

Diagnosis and Management of T2-High Asthma



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Learning objectives:

1. To identify the various phenotypes in asthma, particularly to identify the features of type 2 (T2)-high asthma.
2. To understand which tests are helpful in identifying patients with T2-high asthma.
3. To identify potential treatment options for patients with T2-high asthma.

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Type 2 (T2) inflammation plays a key role in the pathogenesis of asthma. IL-4, IL-5, and IL-13, along with other inflammatory mediators, lead to increased cellular eosinophilic inflammation. It is likely that around half of all patients with asthma have evidence of T2-high inflammation. Sputum and blood eosinophils, exhaled nitric oxide, blood IgE levels, and

airway gene expression markers are frequently used biomarkers of T2-high asthma. Individuals with T2-high asthma tend to have several features of increased asthma severity, including reduced lung function and increased rates of asthma exacerbations, and T2-high patients demonstrate distinct pathologic features including increased airway remodeling and

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Abbreviations used

FDA- Food and Drug Administration

FENO- Fractional exhaled nitric oxide

ICS- Inhaled corticosteroid

IV- Intravenous

mAb- Monoclonal antibody

T2- Type 2

alterations in airway mucus production. Several monoclonal antibodies are now available to treat individuals with T2-high asthma and these medications significantly reduce asthma exacerbation rates. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:442-50)

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PATHOPHYSIOLOGY OF TYPE 2–HIGH ASTHMA

Asthma is a chronic disease characterized by reversible airflow obstruction precipitated by acute bronchospasm and airway inflammation. The mainstay of asthma treatment remains bronchodilators and corticosteroids because these medications reverse bronchoconstriction and decrease airway inflammation. The acute and chronic inflammation in asthma is mediated by the complex interaction between the innate and adaptive immune system. Mouse models identified airway type 2 (T₂), or T_H2, inflammation as a key molecular mechanism of asthma and a primary inducer of bronchial hyperresponsiveness¹ (Figure 1). Classically, the T₂ cytokines include IL-4, IL-5, and IL-13, with IL-3, IL-9, IL-10, and GM-CSF included in broader classification schemes.²⁻⁴ IL-4 plays a large role in the activation and production of IgE by B lymphocytes, increases the expression of CD23 (FcεRII), the “low-affinity” IgE receptor, on B lymphocytes and macrophages, and promotes the differentiation of naive CD4⁺ T_H cells to a T_H2 phenotype.² IL-5 is a critical regulator of eosinophils and is essential for the maturation, activation, and chemoattraction of eosinophils from the systemic circulation into the lung parenchyma. Because IL-4 and IL-13 share a common receptor subunit, IL-4Rα, there is significant immunologic redundancy between these 2 cytokines.² Both increase expression of CD23, and promote IgE synthesis. Independent of IL-4, IL-13 can induce goblet cell metaplasia, increase mucus production, and increase production of MUC5AC, while decreasing MUC5B, shifting the gel-forming mucin ratio in the airway, leading to mucus obstruction.^{5,6}

Given the role of IL-5 and IL-13 in T₂ inflammation and their effects on eosinophils, as expected, eosinophilia is a predominant cellular feature of the airway in T₂-high asthma.⁷ In addition to eosinophils, mast cells may play a substantial role in the pathogenesis of T₂-high asthma, with emerging evidence to suggest that the mast cells in asthma may have an altered subtype, particularly with mast-cell–specific proteases, tryptase and carboxypeptidase A3.⁸⁻¹⁰ T₂-high asthma is also associated with increased CD3⁺, CD4⁺, and CD8⁺ lymphocytes⁸ and altered dendritic cells.¹¹ There also appears to be a role of innate lymphoid cells along with basophils in controlling the airway cellular inflammation in asthma.^{1,11}

Multiple studies have confirmed the presence of T₂ inflammation in patients with asthma^{3,4,6}; however, research into understanding the pathogenesis of asthma has determined that only a subgroup of patients with asthma demonstrate increases in airway T₂ inflammation. Patients exhibiting this pathobiological mechanism, or endotype, are now classified as “T₂-high” asthmatic patients, whereas the remaining patients have “T₂-low” asthma. Thus, treatment approaches in asthma have started to move away from a one-size-fits-all approach to a more personalized medicine approach to asthma management. This precision medicine approach requires biomarkers that can distinguish T₂-high from T₂-low asthma, and medications that are effective in T₂-high patients are less effective in patients with T₂-low disease. Here, we will discuss the current state of T₂-high and T₂-low asthma with a focus on the T₂-high endotype as it pertains to children and adults with asthma and provide a treatment approach for patients with T₂-high disease.

