

Controversies in Allergy: Should Severe Asthma with Eosinophilic Phenotype Always Be Treated with Anti-IL-5 Therapies



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Key words: Severe asthma; Eosinophilic phenotype; Anti-IL-5 therapies; Anti-IL-4/13 therapy

There have been major advances in the assessment and management of severe asthma over the last 10 years. As a result, many patients with severe asthma have new, targeted biological treatment options. These biologic therapies are only effective in subgroups (phenotypes) of patients defined using clinical parameters and biomarkers. All biologic therapies approved at the moment target type 2 high or eosinophilic airway inflammation. We use a case-based discussion approach to discuss biological treatment options for a patient presenting with severe eosinophilic asthma. There remains much debate on the choice of specific biologic in such a case. This issue is the focus of this article that presents a debate as to whether to use biologics targeting IL-5 or other biologics in this case.

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No funding was received for this work.

Conflicts of interest: In the last 5 years, I. D. Pavord has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, and GlaxoSmithKline; has received payments for organizing educational events from AstraZeneca, GlaxoSmithKline, Sanofi/Regeneron, and Teva; has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi, and Knopp; has received payments to support Food and Drug Administration approval meetings from GSK; has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Teva, and Chiesi; has received a grant from Chiesi to support a phase 2 clinical trial in Oxford; is copatent holder of the rights to the Leicester Cough Questionnaire, has received payments for its use in clinical trials from Merck, Bayer, and Insmad; and has served as an expert witness for a patent dispute involving AstraZeneca and Teva. N. A. Hanania has received honoraria for serving on advisory boards or as a consultant with AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi/Regeneron, Mylan, Sunovion, and Gossamer Bio; his institution received research grant support of his behalf to conduct clinical trials from GlaxoSmithKline, AstraZeneca, Gossamer Bio, and Boehringer Ingelheim.

Received for publication March 6, 2019; revised manuscript received and accepted for publication March 13, 2019.

Available online April 5, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.03.010>

CASE

A 46-year-old man is referred for assessment of a 12-month history of troublesome wheeze, cough, and breathlessness. His symptoms are worse at night and after exercise. He reports increasing use of albuterol (1 inhaler every 4 weeks) and 6 exacerbations requiring short courses of oral prednisone in the last 12 months. He does find oral prednisone helpful. His asthma was first diagnosed in childhood and he has been taking regular inhaled corticosteroids (ICS) for more than 30 years. His current medication regimen includes fluticasone dipropionate/salmeterol 500/50 twice daily by a dry powder inhaler (DPI). He gives a longer history of nasal stuffiness and postnasal drip for which he has been prescribed nasal fluticasone. He had been seen once by an ENT specialist who diagnosed him with nasal polyposis. His primary care clinician has recorded an Asthma Control Test score of 12; peak expiratory flow rate (PEF) values varying between 300 and 500 L/min at different visits; and a forced expiratory volume in 1 second (FEV₁) of 2.5 and forced vital capacity (FVC) of 4.5 L (predicted 3.7 and 4.8 L). He is a nonsmoker, has no pets at home, and works as a carpenter. He denies work-related symptoms or exposure to respiratory sensitizers.

On first assessment, the patient is judged to be adherent to his medication regimen after a careful review of his primary care and pharmacy records. His techniques using his dry powdered and metered dose inhalers are adequate. His fraction of exhaled nitric oxide level (FeNO) is 134 ppb (normal <25 ppb) and absolute blood eosinophil count $0.57 \times 10^9/L$. His serum IgE is 410 IU/L and he has weakly positive specific IgE to house dust mite but not to other perennial allergens. His weight is 120 kg and body mass index 34 kg/m².

Case discussion

Many patients referred for assessment of uncontrolled asthma have persistent morbidity either because the diagnosis is wrong, or because of comorbid factors, which may or may not be related to asthma.¹ Potentially relevant comorbid factors include rhinosinusitis, chronic obstructive pulmonary disease, bronchiectasis, obstructive sleep apnea, vocal cord dysfunction, and obesity. All of these can also coexist with asthma or be the sole cause of asthma-like symptoms unresponsive to treatment. In addition, continuous exposure to triggers including aeroallergens and irritants as well as poor adherence to therapy is the major cause of uncontrolled disease. The patient described above has uncontrolled asthma as evidenced by the persistent symptoms and the objective measurements reflecting variability in PEF between clinic visits and reduced FEV₁ and FEV₁/FVC.

