

Rostrum

Pragmatic Clinical Perspective on Biologics for Severe Refractory Type 2 Asthma

Rory Chan, MBChB, Chris RuiWen Kuo, MBChB, and Brian Lipworth, MD *Dundee, Scotland, United Kingdom*

Patients with severe refractory asthma present a challenging clinical conundrum for practicing clinicians. Biologics that target key mediators in the type 2 inflammation cascade, including IL-4, IL-5, IL-13, and IgE, can be effective strategies for these patients. However, with various biologics available, choosing the optimal one for a particular patient becomes a nuanced decision. We propose a pragmatic algorithm that identifies the optimal biologic class for patients who have specific type 2 disease endotypes. Patients with eosinophilic endotypes fare well with anti-IL-5(α) medications, comprising mepolizumab, benralizumab, and reslizumab because they have been shown to reduce exacerbations in severe eosinophilic asthma by approximately 50%. In patients with fractional exhaled nitric oxide–high endotypes, anti-IL-4/ α such as dupilumab is deemed to be most effective and has demonstrated a 47% reduction in asthma exacerbations. For patients with severe uncontrolled allergic asthma, anti-IgE (omalizumab) is effective and has been shown to confer a 25% reduction in asthma exacerbations. Type 2 comorbidities including chronic rhinosinusitis with nasal polyps, atopic dermatitis, chronic idiopathic urticaria, and eosinophilic esophagitis are important to bear in mind before the prescription of biologics. Further head-to-head studies are indicated to compare biologics in patients with mixed endotypes according to peripheral blood eosinophils, fractional exhaled nitric oxide, and allergic status. The evidence strongly supports endotype-driven prescribing of

biologics to achieve clinically relevant outcomes in severe refractory asthma and related comorbidities. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Allergy; Asthma; Benralizumab; Dupilumab; Eosinophils; FENO; Mepolizumab; Omalizumab; Type 2 inflammation

INTRODUCTION

Patients with severe uncontrolled asthma present a challenging clinical conundrum for practicing clinicians because of their requirement for extensive diagnostic evaluation, high consumption of health care resources, and heavy symptom burden.¹ The Global INitiative for Asthma defines severe asthma as uncontrolled despite adherence with maximal optimized therapy (step 4 or 5) and treatment of contributory factors, or that worsens when high-dose treatment is decreased, affecting an estimated 3.7% of patients with asthma.

Type 2 (T2) inflammation asthma is primarily driven by various cytokines including IL-4, IL-5, and IL-13, and these in turn regulate the production of quantifiable biomarkers, namely, IgE, eosinophils, and fractional exhaled nitric oxide (FENO) (Figure 1). It is thought that despite optimized inhaled corticosteroid (ICS) therapy, many patients with asthma have persistent airway T2 inflammation, with this cohort of patients being older and having more severe disease.²

This article is not intended to be an exhaustive systematic review, nor will it explore non-T2 asthma and the follow-up decisions surrounding biological therapies such as stopping and switching decisions, because these have already been covered in detail elsewhere.³⁻⁶ Instead, its purpose is to provide a focused pragmatic real-life practice guide for physicians based on current available guidance on biological therapies with particular reference to common T2 endotypes. This is admittedly a challenging feat because most of the evidence is based on trials that were restricted to a specific endotype appropriate to the molecular target of the treatment and/or had inconsistent eligibility criteria that excluded certain populations of interest.⁷

It is always prudent to confirm the original asthma diagnosis.⁸ Second, optimization of inhaler technique, medication adherence, and management of comorbidities, modifiable risk factors, and psychosocial circumstances is mandatory. For severe uncontrolled asthma, discussion at a severe asthma multidisciplinary team (MDT) should occur because there is growing evidence that this significantly reduces asthma-related hospital admissions and hospital days.⁹ Indeed, our Tayside severe asthma MDT has meetings on a weekly basis.

In patients with T2 asthma, mAbs targeting IgE, IL-4 receptor alpha (IL-4 α), and IL-5 are attractive therapeutic options

Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Dundee, Scotland, United Kingdom

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Corresponding author: Brian Lipworth, MD, Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, UK. E-mail: b.j.lipworth@dundee.ac.uk.

