators, including decreased levels of prostaglandin E2 (PGE₂) and overproduction of both prostaglandin D2 (PGD₂) and cysteinyl leukotrienes (CysLTs) [30–34]. Mast cells, eosinophils, ILC2s and platelet adherent leukocytes also contribute to the immune dysregulation in AERD. What results is chronic airway inflammation, which is significantly exacerbated by COX-1 inhibiting drugs [35].

Therapeutic options in AERD include standard treatment for asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP), often in conjunction with aspirin desensitization and subsequent high-dose aspirin therapy [35]. However, biologics also are emerging as a treatment option for this complex respiratory disease and may be used as an adjunct or alternative to aspirin in patients who cannot tolerate this therapy due to gastrointestinal or bleeding side effects. Dupilumab has been shown to significantly improve asthma control and also reduces the burden of CRSwNP in AERD [36,37]. Omalizumab has demonstrated improved asthma control in AERD and has likely does so at least in part by stabilizing mast cells and suppressing PGD₂ and CysLT production [38,39]. Ant-IL-5 biologics mepolizumab and reslizumab have demonstrated similar efficacy for asthma in AERD, likely through the reduction of eosinophilic inflammation [40,41,42]. Omalizumab has also shown benefit in CRSwNP, and phase III studies exploring mepolizumab for nasal polyposis have demonstrated efficacy of this biologic [41,43,44]. At the time of writing this article, only dupilumab is FDA approved for comorbid asthma and CRSwNP. Therefore, it is perhaps the most practical biologic for use in AERD to date.

Eosinophilic asthma and chronic rhinosinusitis with nasal polyposis

The phenotype of eosinophilic asthma with comorbid CRSwNP is similar in many ways to AERD,

though there is no sensitivity COX-1 inhibitors. Patients with CRSwNP have an endotype that often involves T2-high inflammation [45]. The anti-IL-4R biologic dupilumab has shown benefit in eosinophilic asthma, and also reduces nasal polyp size, improves nasal symptoms and reduces the frequency of endoscopic sinus surgeries in CRSwNP [20,46,47]. As previously mentioned, only dupilumab is FDA approved for both eosinophilic asthma and CRSwNP, though other biologics have convincing data of efficacy in CRSwNP. The European Commission has recently approved omalizumab for CRSwNP, as it has been shown to reduce nasal polyp size and improve symptoms in phase III studies [48]. Anti-IL-5 therapy with mepolizumab may be an option in the near future with promising phase III data [41,43,44]. Benralizumab has ongoing clinical trials exploring its efficacy and safety for nasal polyposis.

Allergic bronchopulmonary aspergillosis

In patients with asthma or cystic fibrosis, an allergic hypersensitivity to *Aspergillus fumigatus* colonization may result in chronic airway inflammation, resulting in a condition known as allergic bronchopulmonary aspergillosis (ABPA). It has been proposed that 2.5% of asthmatics have ABPA [49]. This endotype of asthma involves an IgE and IgG-mediated hypersensitivity to *A. fumigatus* in association with elevated serum total IgE (minimum obligatory criteria of greater than 1000 IU/ml) often with elevated blood AEC [50,51]. Radiographically, pulmonary infiltrates or bronchiectasis are commonly observed [50].

Treatment of ABPA involves inhaled and systemic glucocorticoids, though antifungal therapy may also be considered [52]. Biologics have also demonstrated efficacy in this disease. Omalizumab has been well studied in ABPA, and a randomized placebo-controlled trial showed a reduction in exacerbations when used as an adjunct to standard therapy [53]. Clinical improvement was observed despite total IgE well above standard recommendations for omalizumab (mean total IgE 2314 ± 2125 IU/ml) [53]. Case reports have shown efficacy of mepolizumab in ABPA, though further study is required to explore this possible treatment modality [54,55].

T2-low asthma

Although widely pervasive, less is known about T2-low asthma. Generally, the associated phenotype is late-onset with a severe and corticosteroid-resistant disease [56]. In contrast to T2-high asthma, T2-low

asthma is not typically associated with airway or blood eosinophilia. Heightened activation of Th1 and Th17 cells are believed to play a role, and sputum cytometry may show neutrophils, mixed or paucigranulocytic airway inflammation [15]. The biomarker FeNO is often normal, as nitric oxide production is induced by cytokines associated with T2-high airway inflammation [18,57]. Cell mediators that may contribute to T2-low asthma include interferons, tumour necrosis factor alpha (TNF α), IL-1, IL-6, IL-8, IL-17, IL-25 and IL-33 [6,20,56]. There are likely several endotypes within T2-low asthma, though research is ongoing and these endotypes have not yet been clearly defined.

