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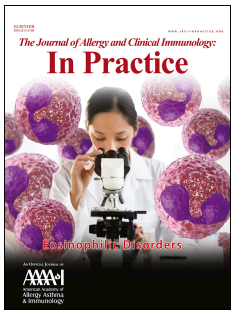

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Abbreviations

ACQ	asthma control questionnaire
AD	atopic dermatitis
AQLQ	asthma quality of life questionnaire
BENRA	Benralizumab
CIU	chronic idiopathic urticaria
CRSwNP	chronic rhinosinusitis and nasal polyposis
DUPI	Dupilumab
EE	eosinophilic oesophagitis
EGPA	eosinophilic granulomatosis with polyangiitis
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IgE	immunoglobulin type E
IL4rα	interleukin 4 receptor alpha
IL5(rα)	interleukin 5 (receptor alpha)
MCID	minimum clinical important difference
MDT	multidisciplinary team
MEPO	Mepolizumab
NICE	National Institute for Health and Care Excellence
OCS	oral corticosteroid
OMAL	Omalizumab
PBE	peripheral blood eosinophils
RESLI	Reslizumab
SEA	severe eosinophilic asthma
TEZE	Tezepelumab
T2	type 2

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Abstract

Patients with severe refractory asthma present a challenging clinical conundrum for practising clinicians. Biologics that target key mediators in the type 2 (T2) 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 which identifies the optimal biologic class for patients who have specific T2 disease endotypes. Patients with eosinophilic endotypes fare well with anti-IL5(rα) medications, comprising mepolizumab, benralizumab and reslizumab as they have been shown to reduce exacerbations in severe eosinophilic asthma by approximately 50%. In patients with FeNO-high endotypes, anti-IL4rα such as dupilumab is deemed to be most effective and has demonstrated a 47% reduction in asthma exacerbations although a recent indirect treatment comparison suggests further promising results. For patients with severe uncontrolled allergic asthma, anti-IgE (omalizumab) is effective and has been shown to confer a 25% reduction in asthma exacerbations. T2 comorbidities including chronic rhinosinusitis with nasal polyps, atopic dermatitis, chronic idiopathic urticaria and eosinophilic esophagitis are important to bear in mind prior to the prescription of biologics. Further head-to-head studies are indicated to compare biologics in patients with mixed endotypes according to peripheral blood eosinophils, FeNO and allergic status. The evidence strongly supports endotype-driven prescribing of biologics in order to achieve clinically relevant outcomes in severe refractory asthma and related comorbidities.

Word count 232

Keywords: allergy, asthma, benralizumab, dupilumab, eosinophils, FeNO, mepolizumab, omalizumab, type 2 inflammation

Introduction

Patients with severe uncontrolled asthma present a challenging clinical conundrum for practising clinicians due to their requirement for extensive diagnostic evaluation, high consumption of healthcare resources and heavy symptom burden.[1] Global Initiative for Asthma (GINA) defines severe asthma as uncontrolled despite adherence with maximal optimised 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 optimised inhaled corticosteroid (ICS) therapy many asthmatics 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, as these have already been covered in detail elsewhere.[3-6] Instead its purpose is to provide a focussed 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 as most of the evidence is based from 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] Secondly, optimisation 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 as there is growing evidence that this significantly reduces asthma-related hospital admissions and hospital days.[9] Indeed, our Tayside severe asthma MDT have meetings on a weekly basis.