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Abbreviations used

BENRA- Benralizumab
CRSwNP- Chronic rhinosinusitis with nasal polyposis
DUPIL- Dupilumab
FENO- Fractional exhaled nitric oxide
ICS- Inhaled corticosteroid
IL-4 α - IL-4 receptor alpha
IL-5(α)- IL-5 (receptor alpha)
MCID- Minimum clinically important difference
MDT- Multidisciplinary team
MEPO- Mepolizumab
OCS- Oral corticosteroid
OMAL- Omalizumab
PBE- Peripheral blood eosinophil
ppb- Parts per billion
RESLI- Reslizumab
T2- Type 2

because they reduce exacerbation rate and oral corticosteroid (OCS) dose requirement, as well as improve quality of life, pulmonary function, and symptom control to varying degrees (Table 1).¹⁰⁻¹² This begs the question of which biologic is best suited to a patient with asthma on the basis of their particular disease endotype. Peripheral blood eosinophils (PBEs), FENO, and allergic status are the most commonly used T2 biomarkers in clinical practice for assessing asthma and assisting in generating specialist decisions. Here, we propose a simplified clinical algorithm to assist practicing clinicians in determining the optimal biologic depending on the specific combination of T2 biomarkers in patients presenting with severe uncontrolled asthma based on common endotypes (Figures 2 and 3).

There is only 1 study in which it was possible to estimate the relative prevalence of different T2 endotypes because enrollment was independent of biomarkers. Here, the relative prevalence of endotypes was shown to be 42% for PBE greater than or equal to 150/ μ L, FENO greater than or equal to 25 parts per billion (ppb); 30% in PBE greater than or equal to 150/ μ L, FENO less than 25 ppb; and 9% in PBE less than 150/ μ L, FENO greater than or equal to 25 ppb, while the remaining 19% had PBE less than 150/ μ L and FENO less than 25 ppb.¹³ In essence, a large proportion (72%) of patients with severe asthma appear to have an eosinophilic endotype, albeit using a rather low cutoff point of greater than or equal to 150/ μ L. This breakdown did not factor in the presence or absence of an allergic endotype. Furthermore, a recent retrospective observational cohort analysis demonstrated that 34% of patients with severe asthma have an eosinophilic endotype using the more clinically relevant cutoff point of 300/ μ L.¹⁴

Allergic asthma (defined as at least 1 positive allergen-specific test result) is widely regarded as the most common endotype with a prevalence of around 56%.¹⁵ The Severe Asthma Research Program study estimated that the proportion of patients with severe asthma with a negative skin prick test result varied between 17% and 34%,¹⁶ in keeping with the Unbiased BIOmarkers in PREdiction of respiratory disease outcomes (U-BIOPRED) cohort's approximation.¹⁷

For the purposes of this review article, allergy in keeping with the omalizumab label indication is defined as a total serum IgE level greater than or equal to 30 IU/mL and 1 or more perennial aeroallergen-specific IgE level greater than or equal to 0.35 kU/L

at baseline.¹⁸ However, in real-life clinical practice, our Tayside severe asthma MDT meeting would only designate a patient with a total serum IgE level greater than or equal to 100 IU/mL and 2 or more aeroallergen-specific IgE levels greater than or equal to 0.35 kU/L or positive skin prick test results at baseline to be a clinically relevant allergic endotype.¹⁹ This definition is based on our regional experience that has been pragmatically adapted from clinical practice, but we duly appreciate that most of the studies and evidence base use the former criteria for defining allergy. Similarly, we would classify patients into an eosinophilic endotype only if their PBE count exceeded 300/ μ L, ideally over 2 different time points in the preceding 6 months. Clinicians should recognize that significant variability in blood eosinophils in patients with severe asthma exists, further stressing the importance of repeat measurements over time for the appropriate allocation of therapeutic interventions.²⁰ At this juncture, it is also important to point out that the presence of raised FENO is highly dependent on adherence to ICS therapy or the use of OCSs, both of which suppress FENO. For the purpose of this review, we will adopt a pragmatic cutoff of greater than or equal to 25 ppb while taking ICS to denote a patient with a high FENO endotype.

EOSINOPHILIC ENDOTYPES

A recent Cochrane review indicates that the 3 anti-IL-5 (receptor α) (IL-5(α)) agents—mepolizumab (MEPO), benralizumab (BENRA), and reslizumab (RESLI)—reduce rates of clinically significant asthma exacerbations by approximately 50% in patients with severe eosinophilic asthma on standard of care.²¹ Furthermore, they were shown to produce a small (80-110 mL) but statistically significant improvement in FEV₁, although it is perhaps worth noting that the minimum clinically important difference (MCID) is traditionally considered to be 230 mL.²² Patients also experienced modest improvements in their asthma control questionnaire and asthma quality of life questionnaire scores, but these were both also below the conventional MCID of 0.5.²³ In the United Kingdom, the National Institute for Health and Care Excellence guidance for MEPO and BENRA suggest at least 4 severe exacerbations needing systemic steroids along with PBE greater than or equal to 300 cells/ μ L in the past year or continuous OCS requirement over the previous 6 months. RESLI and BENRA are also indicated in the United Kingdom for patients with PBE greater than or equal to 400/ μ L and at least 3 exacerbations in the past 12 months.