Treatment of T2-low asthma can be challenging given the resistance to standard asthma therapy [56]. In obese patients with T2-low asthma, weight reduction and exercise are critical [19,58]. Macrolide antibiotics may confer benefit, and the 2019 GINA guidelines suggest a trial of low-dose macrolides in asthmatic individuals resistant to standard treatment modalities [19]. There are no biologics currently approved for T2-low asthma.

PRACTICAL CONSIDERATIONS

There are several additional practical considerations that may also help guide selection of biologic therapy in asthma. One such factor is the age of the patient. The only FDA-approved biologics for children ages 6–11 years are omalizumab and mepolizumab. The route of administration also should be taken into account. All asthma biologics are administered subcutaneously except reslizumab, which is administered intravenously (i.v.). Reslizumab's parenteral route has a theoretical advantage for obese patients given its weight-based dosing. Subcutaneous administration is considered more convenient, and of the subcutaneous biologics, dupilumab, mepolizumab and benralizumab are approved for self-administration. In pediatric patients, mepolizumab requires in-office administration. For patients hoping to minimize injections, benralizumab is the only biologic that can eventually be administered every 8 weeks after a 3-month loading period of every 4-week injections.

Providers should also consider any potential comorbidities that might make certain biologics preferable. For example, omalizumab is FDA approved for chronic urticaria, while dupilumab is approved for CRSwNP and atopic dermatitis. Mepolizumab is approved for treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). Therefore, in patients with such comorbidities associated with T2-high asthma, this may influence selection of a biologic therapy. Safety data

should also be examined. Omalizumab has the longest overall safety data [20,59]. Of the anti-IL-5 biologics, mepolizumab has the longest-term safety data [60,61] followed closely by benralizumab [62]. Dupilumab has demonstrated a risk of hyper-eosinophilia with AEC more than 3000 cells/ μ l [20], and in phase III studies of dupilumab, patients with an AEC more than 1500 cells/ μ l were excluded from participation [28,63]. Lastly, cost is an important consideration, as biologic therapies are often significantly more expensive than other currently available treatment options for asthma.

CONCLUSION

Asthma impacts millions of individuals across the globe and is a widely heterogeneous disease with distinct phenotypes and endotypes that result in varying responses to the available treatment modalities. When considering a biologic as add-on maintenance therapy for uncontrolled moderate-to-severe T2-high asthma, biomarkers may be used as a tool to home in on the phenotypes and endotypes of the disease to help guide selection of optimal therapy. The treatment of T2-low asthma remains a challenge, and improved therapies are necessary. More research is needed to provide clinically validated biomarkers to help distinguish between the phenotypes and endotypes of asthma.

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Conflicts of interest

K.W. is on the speaker's bureau for Astra Zeneca, GSK, Takeda. She is also on the advisory Board for GSK, Astra Zeneca and Regeneron. H.W. declares no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. C.D.C.. Asthma data, statistics, and surveillance. United States: U.S. Department of Health & Human Services; 2020.
2. Disease, G.B.D., I. Injury, and C. Prevalence, Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*, 2016. 388: p. 1545–1602.
3. Disease, G.B.D., I. Injury, and C. Prevalence, Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, 2017. 390: p. 1211–1259.