T2-HIGH AND T2-LOW ASTHMA

The identification of T₂-high asthma¹² grew from a pivotal study from Woodruff et al.⁶ In this work, bronchial epithelial brushings from adults with asthma, smokers with airflow obstruction, and healthy controls were analyzed using microarray and quantitative PCR confirmation.⁶ Using a 3-gene expression signature of IL-13 activation (*CLCA1*, *POSTN*, and *SERPINB2*; “3-gene mean”), the authors subdivided patients with asthma into those with elevations in this gene signature (“T₂-high”) and those with low measures of this gene signature (“T₂-low” asthma). Patients with the T₂-high signature demonstrated unique pathobiologic features including increases in subepithelial fibrosis, airway eosinophilia, and increases in the ratio of MUC5AC to MUC5B mucins. Importantly, the T₂-high asthma subgroup improved after inhaled corticosteroid (ICS) challenge, whereas the T₂-low asthmatic patients demonstrated no improvement. Thus, this was the first study to definitively demonstrate that measures of airway T₂ inflammation predict response to asthma medications.⁶ However, multiple limitations should be pointed out in this pivotal and ground-breaking study. First, this trial was limited by relatively small subject numbers (n = 42) and the patients in this study had mild asthma. Second, the outcome of this trial was improvement in FEV₁% predicted over a short 8-week follow-up period. Thus, although this study did suggest a differential response to ICSs between T₂-high and T₂-low asthma, it was not sufficient evidence to definitively prove that T₂-high asthma is steroid-responsive and T₂-low asthma is steroid-resistant. Despite these limitations, this trial did foster a critical change in the philosophy of asthma management and research. Primarily, that some subjects have airway T₂-inflammation and these patients benefit from ICSs, whereas some subjects do not have airway T₂-inflammation and in these patients with T₂-low asthma the benefit from ICSs is significantly less.

BIOMARKERS OF T2-HIGH ASTHMA

Protein measurements of IL-4, IL-5, and IL-13 cannot be reliably obtained in human biospecimens and gene expression signatures of airway samples require rigorous processing methods that are difficult to implement in clinical practice. Thus, there was a need to develop more accessible biomarkers of airway T₂ inflammation. Because the T₂ cytokines promote eosinophil