The more common endotypes discussed in this article are depicted in Figure 3: PBE-high, FENO-high, allergic (endotype 1); PBE-high, FENO-high, nonallergic (endotype 2); PBE-high, FENO-low, nonallergic (endotype 3); and PBE-low, FENO-high, allergic (endotype 4). Patients with elevated PBE comprising endotypes 1 to 3 likely experience most benefit from anti-IL-5(α) therapy because eosinophilic proliferation, maturation, and survival are governed by IL-5.²⁴ Exploratory modeling of baseline characteristics of patients in phase 3 studies support substantial reductions in the rate of severe exacerbations with MEPO in patients with higher PBE counts.^{12,25} Likewise, higher PBE counts predicted response in patients with severe eosinophilic asthma treated with RESLI or BENRA.^{26,27} Moreover, real-world MEPO data suggest more impressive results compared with randomized controlled trials on reduction in exacerbations, hospitalizations along with an improvement in asthma control

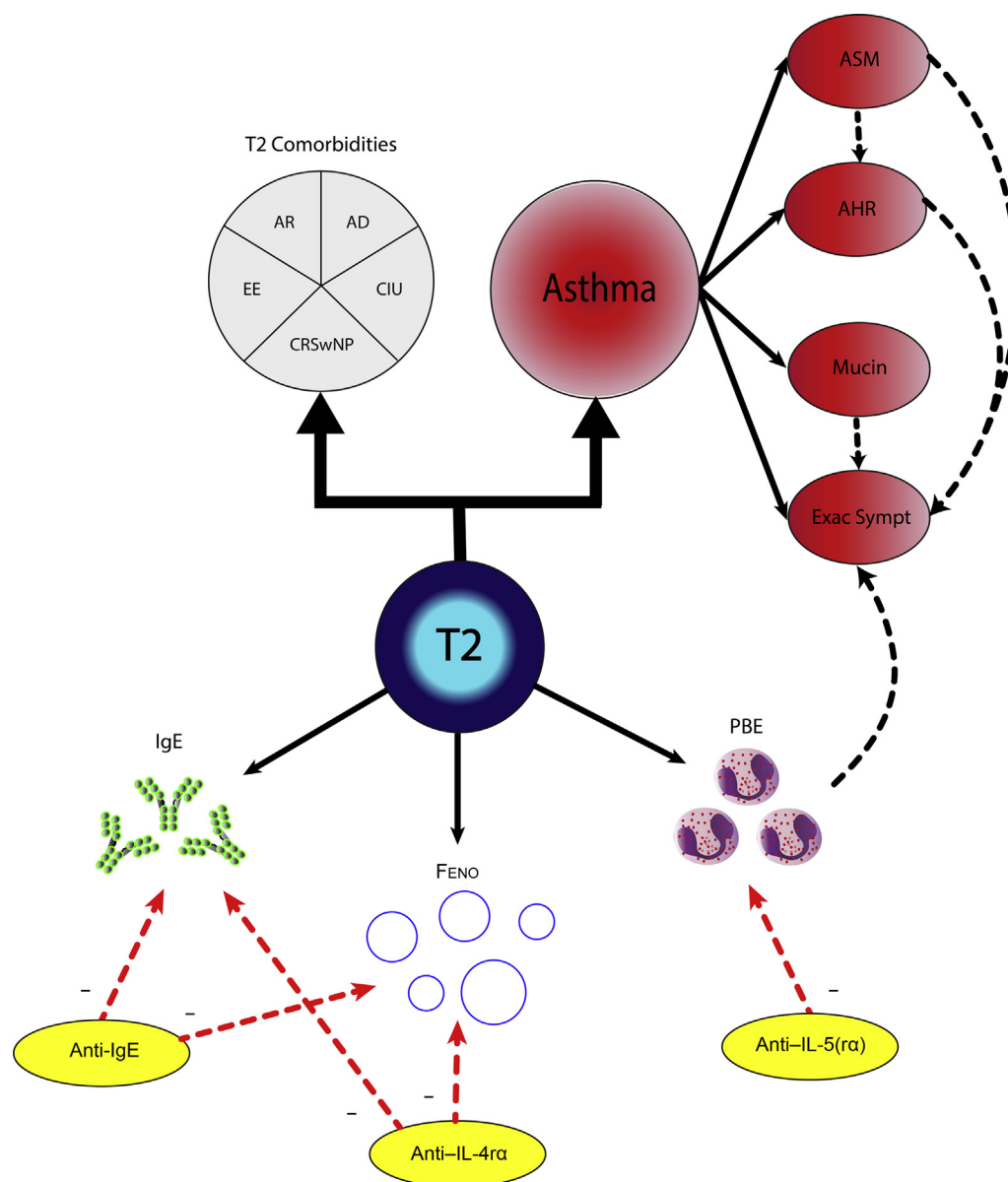


FIGURE 1. Activation of T2 inflammation elevates levels of IgE, FENO, and PBE. These biomarkers are targeted by various biological therapies as depicted. Relationship between T2 inflammation with asthma and relevant comorbidities shown. *AD*, Atopic dermatitis; *AHR*, airway hyperresponsiveness; *AR*, allergic rhinitis; *ASM*, airway smooth muscle; *CIU*, chronic idiopathic urticaria; *EE*, eosinophilic esophagitis; *Exac*, exacerbations; *Sympt*, symptoms.

questionnaire score of 2.0 points at 6 months, which far exceeds the MCID of 0.5, although the placebo effect should be considered when interpreting these data.²⁸