In patients with T2 asthma, monoclonal antibodies targeting immunoglobulin type E (IgE), interleukin 4 receptor alpha (IL4rα) and interleukin 5 (IL5) are attractive therapeutic options as 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 an asthmatic patient based on their particular disease endotype. Peripheral blood eosinophils (PBE), FeNO and allergic status are the most commonly utilised T2 biomarkers in clinical practice for assessing asthma and assisting in generating specialist decisions. Here we propose a simplified clinical algorithm to assist practising 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 one study where it is possible to estimate the relative prevalence of different T2 endotypes as enrolment was independent of biomarkers. Here the relative prevalence of endotypes was shown to be 42% for PBE ≥150/µl, FeNO ≥25ppb; 30% in PBE ≥150/µl, FeNO <25ppb; and 9% in PBE <150/µl FeNO ≥25ppb; while the remaining 19% had PBE <150/µl and FeNO <25ppb.[13] In essence, a large proportion (72%) of patients with severe asthma appear to have an eosinophilic endotype, albeit using a rather low cut point of ≥150/µl. This breakdown did not factor in the presence or absence of an allergic endotype. Furthermore, one recent retrospective observational

cohort analysis demonstrated that 34% of severe asthma patients have an eosinophilic endotype using the more clinically relevant cut-point of 300/µl.[14]

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

For the purposes of this review article, allergy in keeping with the Omazilumab label indication is defined as a total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen specific IgE ≥0.35 kU/L at baseline.[18] However in real life clinical practice, our Tayside severe asthma multidisciplinary team (MDT) meeting would only designate a patient with a total serum IgE ≥100 IU/mL and ≥2 aeroallergen specific IgE ≥0.35 kU/L or positive skin prick tests 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 only classify patients into an eosinophilic endotype if their PBE count exceeded 300/µl, ideally over 2 different time points in the preceding 6 months. Clinicians should recognise that significant variability of 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 oral corticosteroids (OCS), both of which suppress FeNO. For the purpose of this review we will adopt a pragmatic cut off of ≥25ppb while taking ICS to denote a patient with a high FeNO endotype.

Eosinophilic endotypes

A recent Cochrane review indicates that the three anti-IL5(rα) 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 – 110ml) but statistically significant improvement in forced expiratory volume in 1 second (FEV_1), although it is perhaps worth noting that the minimum clinical important difference (MCID) is traditionally considered to be 230ml.[22] Patients also experienced modest improvements in their asthma control questionnaire (ACQ) and asthma quality of life questionnaire (AQLQ) but these were both also below the conventional MCID of 0.5.[23] In the UK, the National Institute for Health and Care Excellence (NICE) guidance for MEPO and BENRA suggest at least 4 severe exacerbations needing systemic steroids along with PBE ≥300 cells/µl in the past year or continuous OCS requirement over the previous 6 months. RESLI and BENRA are also indicated in UK for patients with PBE ≥400/µl 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, non-allergic (endotype 2); PBE-high, FeNO-low, non-allergic (endotype 3); and PBE-low, FeNO-high and allergic (endotype 4). Patients with elevated PBE comprising endotypes 1-3 likely experience most benefit from anti-IL5(rα) therapy as eosinophilic proliferation, maturation and survival are governed by IL5.[24] Exploratory modelling 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 (SEA) treated with RESLI or BENRA.[26, 27] Moreover, real world MEPO data suggests more impressive results compared to randomised controlled trials on reduction in exacerbations, hospitalisations along with an improvement in ACQ

score of 2.0 points at six months which far exceeds 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 ≥300/µl, we would generally propose anti-IL5(rα) therapy as first line therapy 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-IL5(rα) (50%) or anti-IL4rα (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-IL4rα, we would proffer a degree of caution in advocating dupilumab as equal first line therapy with anti-IL5(rα) 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 monoclonal antibodies directed against IL5(rα), IL4rα 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-IL5(rα) or anti-IL4rα compared to those on anti-IgE.[11, 21, 29] Therefore, in the absence of any defining comorbidities, our MDT would recommend anti-IL5(rα) or anti-IL4rα as first line, with anti-IgE as second line in patients with endotype 1 (figure 2). In real life clinical practice, the choice of biologic in patients with this endotype would rest upon 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-IL5(rα) or anti-IL4rα 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 SEA 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 cut-off of ≥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 FEV_1 improvement relative to placebo that appears to occur around PBE ≥300/µl[31] when plotted as a continuous variable. For instance, in the comparison between BENRA 30mg q8wk and placebo, patients with PBE ≥300/µl and ≥3 exacerbations in the prior year experienced a relative exacerbation rate reduction of 55% and FEV_1 improvement of 252ml (above MCID of 230 ml).