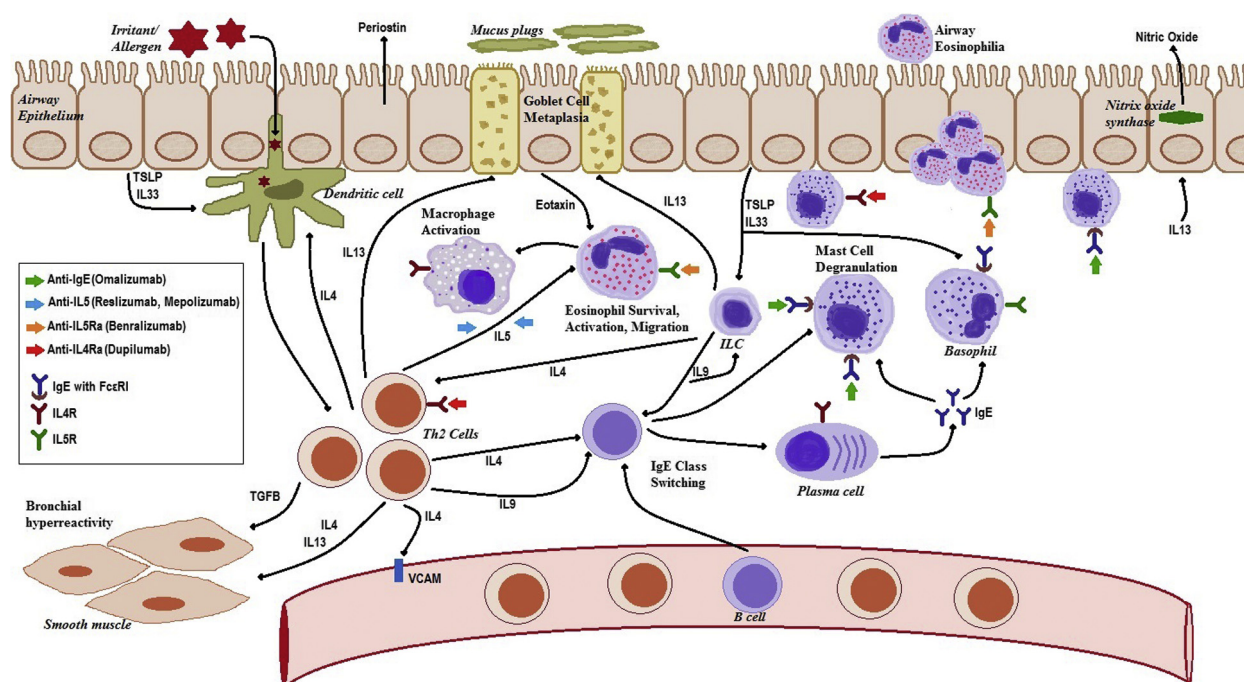


FIGURE 1. Schematic of the molecular mechanisms of T2-high asthma and sites of biologic agent action. *ILC*, Innate lymphoid cell; *TGFβ*, transforming growth factor beta; *TSLP*, thymic stromal lymphopoietin; *VCAM*, vascular cell adhesion molecule.

survival and maturation, quantification of blood or sputum eosinophil cell counts became obvious potential T2 biomarkers. Indeed, sputum eosinophilia reliably predicts T2 gene expression in induced sputum.¹² However, sputum is a difficult bi-specimen to analyze and sputum eosinophil cell counts are not easily obtained at most clinical centers. Alternatively, blood eosinophil cell counts are relatively easy to obtain, and this ease of measuring blood eosinophilia has promoted the widespread use of blood eosinophilia as a surrogate biomarker of airway T2 inflammation. Although surprisingly few studies have evaluated the effectiveness of blood eosinophil measures when compared with sputum eosinophilia,¹² the use of blood eosinophil cell counts has successfully distinguished “responders” from “non-responders” in recent clinical trials testing T2 biologic medications in asthma. To date, blood eosinophilia is the most accepted test for T2 inflammation used in clinical practice. There remains some debate as to what threshold distinguishes eosinophilic (T2-high) from noneosinophilic (T2-low) asthma, but most studies have used a cutoff between 250 cells/μL and 300 cells/μL.¹³⁻¹⁶

Epithelial exposure to IL-13 induces nitric oxide synthase, leading to increased production of nitric oxide and increases in fractional exhaled nitric oxide (FENO) measurements^{17,18}; thus FENO has been used as a noninvasive measure of airway T2 inflammation. The ease of obtaining FENO measurements has prompted enthusiasm for FENO as a biomarker of T2 inflammation and asthma severity.¹⁹ FENO correlates with sputum and peripheral blood eosinophils,^{20,21} the “3-gene mean” in bronchial epithelium,²² and sputum gene expression metrics of T2 inflammation.²³ Thus, FENO is a reasonable biomarker to consider in asthma. Furthermore, FENO provides additional benefit of identifying individuals who may respond to T2-targeted therapies, particularly when eosinophil counts are not elevated.²⁴

Periostin, an extracellular protein secreted from bronchial epithelial cells through stimulation by IL-13, has been used in several studies as a biomarker of T2-high asthma, and early use suggested it had potential for identifying subjects with airway eosinophilia.²⁵ There has been variability between studies in both adults and children regarding how well periostin correlates with other measures of T2-high asthma, such as blood eosinophils, IgE, or FENO,²⁶⁻²⁹ or identifies lung function responses to therapy.^{28,30} Periostin was the least useful biomarker for predicting airway eosinophilia²⁰ and asthma exacerbations²⁸ when compared with either FENO or blood eosinophils. Periostin levels are typically measured with ELISAs, but these assays are currently available for research purposes only and no clinically marketed assay is available at this time. Given the availability of other reliable biomarkers, the use of periostin levels in defining T2-high asthma is limited.