Therefore, for any of the eosinophilic endotypes defined by PBE greater than or equal to 300/ μ L, we would generally propose anti-IL-5(r α) therapy as first-line unless there was a specific reason otherwise (Figure 2). This is based on the current evidence suggesting a higher exacerbation risk reduction with either anti-IL-5(r α) (50%) or anti-IL-4 α (47%) versus anti-IgE therapy (25%). Our tentative position here is that until there is good evidence showing reductions in airway eosinophilia from sputum or bronchial biopsy with anti-IL-4 α , we would proffer a degree of caution in advocating dupilumab as equal first-line

therapy with anti-IL-5(r α) for such patients despite similar reductions in exacerbations. The following discussion delves deeper into the individual eosinophilic endotypes and implications for biologic therapy.

For endotype 1, any of the mAbs directed against IL-5(r α), IL-4 α , or IgE might in theory be considered equivalent first-line options. However, currently available evidence seems to suggest a greater decrease in asthma exacerbation rates and OCS dose requirement in patients treated with anti-IL-5(r α) or anti-IL-4 α compared with those on anti-IgE.^{11,21,29} Therefore, in the absence of any defining comorbidities, our MDT would recommend anti-IL-5(r α) or anti-IL-4 α as first line, with anti-IgE as second line in patients with endotype 1 (Figure 2). In real-

TABLE I. Effects of biologics on key patient outcomes and T2 inflammatory biomarkers

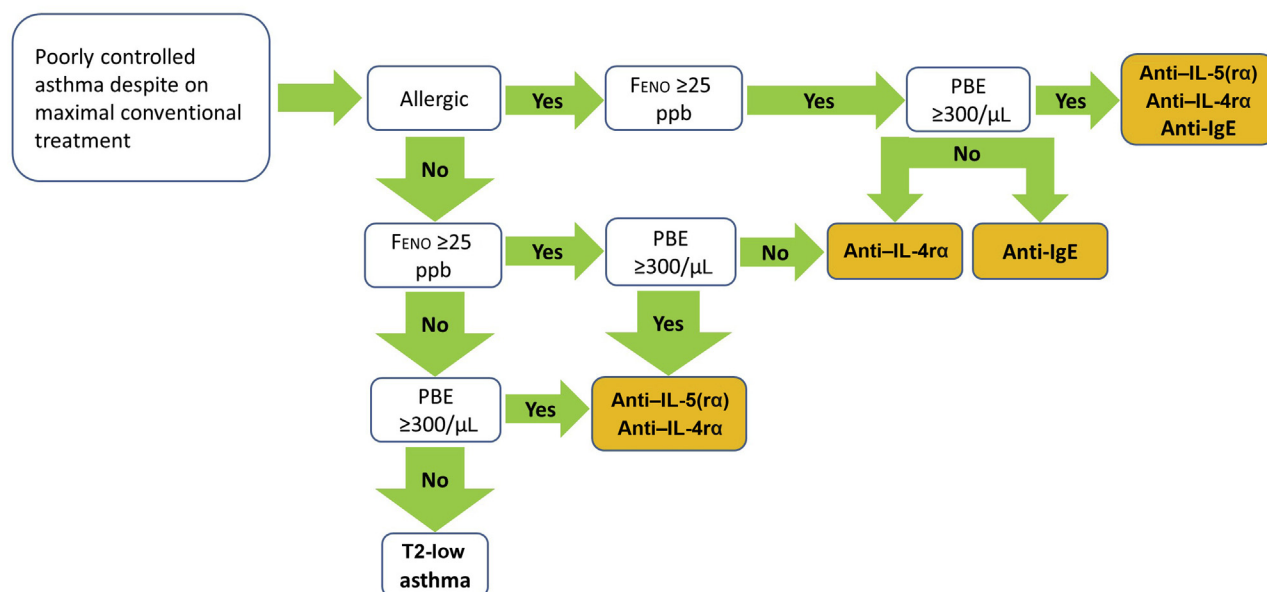
MAb	Exac	FEV ₁	ACQ/QOL	OCS sparing	PBE	IgE	FENO
Anti-IL-5	+++	+	+	++	+++	—	—
Anti-IL-4 α	+++	++	+	++	—	++	++
Anti-IgE	++	+	+	+/-*	+	+/-†	+

ACQ, Asthma control questionnaire; Exac, exacerbations; QOL, quality of life.