4. Backman HJ, Stridsman SA, Eriksson C, *et al*. Severe asthma among adults: prevalence and clinical characteristics. *Eur Respir J* 2018; 52(Suppl 62):A3918.
5. Chung KF, Wenzel SE, Brozek JL, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343–373.
6. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol* 2019; 56:219–233.
- A useful review discussing the heterogeneity of asthma and the unique phenotypes and endotypes of disease.
7. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med* 2019; 199:433–445.
- An informative review highlighting the evidence supporting the use of biologics for asthma management.
8. Lotvall J, Akdis CA, Bacharier LB, *et al*. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127:355–360.
9. Jutel M, Gajdanowicz P. Chapter 5 - revised disease nomenclature including disease endotypes, in implementing precision medicine in best practices of chronic airway diseases. Academic Press; 2019; p. 27–29.
10. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol* 2019; 144:1–12.
- An excellent review detailing how identifying asthma phenotypes and endotypes may result in a more personalized approach to asthma management.
11. Lefauveux D, De Meulder B, Loza MJ, *et al*. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. *J Allergy Clin Immunol* 2017; 139:1797–1807.
12. Moore WC, Meyers DA, Wenzel SE, *et al*. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181:315–323.
13. Wenzel SE, Langmack SL, Halliday EL, *et al*. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999; 160:1001–1008.
14. Svenningsen S, Nair P. Asthma endotypes and an overview of targeted therapy for asthma. *Front Med (Lausanne)* 2017; 4:158.
15. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006; 11:54–61.
16. Korevaar DA, Westerhof GA, Wang J, *et al*. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med* 2015; 3:290–300.
17. Westerhof GA, Korevaar DA, Amelink M, *et al*. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J* 2015; 46:688–696.
18. Carr TF, Kraft M. Use of biomarkers to identify phenotypes and endotypes of severe asthma. *Ann Allergy Asthma Immunol* 2018; 121:414–420.
- An informative review summarizing clinically relevant biomarkers and their utility in the management of patients with asthma.
19. GINA, Global Initiative for Asthma: Difficult-to-treat and Severe Asthma in adolescent and adult patients diagnosis and management. 2019.
20. Doroudchi A, Pathria M, Modena BD. Asthma biologics: comparing trial designs, patient cohorts and study results. *Ann Allergy Asthma Immunol* 2020; 124:44–56.
- An excellent and thorough review that summarizes relevant distinctions among the major clinical trials exploring the use of biologics in asthma.
21. Modena BD, Tedrow JR, Milosevic J, *et al*. Gene expression in relation to exhaled nitric oxide identifies novel asthma phenotypes with unique biomolecular pathways. *Am J Respir Crit Care Med* 2014; 190:1363–1372.
22. Casale TB, Luskin AT, Busse W, *et al*. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract* 2019; 7:156–164e1.
- A noteworthy clinical trial that reported improved outcomes in patients with asthma treated with Omalizumab regardless of their biomarker status.
23. Boonpiyathad T, Sozener ZC, Satitsuksanoa P, Akdis CA, *et al*. Immunologic mechanisms in asthma. *Semin Immunol* 2019; 46:101333.
- A useful review that explores the immunology of asthma and how this relates to our current understanding of asthma endotypes.
24. Nair P, Wenzel S, Rabe KF, *et al*. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376:2448–2458.
25. Wenzel S, Ford L, Pearlman D, *et al*. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368:2455–2466.
26. FitzGerald JM, *et al*. Bleecker ER, Nair P. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2128–2141.
27. Bleecker ER, FitzGerald JM, Chanez P, *et al*. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2115–2127.
28. Rabe KF, Nair P, Brusselle G, *et al*. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378:2475–2485.
29. Divekar R, Patel N, Jin J, *et al*. Symptom-based clustering in chronic rhinosinusitis relates to history of aspirin sensitivity and postsurgical outcomes. *J Allergy Clin Immunol Pract* 2015; 3:934–940e3.
30. Machado-Carvalho L, Martin M, Torres R, *et al*. Low E-prostanoid 2 receptor levels and deficient induction of the IL-1beta/IL-1 type I receptor/COX-2 pathway: vicious circle in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016; 137:99–107e7.
31. Mastalerz L, Tyrak KE, Ignacak M, *et al*. Prostaglandin E2 decrease in induced sputum of hypersensitive asthmatics during oral challenge with aspirin. *Allergy* 2019; 74:922–932.
32. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM, *et al*. Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015; 135:245–252.
33. Liu T, Barrett NA, Kanaoka Y, *et al*. Type 2 cysteinyl leukotriene receptors drive IL-33-dependent type 2 immunopathology and aspirin sensitivity. *J Immunol* 2018; 200:915–927.
34. Wangberg H, White AA. Aspirin-exacerbated respiratory disease. *Curr Opin Immunol* 2020; 66:9–13.
35. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med* 2018; 379:2281–2282.
- A useful review summarizing AERD.
36. Laidlaw TM, Mullol J, Fan C, *et al*. Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD. *J Allergy Clin Immunol Pract* 2019; 7:2462–2465e1.
- A noteworthy article that provides evidence supporting the use of Dupilumab in patients with AERD.
37. Bachert C, Han JK, Desrosiers M, *et al*. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019; 394:1638–1650.
38. Hayashi H, Mitsui C, Nakatani E, *et al*. Omalizumab reduces cysteinyl leukotriene and 9alpha,11beta-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016; 137:1585–1587e4.
39. Taniguchi M, Mitsui C, Hayashi H, *et al*. Aspirin-exacerbated respiratory disease (AERD): current understanding of AERD. *Allergol Int* 2019; 68:289–295.
40. Mahdavinia M, Batra PS, Codispoti C. Mepolizumab utility in successful aspirin desensitization in aspirin-exacerbated respiratory disease in a refractory case. *Ann Allergy Asthma Immunol* 2019; 123:311–312.
41. Gevaert P, Van Bruene N, Cattaert T, *et al*. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011; 128:989–995e1-8.
42. Weinstein SF, Katial RK, Bardin P, *et al*. Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract* 2019; 7:589–596e3.
- This relevant post hoc analysis of pooled data supports the efficacy of Reslizumab for patients with comorbid eosinophilic asthma and self-reported nasal polyps.
43. Bachert C, Sousa AR, Lund VJ, *et al*. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol* 2017; 140:1024–1031e14.
44. (GSK), Nucala (Mepolizumab) is the first anti-IL-5 biologic to report positive phase 3 results in patients with nasal polyps. 3 April 2020: Online Press Release.
45. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol* 2017; 12:331–357.
46. Bachert C, Hellings PW, Mullol J, *et al*. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract* 2019; 7:2447–2449e2.
- This important RCT supports the use of Dupilumab in patients with both nasal polyps and asthma.
47. Bachert C, Mannent L, Naclerio RM, *et al*. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016; 315:469–479.
48. Gevaert P, Omachi TA, Corren J, *et al*. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020.
- Data presented in this article summarize that numerous outcomes improved in patient with nasal polyps treated with Omalizumab.
49. Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol* 2013; 51:361–370.
50. Patel AR, Patel AR, Singh S, *et al*. Diagnosing allergic bronchopulmonary aspergillosis: a review. *Cureus* 2019; 11:e4550.
- A helpful review summarizing the evidence-based diagnostic approach for ABPA.
51. Agarwal R, Shah CA, Gupta A, *et al*. ABPA complicating asthma ISHAM working group Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013; 43:850–873.
52. Patel AR, Patel AR, Singh S, *et al*. Treating allergic bronchopulmonary aspergillosis: a review. *Cureus* 2019; 11:e4538.
- Another useful review summarizing the evidence-based treatment recommendations for ABPA.