In a post-hoc analysis of the pivotal DUPI trials, using 200mg q2wk, exacerbations were reduced by 68% in patients with PBE ≥150/µl, FeNO ≥25ppb as opposed to 33% in patients with PBE ≥150/µl, FeNO <25ppb.[32] This infers that DUPI could potentially be more effective in patients with endotypes 1 and 2 with high FeNO rather than those with endotype 3 with low FeNO. Unfortunately, no data were available for DUPI stratified at PBE ≥300/µl according to FeNO ≥25ppb vs <25ppb which in our opinion would have been more informative. Prospective head to head trials would be required to assess whether anti-IL4rα or anti-IL5(rα) is more effective first line treatment for patients with both FeNO ≥25ppb and PBE ≥300/µl in endotypes 1 and 2. In the same post-hoc analysis for patients on MEPO with PBE ≥150/µl, exacerbation rate was reduced by 62% for FeNO ≥25ppb but only 36% for <25ppb.[32] MEPO also resulted in modest FEV_1 improvements (122ml for ≥25 ppb and 101ml for <25ppb) in patients with PBE ≥150/µl, albeit this was below MCID.[22] For patients on MEPO with PBE

≥300/µl the exacerbation rate reduction was 62% for FeNO ≥25ppb and 53% for <25ppb, in keeping with the lack of effect of IL5 signalling on FeNO.

For endotype 3 i.e. PBE-high, FeNO-low and non-allergic, one might not expect patients to experience significant benefit from anti-IL4rα therapy as it acts on both IL4 and IL13, the latter of which regulates FeNO.[33] However, the aforementioned data[32] 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 ≥300/µl according to FeNO ≥ or <25ppb. Nonetheless in the primary analysis[11] DUPI 300mg q2wk produced a 67% exacerbation reduction in those with PBE ≥300/µl irrespective of FeNO, perhaps supporting a recommendation that both anti-IL5(rα) or anti-IL4rα therapy may be considered as suitable first line options for endotypes 1, 2 and 3.

Despite the promising results seen with anti-IL5(rα) therapy, recent data suggests that 43% of patients who fulfil the current approved treatment criteria are so-called suboptimal responders.[34] Sputum analysis in this subset of patients suggests a possible underlying autoimmune mediated aetiology related to the presence of anti-eosinophil 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 also includes patients with the PBE-low, FeNO-high, allergic endotype 4. Patients with either of these three FeNO-high endotypes would in theory be expected to have a favourable response to anti-IL4rα therapy as FeNO is closely regulated by IL13,[33] however the results of the pivotal trials with tralokinumab and lebrikizumab which block IL13 signalling were equivocal.[35, 36] This in turn suggests that blocking signalling of both IL4 and IL13 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 <150/µl, FeNO ≥25ppb.[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 300mg q2wk[11] for patients with PBE ≥150/µl, FeNO <25ppb there appeared to be discordance in terms of a significant reduction in exacerbations but no improvement in FEV_1 relative to placebo, whilst in patients with PBE <150/µl, FeNO ≥25ppb effects of DUPI were concordant on both exacerbations and FEV_1. In another post-hoc analysis DUPI showed equivalent efficacy in allergic and non-allergic asthma,[18] although the definition of allergy was tenuously based on total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L. Notably, no comparison of response was made across a range of IgE cut points. Nevertheless, anti-IL4rα 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 emphasises 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 randomised controlled trials demonstrated that DUPI was associated with a significantly greater reduction in annualised severe asthma exacerbation rate (26% greater reduction versus omalizumab (OMAL) and 28 – 54% versus anti-IL5(rα)).[38] A 60 – 140ml improvement in FEV_1 was also seen with DUPI versus the other biologics although this is below the MCID of 230ml.