No. of “+” symbols denotes the degree of positive effect.

*Evidence for OCS-sparing effect of omalizumab is equivocal.

†Omalizumab paradoxically elevates bound total and specific IgE levels but reduces free IgE.

**FIGURE 2.** Proposed pragmatic clinical decision-making algorithm for the management of uncontrolled severe refractory T2 asthma in relation to the current available biologics.

life clinical practice, the choice of biologic in patients with this endotype would rest on physician experience and preference, informed patient choice, cost, and presence of any other relevant comorbidities, which are explored in more detail later. For example, patients leading a busy life might prefer the convenience of taking maintenance therapy with BENRA every 8 weeks rather than dupilumab (DUPI) every 2 weeks.

Similarly, for endotype 2, evidence seems to support that either anti-IL-5(α) or anti-IL-4 α could be considered first-line therapy. For instance, pooled analysis of the BENRA trials revealed that it maintains its effect on exacerbation reduction and lung function improvement for patients with severe eosinophilic asthma irrespective of allergic status.³⁰ It is worth noting that in this analysis, allergy was defined with a perhaps more clinically relevant serum total IgE cutoff of greater than or equal to 150 kU/L.

To determine what actually constitutes clinically relevant eosinophilia, closer examination of a secondary analysis of the pivotal BENRA trials reveals a so-called sweet spot for exacerbation rate reduction and FEV₁ improvement relative to placebo that appears to occur around PBE greater than or equal to 300/ μ L³¹ when plotted as a continuous variable. For instance, in the comparison between BENRA 30 mg every 8 weeks and placebo, patients with PBE greater than or equal to 300/ μ L and greater

than or equal to 3 exacerbations in the previous year experienced a relative exacerbation rate reduction of 55% and FEV₁ improvement of 252 mL (above MCID of 230 mL).

In a post hoc analysis of the pivotal DUPI trials, using 200 mg every 2 weeks, exacerbations were reduced by 68% in patients with PBE greater than or equal to 150/ μ L and FENO greater than or equal to 25 ppb as opposed to 33% in patients with PBE greater than or equal to 150/ μ L and FENO less than 25 ppb.³² This infers that DUPI could potentially be more effective in patients with endotypes 1 and 2 with high FENO rather than in those with endotype 3 with low FENO. Unfortunately, no data were available for DUPI stratified at PBE greater than or equal to 300/ μ L according to FENO greater than or equal to 25 ppb versus less than 25 ppb, which in our opinion would have been more informative. Prospective head-to-head trials would be required to assess whether anti-IL-4 α or anti-IL-5(α) is a more effective first-line treatment for patients with both FENO greater than or equal to 25 ppb and PBE greater than or equal to 300/ μ L in endotypes 1 and 2. In the same post hoc analysis for patients on MEPO with PBE greater than or equal to 150/ μ L, exacerbation rate was reduced by 62% for FENO greater than or equal to 25 ppb but only 36% for less than 25 ppb.³² MEPO also resulted in modest FEV₁ improvements (122 mL for $\geq$ 25 ppb and 101 mL for <25 ppb) in patients with PBE greater than or equal to 150/