Blood IgE levels are easy to collect and are frequently used to quantify the degree of atopy. However, the utility of blood IgE measures as a biomarker of airway T2 inflammation appears limited, suggesting that atopy alone is not essential for the generation of the T2 cytokines. For example, older patients with asthma are likely to have elevations in airway T2 inflammation in spite of normal blood measures of IgE.^{21,22,31}

More recently, imaging studies have been used to identify pathological changes and perhaps serve as another noninvasive method to phenotype patients with asthma. Dunican et al³² created a mucus score on the basis of multidetector computed tomography scans of the lungs in a group of 146 adults with asthma and 22 healthy controls. Mucus plugging on multidetector computed tomography was significantly higher in patients with asthma when compared with healthy control subjects, and patients with high airway mucus plug scores were also

characterized by elevations in measures of airway T2 inflammation, including increased sputum and blood eosinophil cell counts, high FENO measures, and sputum gene expression measures for IL-4, IL-5, and IL-13. Although still in development, use of a mucus score on multidetector computed tomography could not only identify patients with asthma apt to respond to interventions that eradicate airway mucus plugs but may also identify those individuals with a T2-high phenotype who may benefit from therapies targeted toward reduction of goblet cell metaplasia, such as IL-13 antagonists. In addition, because eosinophilic by-products such as Gal10 can promote mucus plugging, inhibiting Gal10 activity could prove to be an important novel target in T2-high asthma.³³

To summarize, because blood eosinophil cell counts are relatively easy to obtain and have demonstrated clinical efficacy at distinguishing responders from nonresponders in T2-biologic trials, they remain the most established test to distinguish T2-high from T2-low asthma. Other biomarkers, such as sputum eosinophil cell counts or IgE, are either too difficult to obtain in clinical practice or lack the clinical evidence to support widespread use. FENO is easily obtained, and although use as a T2 biomarker remains controversial, it may provide added benefit when compared with blood eosinophil measures or in instances when eosinophil count is low but suspicion for T2 inflammation is high.

CLINICAL FEATURES OF T2-HIGH ASTHMA

In addition to the described cellular airway features, there are several pathological changes that occur in T2-high asthma with findings of airway remodeling. Endobronchial biopsies obtained via bronchoscopy identified that an increase in basement membrane thickness occurs in those with T2-high or eosinophilic asthma.^{8,31} In addition, there is altered expression of mucin genes, with those with T2-high asthma having an increased MUC5AC to MUC5B ratio, including increased mucin stores.³¹ This goblet cell metaplasia³⁴ likely leads to mucus plugging, a pathological feature, which leads to further airflow obstruction.³²

The exact prevalence of T2-high asthma is a bit unknown though estimates from multiple phenotyping studies would suggest that approximately 50% of patients with asthma have T2-high asthma^{12,31,35}; however, these estimates may be significantly lower in those with more mild asthma.³⁶ Although some studies have shown a lack of association of T2 biomarkers with lung function³¹ or asthma severity,³⁷ there is emerging evidence that suggests that T2-high asthma is associated with a diagnosis of severe asthma^{7,22,38} as well as other features indicative of greater asthma severity. Lung function, particularly FEV₁% predicted, is reduced in T2-high asthma.^{12,22,32,39} Individuals with T2-high asthma also tend to have a greater degree of airway hyperresponsiveness.^{21,31} T2-high asthma is associated with greater health care utilization, including more oral corticosteroid use⁴⁰ and emergency room visits,⁴¹ as well as worse asthma control.^{12,32} Multiple studies indicate that T2-high asthma increases the risk of asthma exacerbations.^{22,35,40-42}

In addition to identifying clinical features of asthma, T2 biomarkers may help identify those who may be more likely to respond to traditional therapies. Changes in the expression of the surrogate epithelial T2 genes, *CLCA1*, *POSTN*, and *SERPINB2*, were associated with improvements in lung function (FEV₁) after initiation of ICSs.⁶ The improvement in lung function after ICS

use was limited to those with T2-high asthma,³¹ suggesting that this endotype might have better response to treatment with corticosteroids. The higher the expression of these 3 genes, the greater the improvement in FEV₁ with ICS use.²¹ Sputum T2 gene expression was also useful in predicting those who were likely to have an improvement in FEV₁ of at least 5% after triamcinolone use.²² Moreover, the Severe Asthma Research Program III cohort also identified that blood eosinophils, sputum eosinophils (in adults only), and FENO were all predictive of a response of at least 10% improvement in FEV₁ after triamcinolone use.⁴³