Abbreviations used

FeNO- Fraction of exhaled nitric oxide level
FEV₁- Forced expiratory volume in 1 second
FVC- Forced vital capacity
ICS- Inhaled corticosteroids
PEF- Peak expiratory flow rate

Assessment of adherence to treatment, inhaler technique, the patient's environment, and asthma self-management skills are important first steps in any patient with suspected severe asthma. Prescription records, blood prednisolone levels, and FeNO suppression testing² can be useful to verify treatment adherence. In our case, the patient is reportedly adherent to his medications and his comorbidities are well managed. Therefore, his symptoms, exacerbation history, and need for high-dose ICS and other controllers are consistent with a diagnosis of severe asthma. The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines³ define severe asthma as "asthma which requires treatment with high dose inhaled corticosteroids (i.e. fluticasone dipropionate 1000 mcg/day or more) and long acting beta2 agonist or leukotriene modifier/theophylline for the previous year or systemic corticosteroids for >50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy."

Once severe asthma is diagnosed, the second step is to measure biomarkers to identify the lower airway inflammatory phenotype associated with the disease. Lower airway pathology is typically highly heterogeneous in patients with severe asthma.⁴ A broad distinction between type 2 high and type 2 low inflammation is clinically helpful as patients with type 2 high airway inflammation are at increased risk of asthma exacerbations and tend to respond well to corticosteroid and available biological treatments. Type 2 airway inflammation is orchestrated either by T-helper2 lymphocytes on exposure to allergens or by type 2 innate lymphocytes triggered by other exposures and is propagated by type 2 cytokines including IL-5, IL-13, and IL-4. Patients may have "inflammation predominant" disease, with few reported symptoms, minimal impairment of lung function but recurrent asthma exacerbations.⁵ Nasal disease (rhinosinusitis) is the most common reported comorbidity to be associated with severe type 2 high asthma. Others include nasal polyposis and atopic dermatitis.

Type 2 low severe asthma is much less well understood as it is much more heterogeneous.⁶ There are probably phenotypes associated with obesity and another associated with airway infection or other exposures such as cigarette smoking. The main clinical priority in these patients is to avoid exposure to high doses of corticosteroids because the response to treatment is poor.

Biomarkers that characterize type 2 airway inflammation include blood or sputum eosinophil count and exhaled nitric oxide (FeNO). Assessment of these is important in characterizing the lower airway inflammatory phenotype and in assessing suitability for biological agents targeting type 2 cytokines. In addition, serum IgE and allergen-specific IgE are crucial in assessing allergen sensitization and help, along with the clinical presentation, in differentiating allergic versus nonallergic phenotypes within type 2 high asthma.

Measurement of FeNO involves a simple breath test. Nitric oxide is produced by airway epithelial cells as a result of IL-13-

induced induction of nitric oxide synthase in the airway epithelium.^{7,8} A raised FeNO is strongly associated with a positive response to corticosteroids.⁹ Values are raised (typically >50 ppb) in patients with type 2 high inflammation independent of whether they are allergic or not.¹⁰ In addition, FeNO levels have prognostic value with high levels predicting an increased risk of exacerbation. Finally, the FeNO level has important pharmacodynamic properties as it is reduced after therapy with steroids (oral and inhaled) as well as therapies blocking the IL-13 pathway. The blood eosinophil count can be variable in patients with type 2 airway inflammation although it is usually $>0.3 \times 10^9/L$ whether the patient is allergic or nonallergic. This results from the increased airway and systemic production of IL-5.¹⁰ Raised blood eosinophil counts are also commonly seen in patients with nasal polyposis and atopic dermatitis so the demonstration of an eosinophilia is not necessarily a specific marker of eosinophilic airway inflammation. However, it is very likely to be a marker of eosinophilic airway inflammation when patients also have a raised FeNO. Anti-IL-5 and oral corticosteroids reduce the blood eosinophil count markedly, whereas anti-IL-13 increases it, at least in the short term, which is thought to be as a result of inhibition of migration of eosinophils from the vascular compartment to the airway mucosa^{10,11} (Figure 1). Dupilumab, which blocks IL-4 and IL-13 by binding to subunits of the IL-4 and IL-13 receptors, also causes an increase in the blood eosinophil count for the first few months of treatment, but the level then declines toward baseline, possibly as a result of reduced numbers of type 2 cytokine-producing cells in the airway mucosa.¹¹ FeNO is unaffected by anti-IL-5 treatment but is reduced markedly by anti-IL-13, anti-IL-13/4, and anti-IgE therapies (Figure 1).