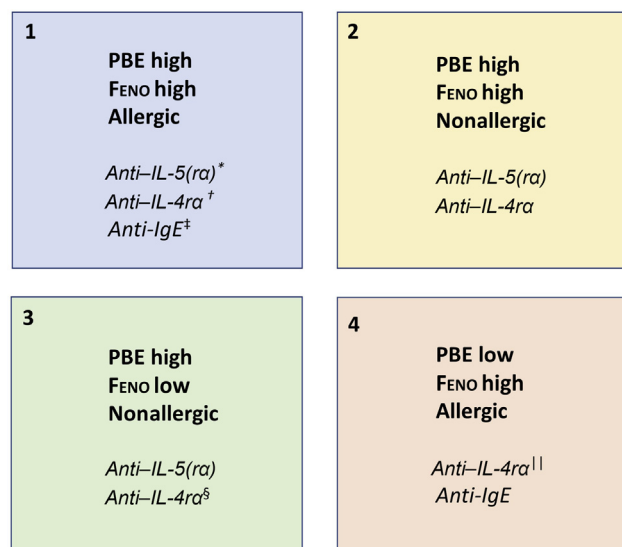


FIGURE 3. Commonly occurring patterns of T2 inflammation in relation to choosing optimal biological therapy for severe uncontrolled asthma. Numbering corresponds to the various endotypes referred to in the text. *Preferred for concomitant eosinophilic esophagitis. †Preferred for concomitant chronic rhinosinusitis with nasal polyps or concomitant atopic dermatitis. ‡Preferred for concomitant chronic idiopathic urticaria. §Comparable efficacy of anti-IL-5(α) and anti-IL-4 α if PBE greater than or equal to 150/ μ L. ||Anti-IL-4 α preferred over anti-IgE due to greater exacerbation rate reduction. Anti-IL-5(α) preferred over anti-IL-4 α for patients with endotypes 1, 2, and 3 if PBE greater than or equal to 1000/ μ L.

μ L, albeit this was below the MCID.²² For patients on MEPO with PBE greater than or equal to 300/ μ L, the exacerbation rate reduction was 62% for FENO greater than or equal to 25 ppb and 53% for less than 25 ppb, in keeping with the lack of effect of IL-5 signaling on FENO.

For endotype 3, that is, PBE-high, FENO-low, and nonallergic, one might not expect patients to experience significant benefit from anti-IL-4 α therapy because it acts on both IL-4 and IL-13, the latter of which regulates FENO.³³ However, the aforementioned data³² still implied a 33% reduction in exacerbation rate, which might be clinically worthwhile. A key limitation here is the absence of available data for patients on DUPI with PBE greater than or equal to 300/ μ L according to FENO greater than or equal to or less than 25 ppb. Nonetheless, in the primary analysis,¹¹ DUPI 300 mg every 2 weeks produced a 67% exacerbation reduction in those with PBE greater than or equal to 300/ μ L irrespective of FENO, perhaps supporting a recommendation that both anti-IL-5(α) and anti-IL-4 α therapy may be considered as suitable first-line options for endotypes 1, 2, and 3.

Despite the promising results seen with anti-IL-5(α) therapy, recent data suggest that 43% of patients who fulfill the current approved treatment criteria are so-called suboptimal responders.³⁴ Sputum analysis in this subset of patients suggests a possible underlying autoimmune-mediated etiology related to the presence of antieosinophil peroxidase IgG, with a caveat that further evaluation is required before this can be considered as part of routine practice.

FENO-HIGH ENDOTYPES

In addition to endotypes 1 and 2, the FENO-high endotype includes patients with the PBE-low, FENO-high, allergic endotype 4. Patients with either of these 3 FENO-high endotypes would in theory be expected to have a favorable response to anti-IL-4 α therapy because FENO is closely regulated by IL-13³³; however, the results of the pivotal trials with tralokinumab and lebrikizumab, which block IL-13 signaling, were equivocal.^{35,36} This in turn suggests that blocking signaling of both IL-4 and IL-13 with dupilumab is required to improve asthma control.³⁷

In the post hoc analysis of the pivotal DUPI trials, exacerbations were reduced by 39% in patients with PBE less than 150/ μ L and FENO greater than or equal to 25 ppb.³² Although not statistically significant due to small sample size, this finding contrasted the absence of therapeutic effect seen with MEPO in this endotype where there was only a 6% reduction. Intriguingly, in an exploratory post hoc analysis of DUPI 300 mg every 2 weeks¹¹ for patients with PBE greater than or equal to 150/ μ L and FENO less than 25 ppb, there appeared to be discordance in terms of a significant reduction in exacerbations but no improvement in FEV₁ relative to placebo, whereas in patients with PBE less than 150/ μ L and FENO greater than or equal to 25 ppb, effects of DUPI were concordant on both exacerbations and FEV₁. In another post hoc analysis, DUPI showed equivalent efficacy in allergic and nonallergic asthma,¹⁸ although the definition of allergy was tenuously based on total serum IgE greater than or equal to 30 IU/mL and 1 or more perennial aeroallergen-specific IgE greater than or equal to 0.35 kU/L. Notably, no comparison of response was made across a range of IgE cutoff points. Nevertheless, anti-IL-4 α would be a suitable option for patients with endotype 4 as we appreciate that most of the studies commonly define allergy using these criteria. Taken together this clearly emphasizes the importance of measuring both PBE and FENO in severe asthma before making an informed decision regarding tailored biologic therapy.