Studies in children with asthma indicate that many of them have features consistent with T2-high asthma. Atopy is a common feature of asthma in children, and atopic disorders are often associated with T2 inflammation; however, it is recognized that just as in adults, severe asthma in children is a heterogeneous disorder,^{44,45} with many exhibiting features of T2-high asthma. Within the Severe Asthma Research Program III cohort, children had higher blood eosinophil counts and serum IgE levels than did adults with asthma.⁴⁶ In addition, FENO decreased with increasing age. Thus, it seems that children with asthma had more features of T2-high asthma than did adults. It is a bit unclear whether T2-high asthma distinguishes children with severe asthma from those with less severe asthma, and indeed, adults with T2-low asthma may have much morbidity.^{8,47} Airway cytokines measured through cytometric bead arrays from bronchoalveolar lavage were unable to distinguish a group of children with severe therapy-resistant asthma from controls;⁴⁸ however, in a larger study of children with asthma, use of FENO combined with blood eosinophils indicated that children with elevated T2 biomarkers had worse asthma control, more exacerbations, worse airflow limitation, and reduced quality of life, all features of more severe asthma.²⁹ Moreover, a study identifying children with T2-high asthma by nasal gene expression found that IL-13 expression levels in the nose were strongly associated with asthma exacerbations.³⁵

CLINICAL APPROACH AND TREATMENT OF T2-HIGH ASTHMA

To date, the initial treatment approach to T2-high asthma is the same as to T2-low asthma. This approach emphasizes the correct diagnosis and the treatment of any comorbidities contributing to asthma disease. Common asthma comorbidities include gastroesophageal reflux, nasal polyposis, and cardiovascular disease. Therefore, inhaler treatments decisions are not robustly different between patients with T2-high and T2-low asthma. However, it is important to recognize that a large subgroup of patients with asthma may not benefit from ICS treatment. This lack of response to ICS was emphasized in a recent clinical trial that found no differential response to ICSs or long-acting muscarinic antagonists in patients with noneosinophilic asthma.³⁶ For this reason, we find it beneficial to obtain blood eosinophil cell counts, or FENO, at a relatively early stage of the diagnostic workup for asthma. The 2019 Global Initiative for Asthma Report has added guidelines for evaluation of suspected T2-high asthma in the treatment algorithm for adults and adolescents with difficult-to-treat and severe asthma.⁴⁹ Of course, asthma education, confirmation of correct inhaler technique, and ensuring inhaler compliance are key components of optimized asthma management. These teachings should be reinforced with

TABLE I. FDA-approved biologic agents used in the treatment of T2-high asthma

Therapy	Target	Biomarker	Availability in United States	Administration	Clinical outcomes
Omalizumab (Xolair)	IgE	Total IgE 30-700 kU/L (≥ 12 y) or 30-1300 kU/L (6-11 y)	Originally approved in 2003; now approved for ≥ 6 y	SQ every 2-4 wk, dose based on IgE level and weight	Reduced exacerbations and OCS use
Reslizumab (Cinqair)	Anti-IL-5	Blood eosinophil $\geq 400/\mu\text{L}$	Approved in 2016 for ≥ 18 y	IV infusion 3 mg/kg every 4 wk	Reduced exacerbations, especially with rhinosinusitis with nasal polyposis
Mepolizumab (Nucala)	Anti-IL-5	Blood eosinophil $\geq 150/\mu\text{L}$	Approved in 2015 for ≥ 12 y; now approved for ≥ 6 y	40 mg (6-11 y) or 100 mg (≥ 12 y) SQ every 4 wk	Reduced exacerbations and improved quality of life and lung function
Benralizumab (Fasenra)	Anti-IL-5Ra	Blood eosinophil $\geq 150/\mu\text{L}$	Approved in 2017 for ≥ 12 y	30 mg SQ every 4 wk $\times 3$, then every 8 wk	Reduced exacerbations and improved lung function
Dupilumab (Dupixent)	Anti-IL-4Ra	Blood eosinophil $\geq 150/\mu\text{L}$	Approved in 2017 for ≥ 12 y	400 or 600 mg loading dose, then 200 or 300 mg SQ every 2 wk	Reduced exacerbations and improved quality of life and lung function

OCS, Oral corticosteroid; SQ, subcutaneous.

each step-up in therapy to enforce patient understanding. If compliance is appropriate, inhaled medications and add-on therapies such as leukotriene antagonists are maximized, and the patient continues to experience exacerbations requiring systemic corticosteroids, then consideration for biologic therapies is warranted. To date 5 T2 biologic agents are Food and Drug Administration (FDA)-approved for the treatment of severe asthma (Table I).