53. Voskamp AL, Gillman A, Symons K, *et al.* Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract* 2015; 3:192–199.
54. Terashima T, Shinozaki T, Iwami E, *et al.* A case of allergic bronchopulmonary aspergillosis successfully treated with mepolizumab. *BMC Pulm Med* 2018; 18:53.
55. Tsubouchi H, Tsuchida S, Yanagi S, *et al.* Successful treatment with mepolizumab in a case of allergic bronchopulmonary aspergillosis complicated with nontuberculous mycobacterial infection. *Respir Med Case Rep* 2019; 28:100875.
Relevant case report in which a patient with ABPA was treated with Mepolizumab.
56. Fitzpatrick AM, Chipps BE, Holguin F, Woodruff PG, *et al.* T2-'Low' asthma: ■ overview and management strategies. *J Allergy Clin Immunol Pract* 2020; 8:452–463.
An excellent review detailing our current understanding of the T2-low asthma endotype.
57. Erzurum SC. New insights in oxidant biology in asthma. *Ann Am Thorac Soc* 2016; 13(Suppl 1):S35–S39.
58. Forno E, Han YY, Mullen J, Celedon JC, *et al.* Overweight, obesity, and lung function in children and adults: a meta-analysis. *J Allergy Clin Immunol Pract* 2018; 6:570–581e10.
59. Zhou B, Lin B, Li J, *et al.* Tolerability, pharmacokinetics and pharmacodynamics of CMAB007, a humanized antiimmunoglobulin E monoclonal antibody, in healthy Chinese subjects. *MAbs* 2012; 4:110–119.
60. Khatri S, Moore W, Gibson PG, *et al.* Assessment of the long-term ■■ safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019; 143:1742–1751e7.
An important article that provides data supporting the extended safety and efficacy of Mepolizumab for the treatment of severe eosinophilic asthma.
61. Lugogo N, Domingo C, Chanez P, *et al.* Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multicenter, open-label, phase IIIb study. *Clin Ther* 2016; 38:2058–2070e1.
62. Busse WW, Bleecker ER, FitzGerald JM, *et al.* Long-term safety and ■■ efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019; 7:46–59.
A highly relevant clinical trial exploring the extended safety and efficacy of Benralizumab for the treatment of severe asthma.
63. Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378:2486–2496.