In the current case, an FeNO of >50 ppb in combination with a blood eosinophil count $>0.3 \times 10^9/L$ makes eosinophilic type 2 high airway inflammation very likely.¹⁰ The fact that his allergen-specific IgE levels for dust mite are positive (although weakly so) and his serum IgE is high, coupled with his upper airway symptoms may suggest allergic eosinophilic asthma. Some non-asthma-related factors might be contributing to his symptoms and requirement for oral corticosteroid bursts, including obesity and nasal polyposis. It is very important to optimize management of these comorbid factors. However, the impact of this is unlikely to be large, and both discussants agree that he is a good candidate for biological treatment.

The choice of which biological treatment to give is difficult as we have no head-to-head data to guide treatment decisions. In the absence of such data, it is important to assess patient factors related to response to treatment, the ease of use of treatment, expense, and the degree to which treatment efficacy has been linked to predictive biomarkers.

Anti-IL-5 is the treatment of choice: pro (Dr. Ian D. Pavord)

Mepolizumab and reslizumab bind to and inactivate IL-5, thereby reducing the peripheral blood eosinophil count to very low levels (ie, cause an eosinopenia).¹⁸ Benralizumab does this by binding to the IL-5 receptor and, as a result of augmentation of eosinophil apoptosis via antibody-dependent cell-mediated cytotoxicity, may do so more completely and quickly than biological agents targeting the cytokine.¹⁹ The main clinical impact of anti-IL-5 treatment is to reduce the frequency of asthma exacerbations. Clinical trials have shown

	Effect on clinical measures						Effect on biomarkers		
	FEV ₁	Symptoms	Exac	PC ₂₀	OCS sparing	Comorbidities	BI eos	FeNO	IgE
Oral steroids	+	+	++	++	NA	++	↓↓↓	↓↓↓	↓
Anti-IL-5	+	+	++	0	++	+	↓↓↓	↔↔	↔↔
Anti-IL-13	+	+	+	?	0	0	↑	↓↓↓	↓
Anti-IL-4 / 13	++	++	++	?	++	++	↑	↓↓↓	↓↓↓
Anti-IgE	+	+	+	0	?	+	↓	↓↓↓	↓*
Anti-TSLP	++	++	++	?	?	?	↓	↓↓↓	↓

BI, blood; eos, eosinophils; Exac, exacerbations; *reduction in free IgE

FIGURE 1. Summary of the effect of different biological treatment options on clinical measures and biomarkers. Double symbols indicate a large effect; ? = no data; 0 = no effect. *FeNO*, Fraction of exhaled nitric oxide; *FEV₁*, forced expiratory volume in 1 second; *NA*, not available; *OCS*, oral corticosteroids; *PC₂₀*, airway responsiveness; *TSLP*, thymic stromal lymphopoietin.

TABLE I. Patient characteristics and clinical effects of different anti-IL-5 biological treatments in phase 3 trials

	Mepolizumab	Benralizumab		Reslizumab
	MENSA ¹²	CALIMA ¹³	SIROCCO ¹⁴	Castro et al ¹⁵
Dose	100 mg SC, 4 weekly	30 mg SC, for 3 doses then 30 mg SC, 8 weekly		3 mg/kg IV, 4 weekly
Blood eosinophils (cells/mm ³)	>150 and/or >300 in last year	>300	>300	>400
No. of patients	576	487	534	953
Placebo exacerbation rate (per year)	1.74	0.93	1.33	1.8-2.1
Percent reduction in exacerbations	53	28	51	50-59
Percent reduction in severe exacerbations	61	-23	63	31-34
Improvement in prebronchodilator FEV ₁ vs placebo (mL)	98	116	159	90-126
Reduction in ACQ vs placebo	0.44	0.1	0.29	0.2-0.27
Reduction in SGRQ vs placebo	7	NA	NA	NA
Median reduction in oral prednisone dose	50% vs 0% with placebo ¹⁶	75% vs 25% with placebo ¹⁷		
Injection site reactions	3 vs 9%	2 vs 2%	2 vs 2%	NA