Omalizumab, a monoclonal antibody (mAb) targeted against IgE, was the first biologic agent developed in asthma treatment and was first FDA-approved for use in asthma in 2003 as Xolair (Genentech and Novartis Pharmaceuticals). One of the early phase III trials in adolescents and adults determined that it was effective in reducing asthma exacerbations and allowing for reduction in ICS dose when compared with placebo.⁵⁰ Since its approval, there have been several more studies of omalizumab performed to evaluate efficacy and sustainability, including further studies in children. Overall, when evaluating randomized controlled trials and real-world studies of subjects with asthma treated with omalizumab, omalizumab has consistently shown an association with reduced exacerbations and is frequently associated with reduced hospitalizations, reduction in oral corticosteroid use and dosage, reduced rescue albuterol use, and improved quality of life.⁵¹⁻⁵⁵ A few open-label observational real-world studies have identified possible biomarkers associated with response to omalizumab defined by reduction in exacerbations, improvement in asthma control, or improvement in lung function. FENO, sex, and eosinophil counts may be useful in addition to the typical criteria for initiation of therapy.^{51,55} Omalizumab is approved for use in the United States down to age 6 years in those with evidence of an elevated total serum IgE and the presence of a positive serum-specific IgE to at least 1 perennial aeroallergen. It is administered for treatment of asthma as 75 to 375 mg subcutaneous injections every 2 to 4 weeks, with dose strength and interval determined by serum IgE level and body weight. It is also approved for use in patients 12 years and older with chronic idiopathic urticaria.

Mepolizumab is an mAb targeted against IL-5. Treatment with intravenous (IV) mepolizumab was associated with a 40%

to 50% reduction in asthma exacerbations and improved quality-of-life measures compared with placebo.^{56,57} In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA),⁵⁸ Efficacy and Safety of Mepolizumab Adjunctive Therapy in Subjects With Severe Eosinophilic Asthma on Markers of Asthma Control (MUSCA),⁵⁹ and Steroid Reduction with Mepolizumab Study (SIRIUS)¹⁵ trials, which evaluated the efficacy of subcutaneous mepolizumab in patients 12 years and older with severe eosinophilic asthma, mepolizumab was shown to reduce exacerbation rates, improve quality of life, and modestly improve asthma control scores. Treatment with mepolizumab also leads to modest improvements of 100 to 120 mL in FEV₁^{58,59} and provides a corticosteroid-sparing effect.¹⁵ Secondary analysis indicates that mepolizumab is most effective at reducing exacerbation rates with higher eosinophil counts and higher eosinophil counts lead to higher response rates.⁶⁰ Mepolizumab is currently available in the United States as Nucala (GlaxoSmithKline) since 2015 and is approved for patients 6 years and older. It is administered as 100 mg subcutaneous injections every 4 weeks for those 12 years of age and older, and as 40 mg subcutaneous injections every 4 weeks for those 6 to 11 years of age. In addition to asthma, mepolizumab is also FDA-approved in adults for the treatment of eosinophilic granulomatosis with polyangiitis.

Reslizumab is an mAb directed against IL-5. Phase 3 trials of reslizumab showed improvements in lung function when blood eosinophils were elevated (>400 u/mL) but these effects were not significant at lower levels of eosinophils.^{14,61-63} Asthma control scores were improved in some studies, but this was not consistent across all studies, nor patient populations, where it seemed that the presence of nasal polyps indicated a population that might be more responsive to reslizumab.⁶¹ More recently, post hoc analysis of phase III studies suggested that reslizumab may be helpful in reducing asthma exacerbations in patients with chronic rhinosinusitis with nasal polyposis.⁶⁴ Long-term follow-up of patients treated during an open-label extension trial confirmed the safety, tolerability, and efficacy of IV reslizumab.⁶⁵ Reslizumab is currently available for use in the United States since 2016 as Cinqair (Teva). It is administered via an IV

infusion of 3 mg/kg every 4 weeks and is approved for use in adults 18 years and older with severe asthma.