Although there are no head-to-head trials comparing various biologics for the treatment of common T2 asthma endotypes, a recent indirect treatment comparison using 14 randomized controlled trials demonstrated that DUPI was associated with a significantly greater reduction in annualized severe asthma exacerbation rate (26% greater reduction vs omalizumab [OMAL] and 28%-54% vs anti-IL-5(α)).³⁸ A 60 to 140 mL improvement in FEV₁ was also seen with DUPI versus the other biologics although this is below the MCID of 230 mL.

ALLERGIC ENDOTYPES

Anti-IgE is a viable alternative for patients with endotypes 1 and 4 as a 2014 Cochrane review evaluating 25 randomized trials using OMAL demonstrated a 25% asthma exacerbation reduction as well as a significant ICS-sparing effect.²⁹ Humbert et al³⁹ showed in a retrospective real-life analysis that OMAL is an effective treatment option for severe allergic asthma irrespective of blood eosinophil count.³⁹ Furthermore, post hoc analysis of an OMAL randomized controlled trial showed that lower baseline IgE concentrations were associated with a smaller benefit in exacerbation reduction and improvement in quality of life.⁴⁰ In another prospective placebo-controlled trial, OMAL produced 39% greater relative exacerbation reduction in patients with FENO greater than or equal to 19.5 ppb versus less than 19.5 ppb and a 23% greater reduction comparing PBE greater than or

equal to 260/ μ L versus less than 260/ μ L.⁴¹ Although anti-IgE therapy is a suitable treatment for patients with endotypes 1 and 4, it may be desirable to consider the other biologics first on the basis of current evidence.

We wish to highlight that the PBE-low, FENO-low, allergic endotype has deliberately been omitted from Figure 3 because in our clinical experience this is an uncommon clinical pattern. We would advocate an interval repeat measurement of PBE in such cases to exclude a false-negative result.

TREATING T2 COMORBIDITIES

When choosing the optimal biologic, the patient's T2 endotype should be a key driver of clinical decision making (Figures 2 and 3). However, prescribers should also take preexisting comorbidities into account because there is a potential opportunity to treat 2 correlated T2 conditions. For example, MEPO is associated with marked decreases in PBE, esophageal eosinophilia, and improved clinical outcomes in patients with eosinophilic esophagitis, although it does not have a licensed indication per se.⁴² DUPI also improves clinical outcomes in eosinophilic esophagitis and reduces submucosal eosinophilia.⁴³ Another example would be coexistent chronic rhinosinusitis with nasal polyposis (CRSwNP), which is associated with a better antiasthmatic response to anti-IL-5⁴⁴ but does not appear to have an impact on nasal polyps per se at least using MEPO at licensed subcutaneous doses.⁴⁵ This reiterates the importance of close monitoring of patients with dual pathology and frequent liaison between different specialties in the event of a disconnected response such as improvement in asthma but not CRSwNP. Patients with CRSwNP tend to have a higher PBE, which probably accounts for the enhanced antiasthmatic response to anti-IL-5 in the presence of this comorbidity. Because anti-IL-4 α has proven efficacy in CRSwNP,⁴⁶ it seems logical to use DUPI for patients with severe asthma especially where concomitant refractory upper airway disease is also present. If PBE is elevated above 1000/ μ L along with other pertinent clinical features, then antilysozyme and anti-proteinase-3 antibodies should be measured to refute a diagnosis of eosinophilic granulomatosis with polyangiitis, particularly if any other clinical features are present. Higher than currently licensed doses of MEPO have been shown to improve disease control in eosinophilic granulomatosis with polyangiitis,⁴⁷ and clinical trials are undergoing to evaluate BENRA (NCT04157348).

For patients with severe T2 asthma and concomitant atopic dermatitis, anti-IL-4 α is a logical option because it results in significant amelioration in disease severity and symptom burden in atopic dermatitis.⁴⁸ Finally, allergic asthmatic patients with concomitant refractory chronic idiopathic urticaria should be trialed with anti-IgE therapy first because this has proven efficacy in both conditions.^{10,49}

FURTHER CLINICAL CONSIDERATIONS

When determining T2 asthma endotype and making practical decisions on commencing biological therapies, we suggest using pragmatic FENO and PBE thresholds of greater than or equal to 25 ppb and greater than or equal to 300/ μ L, respectively. Guideline recommendations for ICS-naïve patients advocate that FENO more than 50 ppb can be used to indicate eosinophilic inflammation and corticosteroid responsiveness.⁵⁰ Nevertheless, we feel that these cutoff points should be lower in patients taking ICS, for instance, using FENO greater than or equal to 25 ppb.⁵¹

Caution should also be exercised when interpreting FENO levels in the presence of comorbidities. For example, a prospective study of patients with severe asthma confirmed elevated FENO and PBE values in patients with nasal polyposis compared with those without.⁵²

For anti-IL-5(α) in the United Kingdom, the National Institute for Health and Care Excellence proposes an optimal PBE threshold of greater than or equal to 300/ μ L in keeping with the pooled analysis from the MEPO and BENRA trials^{31,53} where PBE has been plotted as a continuous variable for exacerbation reductions. The exception to this would be for patients who are taking maintenance OCS, which markedly suppress PBE.