ACQ, Asthma Control Questionnaire; *FEV₁*, forced expiratory volume in 1 second; *IV*, intravenous; *NA*, not available; *SC*, subcutaneous; *SGRQ*, St. George's Respiratory Questionnaire.

an approximately 50% reduction in the number of these episodes (Table I).^{12,18} Treatment also has oral corticosteroid sparing effects,¹⁶ and improvements in lung function, symptoms, and quality of life are often seen, particularly in patients with higher blood eosinophil counts (Table I).²⁰ Efficacy is apparent in patients with allergic and nonallergic asthma and is greater with high prior exacerbation frequency and blood eosinophil count (Figure 2).¹⁸ The presence and severity of symptoms or lung function abnormalities are not associated with treatment efficacy.

I believe that anti-IL-5 is the most attractive treatment option for our patient because eosinophilic airway inflammation appears to be the dominant treatable trait. I argue that in this situation anti-IL-5 treatments are likely to be highly effective. This factor together with the growing clinical experience with these agents and very reassuring safety profile makes it a more attractive option than other biologics. I will not make a case for one anti-IL-5 treatment over another as the clinical efficacy of this class of treatment has been reasonably consistent between studies (Table 1) and it is likely that they have very similar effects.

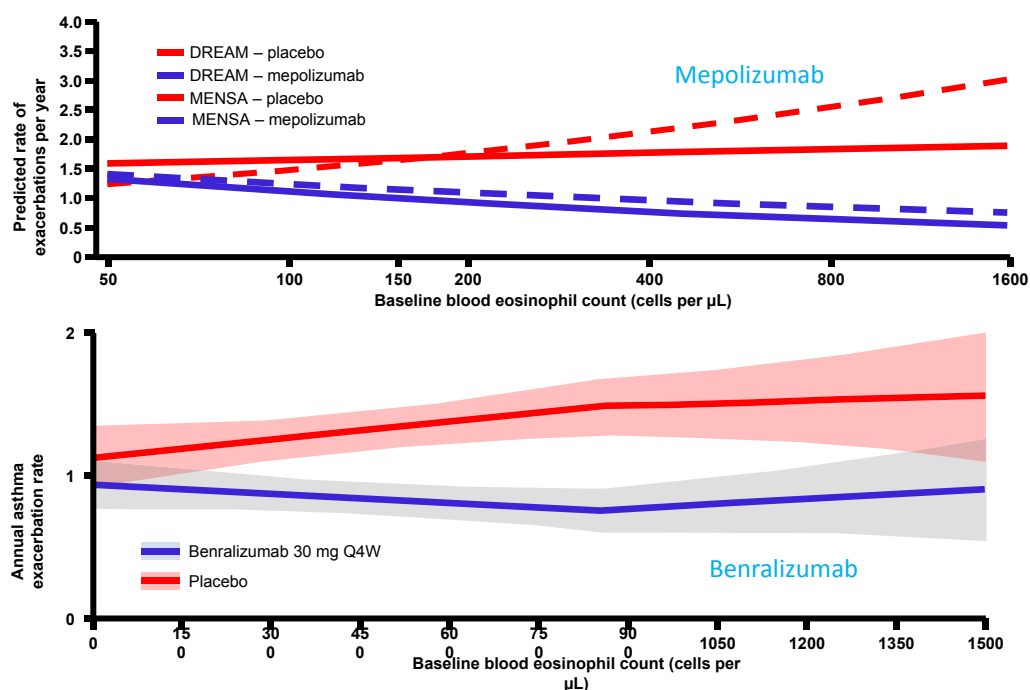


FIGURE 2. Exacerbation rates by blood eosinophil count with placebo, mepolizumab (top)^{12,18} and benralizumab (bottom).²¹