Benralizumab is an mAb directed against the alpha subunit of the IL-5 receptor. Two phase 3 trials, Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β_2 Agonist (CALIMA) and Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients With Uncontrolled Asthma (SIROCCO), were completed evaluating the efficacy and safety of either every 4-week or 8-week benralizumab in subjects aged 12 to 75 years with severe uncontrolled asthma and elevated blood eosinophil. Both studies found that treatment with benralizumab reduced asthma exacerbation rates by 30% to 50% compared with placebo.^{13,66} In addition, significant improvements of 100 to 150 mL in FEV₁ were seen in those with eosinophils greater than 300 cells/ μ L.^{13,66} Pooled analysis of these trials suggested that those with higher blood eosinophil levels and a history of more frequent asthma exacerbations are most likely to benefit from benralizumab in reducing exacerbations.⁶⁷ The Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients With Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA) trial was a 28-week trial that highlighted the oral corticosteroid-sparing effects of benralizumab.⁶⁸ Benralizumab has also been studied in individuals with mild to moderate asthma, but the improvements in lung function, exacerbations, and asthma symptom scores were not seen as they were in those with severe asthma.⁶⁹ Benralizumab is currently available in the United States as of 2017 as Fasenra (AstraZeneca Pharmaceuticals) for patients aged 12 years and older with severe asthma. It is administered as a 30-mg subcutaneous injection every 4 weeks for 3 doses, then once every 8 weeks.

Dupilumab is an mAb directed against the IL-4 receptor alpha, therefore targeting both IL-4 and IL-13 pathways. Several phase IIB and III studies have shown the efficacy of dupilumab in patients with uncontrolled or severe persistent asthma in reducing asthma exacerbations by at least 50% to 70% and improving lung function by approximately 150 to 350 mL.^{16,24,70,71} In the Liberty Asthma QUEST study, which studied patients 12 years and older with moderate to severe persistent uncontrolled asthma, the improvement in lung function was maintained over the study period for those on dupilumab whereas those on placebo had a slight decline in lung function over the 52 weeks of the study.²⁴ In addition, there were improvements in asthma control and quality-of-life measures. The response to dupilumab was greatest in those with higher peripheral blood eosinophil counts. Dupilumab has been shown to be effective in reducing oral corticosteroid use in those with steroid-dependent severe asthma.⁷¹ Post hoc analysis demonstrated that symptoms of allergic rhinitis can also be significantly improved.⁷² Dupilumab is currently available as Dupixent (Sanofi and Regeneron Pharmaceuticals) in the United States since 2017. It is approved for patients 12 years and older with moderate to severe persistent asthma with eosinophilia or oral corticosteroid dependence. It is administered as a 600-mg or 400-mg loading dose followed by 300-mg or 200-mg subcutaneous injections every other week, with the higher dosing strategy recommended for use in those with concomitant oral corticosteroid use and/or comorbid moderate to severe atopic

dermatitis. In addition to asthma, it is approved for the treatment of moderate to severe atopic dermatitis in patients 12 years and older and add-on maintenance to adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

The biggest concern with these biologic agents is the risk of anaphylaxis. This risk is highest with omalizumab and the IV formulation of reslizumab. The other IL-5 inhibitors and dupilumab appear to have a lower risk of anaphylaxis and hence they are now approved for home dosing. All these biologic agents maintain a risk of minor injection-site reactions. The most common adverse effects typically reported are nasopharyngitis, worsening asthma control, and headaches, of which rates are not much different than what was seen in placebo.^{13,15,16,65,66} It is not yet clear how treatments might alter the ability to fight helminthic infections by reducing eosinophilia, so caution is advised if these infections are suspected. Subjects treated for 2 years with benralizumab did not experience any such infections.⁷³ There have been several cases of herpes zoster reported in the studies of mepolizumab. The clinical implications of this remain unclear, and it is reasonable to consider zoster vaccination before initiating anti-IL-5 medications; however, this approach is not considered mandatory.