In patients with raised FENO, clinicians should first of all consider treatment adherence or inhaler technique because low doses of ICSs will usually suppress levels.^{54,55}

A further clinical consideration is the relationship between peripheral blood and sputum eosinophil count, with more data becoming available to cast doubt on the traditionally presumed correlation.⁵⁶ A sputum eosinophil count of greater than or equal to 3% is generally regarded as a raised value, but in reality this has relatively little relevance in real-life clinical practice because most clinicians do not perform induced sputum. Furthermore, some clinicians advocate a disconnect between peripheral blood and sputum eosinophil counts in patients with more severe asthma taking a higher ICS dose.⁵⁷ For example, 1 mg of inhaled fluticasone propionate has the equivalent PBE-suppressive effect as 5 mg of oral prednisolone in adult asthma.⁵⁸ Preliminary data suggest that FENO more than 50 ppb along with PBE greater than or equal to 300/ μ L is associated with an 80% probability of a sputum eosinophilia greater than or equal to 3%.⁵⁹ In another study, FENO was predictive of sputum eosinophilia at a cutoff point of 36 ppb with a sensitivity of 67% and a specificity of 74%, whereas for blood eosinophils at a threshold of 113/ μ L, the sensitivity was 62% and specificity was 78%.⁶⁰ This might be important because the vast majority of patients with asthma with sputum eosinophilia have mucous plugging present on high resolution computed tomography.⁶¹

CONCLUSIONS

Ultimately, the choice of biologic can be determined after careful consideration of the particular endotype, comorbidities, and the existing clinical data as well as relative cost, dosing interval, and availability of self-injection (Table 1). Our clinical experience from the MDT suggests that anti-IL-5(α) is a preferred therapeutic option for patients with severe eosinophilic asthma irrespective of FENO or allergic status at least for patients with PBE greater than or equal to 300/ μ L. A recent indirect treatment comparison of licensed doses showed that in patients with asthma with similar PBE counts, MEPO was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared with RESLI or BENRA⁶²; however, this finding was not reproduced when a matching-adjusted comparison was made.⁶³ There are real-life data albeit preliminary to suggest that in patients who have failed on MEPO despite adequate PBE suppression, switching to BENRA may be associated with improved control,⁶⁴ although it is conceivable that the same might equally apply to BENRA failures. Efficacy of anti-IL-5(α) seems to be unrelated to FENO levels in those patients with high PBE.

Although anti-IL-4 α is most effective in patients with the high FENO endotype, it also exhibits efficacy but to a lesser degree

in patients with raised PBE and low FENO. Until there is evidence to show that DUPI reduces bronchial submucosal or sputum eosinophilia, we would have reservations about using it in patients with PBE greater than or equal to 1000/ μ L because it may also raise PBE levels. Hypereosinophilia was reported in 4.1% of patients receiving DUPI compared with 0.6% receiving placebo.¹¹ Although worsening clinical symptoms were accompanied in only 0.2% of overall patients with hypereosinophilia, a potential clinical challenge clinicians face is the next treatment decision for patients with rising PBE counts but improving asthma. Hence, for patients with PBE greater than or equal to 1000/ μ L, our MDT would suggest that until further long-term safety data are available, anti-IL-5(α) seems to be the logical first-line drug in such cases.

The best evidence for OCS sparing is with using anti-IL-5(α) or anti-IL-4/ α rather than anti-IgE. Because anti-IL-4/ α suppresses IgE levels as well as FENO we would advocate this over anti-IgE in patients with the FENO-high, allergic endotype regardless of PBE status, especially as the magnitude of exacerbation reduction seems to be more impressive. Likewise, we would suggest using anti-IL-5(α) as first line rather than anti-IgE in patients with the PBE-high, allergic endotype irrespective of FENO due to a greater reduction in exacerbations seen with the former.

Ultimately, head-to-head trials are urgently required to compare the different biologics across common type 2 endotypes, such as the PREDICTUMAB trial (NCT03476109) comparing MEPO and OMAL. We also look forward to more data becoming available on tezepelumab [NCT03927157], a mAb directed against thymic stromal lymphopoietin, which has shown promising exacerbation reductions in phase 2.⁶⁵ Because tezepelumab blocks signaling of the IL-4, IL-5, and IL-13 pathways and suppresses PBE, FENO, and IgE, one might consider this to be the most broad spectrum of current biologics.

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