My view that eosinophilic airway inflammation is a dominant treatable trait in this patient is based on a suggestive biomarker profile and the presence of clinical problems linked to this trait. The blood eosinophil count and frequency of asthma exacerbations have both been shown to be independently associated with the response to anti-IL-5 treatment.^{20,21} Patients with active eosinophilic airway inflammation have recurrent exacerbations as the pathology is associated with nonbronchodilator responsive airflow limitation, which may be the result of mucus plugging of the airway.²² Patients with active eosinophilic airway inflammation typically notice a good clinical response to oral corticosteroids. This confirms that the clinical problem is reversible and suggests that depleting circulating eosinophils (which systemic but not ICS do) is likely to be an effective clinical strategy. The presence of nasal polyposis is also associated with eosinophilic airway inflammation, and this comorbidity has been linked to a better response to anti-IL-5.²³ Moreover, anti-IL-5 has been shown to be an effective treatment for nasal polyposis.²⁴

Figure 2 shows the relationship between blood eosinophil count and exacerbation frequency with placebo, mepolizumab, and benralizumab. Our patient's blood eosinophil count of $0.57 \times 10^9/\text{L}$ suggests that he will have a >80% reduction in exacerbations with treatment. A *post hoc* analysis of the phase 3 MENSA study¹² showed that in the 30% of patients recruited who had a baseline blood eosinophil count $>0.5 \times 10^9/\text{L}$, there was a 200 to 300 mL improvement in postbronchodilator FEV₁ and a 12-point improvement in the St George's Respiratory Questionnaire score. These large improvements in outcome would be difficult to achieve with other established treatment options.

What are the other treatment options? Until the advent of biological treatments 15 years ago, regular oral prednisolone was

the only option. These are an effective treatment in patients with persistent eosinophilic airway inflammation despite optimal ICS treatment. However, beneficial effects need to be weighed against the high potential for adverse effects. The most prevalent comorbidities linked to regular oral corticosteroid use in patients with severe asthma are dyspeptic disorders, obesity, psychiatric disorders, hypertension, hypercholesterolemia, osteoporosis and osteopenia, type 2 diabetes mellitus, cardiovascular disease, and sepsis/infection. These adverse effects are dose related across the range of doses of prednisone used in asthma (generally 10-15 mg daily), and they accumulate with time.²⁵ In many patients with severe oral corticosteroid-dependent asthma, they become responsible for very significant morbidity, and it can be difficult to tease out asthma and treatment-related morbidity in a patient who has been on long-term treatment. Both authors agree that the regular use of oral corticosteroid is no longer a viable treatment option in patients with severe eosinophilic asthma and we will not consider it further.

Omalizumab (anti-IgE) was licensed for use in severe allergic asthma 15 years ago. Demonstration of allergic sensitization to a perennial allergen is required for treatment, and serum IgE and weight are used to derive an individualized dose given subcutaneously every 2 to 4 weeks. Treatment has been shown to reduce eosinophil counts in sputum and bronchial biopsy.²⁶ Efficacy is particularly obvious in patients with type 2 high airway inflammation, and both blood eosinophils and FeNO are potential predictive biomarkers of the response to omalizumab,²⁷ although a real-world study did not confirm this finding, potentially because this study did not include a placebo group.^{27,28} Our patient may be eligible for treatment with omalizumab, but his serum allergen-specific IgE is only weakly positive to house dust mite and is negative for other aeroallergens. In addition, his high

serum IgE and weight mean that he would require a relatively high dose and 2-weekly dosing. This adds to the expense of treatment and makes it a less convenient treatment option than mepolizumab and benralizumab, which are delivered subcutaneously every 1 to 2 months in a fixed dose. Published data also suggest less impact on exacerbations, lung function, symptom scores, and quality of life than are seen with anti-IL-5 treatments.²⁹ The requirement to use biomarkers that are not related to treatment efficacy (ie, body weight, allergic status, and serum IgE) to select treatment restricts the availability of this treatment in severe asthma and makes it less possible to target treatment effectively. Finally, there is no validated, highly responsive, predictive biomarker of treatment response. Collectively, these problems suggest that anti-IL-5 would be a much better treatment option.