Because of the lack of direct comparisons between biologic agents, there are several factors to consider when choosing the next step in asthma treatment. For pediatric providers, age is a factor, and for those aged 6 to 11 years, omalizumab and, more recently, mepolizumab are the only available targeted therapies for this age group. There are no approved agents for those younger than 6 years. For the 12 years of age and older group, the options increase to benralizumab and dupilumab, but reslizumab remains available only to those 18 years and older. Although FDA-approved for those aged 12 years and older, the efficacy and safety data are somewhat limited in the pediatric population. The average age for many of the phase 3 trials that included adolescents was around 50 years.^{13,15,24,56,71} and there were limited numbers of adolescents included, perhaps 5% of the study participants.¹³ Studies in adolescents and children are ongoing, and there has been recent published data to support larger trials of mepolizumab in younger children.^{74,75}

For those aged 12 years and older, choosing an agent may depend on total serum IgE and peripheral blood eosinophil levels. If the total IgE is elevated and there is evidence of perennial aeroallergen sensitization in the absence of eosinophilia, omalizumab is the reasonable choice. If eosinophilia is present, it is reasonable to start with an anti-IL-5 or anti-IL-4 treatment. There are no clinical studies directly comparing the efficacies of these biologic agents, and the eosinophil thresholds used to determine eligibility, while similar, did vary between agents and studies. Attempts to compare the IL-5-targeted therapies have been made using indirect treatment comparisons from systematic reviews with varying results.^{76,77} Because of variable outcomes and dosing strategies that vary from clinically relevant doses, comparative data between agents are somewhat limited. However, a review of the medical literature would suggest that the drugs demonstrate reasonably similar efficacy. Specifically, all the anti-IL-5 agents decrease asthma exacerbation rates in eosinophilic patients by 40% to 60% and improve FEV₁ measures by about 100 to 200 mL over placebo.^{13,58,61,66} The effects with dupilumab are similar, with effects sizes of asthma exacerbation reduction in eosinophilic patients of 60% to 70% and FEV₁ improvements between 200 and 300 mL.^{16,24}

It is also reasonable to consider the mode and timing of administration, and comorbidities when selecting an anti-T2 biologic agent. Dupilumab, mepolizumab, and benralizumab are all now offering the option for home administration with prefilled injectors. Benralizumab may be preferable to some because it can be dosed every 2 months. Dupilumab also has FDA approval for atopic dermatitis and chronic rhinosinusitis with nasal polyps, making this agent an excellent choice for those also afflicted by these conditions. Reslizumab is an additional option for those with nasal polyps as studies indicated improved asthma control with this comorbid condition. Because there was no impact on the polyps themselves, dupilumab is likely the superior agent with chronic rhinosinusitis with nasal polyps. One important caveat of dupilumab treatment is that treatment with dupilumab will increase blood eosinophil cell counts. The clinical significance of this increase remains unknown, but this is in sharp contrast to the robust and relatively uniform effect of the anti-IL-5 drugs at decreasing blood eosinophil cell counts.

Although the data for discontinuation are extremely limited, it is reasonable to discontinue medications at 3 to 6 months if there has been no clinical evidence of improvement, and to consider transitioning to an alternative agent. In our experience, some patients will respond to a different T2-biologic agent even if they have previously failed one of the other agents. This may in part be due to the limited biomarkers available and the overlap of T2 phenotypes. Determination of biologic agent eligibility is based on peripheral eosinophilia and may not fully reflect the T2 cytokine and receptor activity. Once started, there are also no established guidelines for when to consider stepping off therapy. The limited evidence available suggests that the effects of these agents are not sustained, and that improvements in exacerbations, eosinophilia, and asthma control are likely to deteriorate back to their baseline measures once therapy is stopped.⁷⁸ In addition, although the improvements in exacerbations and asthma control persist over time while on therapy, increases in FEV₁ may not be sustained, perhaps because of natural disease progression in patients with severe asthma.⁷⁹

CONCLUSIONS

In summary, T2-high asthma is the most established asthma endotype characterized by clinical features of more severe asthma including reduced lung function and frequent exacerbations. Blood eosinophil cell counts remain the most established biomarker of airway T2 inflammation, but considerable debate remains regarding the best biomarkers to discriminate T2-high from T2-low disease. There are now several biologic agents available that can target T2-high asthma, and these medications are extremely effective at reducing asthma exacerbations and improving lung function in the patient population that has T2-high disease.

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