Dupilumab (anti-IL-4 receptor- α) has recently been approved for use in severe eosinophilic asthma. The large efficacy and broad effects on type 2 inflammation-related comorbidities such as nasal polyposis and atopic dermatitis make it an attractive treatment option for many patients. Efficacy against asthma exacerbations, FEV₁, symptom scores, and asthma-related quality of life scores is impressive in patients with evidence of type 2 high eosinophilic airway inflammation, particularly those patients with a raised blood eosinophil count and FeNO¹¹ (Figure 2). Although our patient is in this category, I believe that the requirement for 2-weekly dosing and the relative lack of long-term safety data makes it a less attractive treatment option than anti-IL-5.

Anti-IL-5 is the treatment of choice: con (Dr. Nicola A. Hanania)

Our patient's scenario is very common among many patients referred with severe asthma. Based on his clinical presentation, his comorbid conditions, and biomarker profile, the patient has type 2 high allergic eosinophilic asthma. I agree with my colleague that the prominent eosinophilia in his peripheral blood provides a strong rationale for the use of therapies targeting IL-5. However, although the eosinophil may be considered the most important inflammatory cell involved in the pathogenesis of type 2 high asthma and is the main target for anti-IL-5 biologic therapy, other cells, mediators, and cytokines also play important roles in other aspects of type 2 airway inflammation. It is also very important to consider the fact that a significant overlap of asthma phenotypes with type 2 severe asthma exists and therefore the role of eosinophils in such situations and in each individual may be variable.

In addition to identifying the phenotype of severe asthma, other factors influence the choice of biologic therapy in real life. These include their route and frequency of administration, site of administration (home or clinic setting), cost and insurance coverage, safety, and presence of comorbidities. It is important to keep in mind that none of the biologics currently available to treat this type of asthma is able to completely abolish the risk of future exacerbations of asthma, and thus switching to other options or using more than one may be justified in some situations. In addition, the choice of a biologic should be a shared decision with the patient and/or caregiver.

The rationale for targeting IL-4 receptor- α

Dupilumab is a fully human monoclonal antibody to the alpha subunit of the IL-4 receptor that inhibits both IL-4 and IL-13 signaling via the IL-4 receptor- α (anti-IL4R) and is a strong

alternative option to an anti-IL-5 in the case described. IL-4 and IL-13 are type 2 cytokines implicated in the pathogenesis of asthma. They share structural similarities as well as a shared functional receptor complex (IL-4R α /IL-13R α 1). IL-4 is key to the differentiation of CD4⁺ lymphocytes and the production of IgE. IL-13 is involved in the development of airway hyper-responsiveness, mucus production, and subepithelial fibrosis. Although monoclonal antibodies targeting either IL-4 or IL-13 cytokines individually have failed to demonstrate significant clinical benefits, inhibition of the IL-4/IL-13 signaling cascades may disrupt a broader T2 inflammatory response and indeed may be more efficacious than other monoclonal antibodies that selectively inhibit eosinophil proliferation and activity via blockage of the IL-5 pathway. Furthermore, because IL-4 and IL-13 are cytokines that are key drivers of other type 2 comorbidities, such as atopic dermatitis, asthma, allergic rhinitis, nasal polyps, and food allergies, dupilumab has a potential advantage in such situations. Indeed, it has shown efficacy in many of these type 2 comorbidities such as nasal polyposis³⁰ and atopic dermatitis³¹ (Figure 1).

In a large, phase 3 LIBERTY QUEST trial, patients with moderate-to-severe asthma with history of asthma exacerbation (n = 1902) received subcutaneous dupilumab 200 to 300 mg every 2 weeks or matched placebo for 52 weeks.¹¹ Results showed that severe asthma exacerbations were reduced by 47% in the treatment groups compared with placebo. This difference between the 2 groups was enhanced in subgroup analysis to 65% in patients with uncontrolled asthma and blood eosinophil count ≥ 300 eosinophils/ μ L and FeNO > 25 ppb. In contrast, a poorer response was observed in patients with ≤ 150 eosinophils/ μ L and FeNO < 25 ppb. In addition, at 12 weeks, FEV₁ increased by 0.32 L in the treatment group compared with 0.14 L in the placebo group. In this study, 4% of patients on dupilumab had a transient increase in the level of eosinophils compared with 0.6% of patients in the placebo group. Furthermore, treatment with dupilumab compared with placebo significantly reduced the concentrations of FeNO and suppressed systemic levels of serum total IgE, plasma eotaxin-3, and serum periostin.

In another study that enrolled patients with severe asthma who were dependent on oral corticosteroid, Rabe et al³² randomly assigned 210 patients to receive dupilumab 300 mg or placebo every 2 weeks for 24 weeks. Oral corticosteroids were initially adjusted before randomization for symptom control and then adjusted downward from week 4 to week 20, with stable dose during the last 4 weeks. Primary outcome results showed that oral corticosteroid dose was decreased 70% in the dupilumab group compared with 42% in the placebo group, and nearly 50% of patients in the treatment group completely discontinued oral corticosteroid use compared with 25% in the placebo group. Secondary outcome results showed that, despite a greater reduction in oral corticosteroid dose in the treatment group, the rate of asthma exacerbations was 59% lower and FEV₁ higher by 0.22 L than placebo. These results were also more pronounced for patients with eosinophil counts ≥ 300 cells/ μ L. Treatment was well tolerated with side effects including injection site reaction and more transient blood eosinophilia in the treatment group.

In summary, dupilumab is efficacious and safe in patients with type 2 high asthma such as the case of our patient. It is administered at home every 2 weeks, which may be an advantage to some patients who are inconvenienced by frequent visits to their health provider clinics.

The rationale for targeting IgE

Omalizumab is a humanized monoclonal antibody that targets IgE that has now been approved for the treatment of moderate-to-severe allergic asthma in patients ≥ 6 years of age for 15 years. To be eligible for this biologic, the patient should demonstrate poor control on conventional asthma medications and demonstrate sensitization to one of the perennial allergens either on skin testing or *in vitro* serum test showing an elevated allergen-specific IgE to 1 or more perennial aeroallergens. In addition, the patient should have elevated levels of total IgE that is used in addition to the weight to calculate the dose and frequency (either once a month or every 2 weeks) of subcutaneous administration of the medication. The efficacy and long-term safety of omalizumab has been extensively studied in both clinical trials and real-world observational studies.³³ Omalizumab reduced the annual relative risk of asthma exacerbation by 38% and the risk of emergency visits by 47% compared with controls, according to pooled data from 7 randomized studies ($P < .0001$ vs control for both comparisons; $N = 4308$ patients). Data from clinical trials suggest that patients who have higher levels of T2 inflammation biomarkers, including eosinophil count and FeNO levels, are more likely to respond to omalizumab therapy,²⁷ although more recent data from real-world studies suggest that levels of eosinophils are not predictors of reduction in exacerbations seen with omalizumab, potentially because of the absence of a placebo group.²⁸

Our patient described above does seem to suffer from allergic asthma based on his high level of serum IgE, upper airway symptoms, and positive allergen-specific IgE for dust mite (although weak). One could build a rationale for starting omalizumab in his case. However, because his IgE is significantly high and the dose is determined by the level of IgE and weight, he will most likely require in-clinic administration every 2 weeks, which may not be the most convenient option compared with a monthly injection in the clinic or every 2 weeks at home.

CONCLUSIONS

Five biologics that target type 2 high asthma are now available for clinical use. However, there has been no direct comparison between these biologics. Furthermore, there remains a significant heterogeneity and overlap between the different phenotypes of type 2 high asthma. The presence of high blood eosinophils can be encountered in both allergic and nonallergic asthma. Targeting one cytokine versus another should be based on the better understanding of underlying pathophysiologic mechanisms of the disease and using appropriate biomarkers. Targeting IL-5 is a reasonable option in patients with severe eosinophilic asthma especially in patients with multiple exacerbations and eosinophilic comorbidities such as nasal polyps. Targeting the common subunit of the IL4 and IL13 receptors has the advantage of blocking multiple other pathways and, although a high blood eosinophil level is still a predictor of response, other predictors, including high FeNO levels, oral steroid dependence, and presence of T2 comorbidities such as atopic dermatitis and nasal polyposis, may also influence the choice of this biologic (Figure 1). For patients with allergic severe asthma, targeting IgE should always be entertained whether blood eosinophils are elevated or not. In the event of overlapping phenotypes and when more

than 1 choice is possible, other factors such as patient's input, insurance coverage, frequency, and route of administration should be considered.

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