Allergic endotypes

Anti-IgE is a viable alternative for patients with endotypes 1 and 4 as a 2014 Cochrane review evaluating 25 randomised trials using OMAL demonstrated a 25% asthma exacerbation reduction as well as a significant ICS sparing effect.[29] Humbert et al 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 randomised 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 ≥19.5ppb vs <19.5ppb and a 23% greater reduction comparing PBE ≥260/µl vs <260/µl.[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 based on current evidence.

We wish to highlight that the PBE-low, FeNO-low, allergic endotype has deliberately been ommitted from figure 3 as 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 pre-existing comorbidities into account as there is a potential opportunity to treat two co-related T2 conditions. For example, MEPO is associated with marked decreases in PBE, oesophageal eosinophilia and improved clinical outcomes in patients with eosinophilic esophagitis (EE), although it does not have a licensed indication per se.[42] DUPI also improves clinical outcomes in EE and reduces submucosal eosinophilia.[43] Another example would be coexistent chronic rhinosinusitis and nasal polyposis (CRSwNP) which is associated with a better anti-asthmatic response to anti-IL5[44] but does not appear to 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 higher PBE which probably accounts for the enhanced anti-asthmatic response to anti-IL5 in the presence of this comorbidity. Since anti-IL4rα 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 1,000/µL along with other pertinent clinical features, then anti-myeloperoxidase and anti-proteinase-3 antibodies should be measured to refute a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), particularly if any other clinical features are present. Higher than currently licensed doses of MEPO have been shown to improve disease control in EGPA,[47] and clinical trials are undergoing to evaluate benralizumab (NCT04157348).

For patients with severe T2 asthma and concomitant atopic dermatitis (AD), anti-IL4rα is a logical option as it results in significant amelioration in disease severity and symptom burden in AD.[48] Finally, allergic asthmatic patients with concomitant refractory chronic idiopathic urticaria (CIU) should be trialled with anti-IgE therapy first as 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 ≥25ppb and ≥300/µl respectively. Guideline recommendations for ICS-naïve patients advocate that FeNO >50ppb can be used to indicate eosinophilic inflammation and corticosteroid responsiveness.[50] Nevertheless, we feel that

these cutpoints should be lower in patients taking ICS, for instance using FeNO ≥25 ppb.[51] Caution should also be exercised when interpreting FeNO levels in the presence of comorbidities. For example, one prospective study of severe asthmatics confirmed elevated FeNO and PBE values in patients with nasal polyposis compared to to those without.[52]

For anti-IL5(rα) in the UK, NICE proposes an optimal PBE threshold of ≥300/µl in keeping with the pooled analysis from the MEPO and BENRA trials[31, 53] where PBE has been plotted as a continous 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 as low doses of ICS 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 ≥3% is generally regarded as a raised value but in reality this has relatively little relevance in real life clinical practice as 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 1mg of inhaled fluticasone proprionate has the equivalent PBE suppressive effect as 5mg of oral prednisolone in adult asthma.[58] Preliminary data suggest that FeNO >50ppb along with PBE ≥300/µl is associated with an 80% probability of a sputum eosinophilia ≥3%.[59] In another study, FeNO was predictive of sputum eosinophilia at a cut-off point of 36ppb with a sensitivity of 67% and a specificity of 74%, whilst for blood eosinophils at a threshold of 113/µl the sensitivity was 62% and specificity was 78%.[60] This might be important because the vast majority of asthma patients with sputum eosinophilia have mucous plugging present on HRCT.[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-IL5(rα) is a preferred therapeutic option for patients with SEA irrespective of FeNO or allergic status at least for patients with PBE ≥300/µl. A recent indirect treatment comparison of licensed doses showed that in asthmatic patients with similar PBE counts, MEPO was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared to RESLI or BENRA,[62] 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-IL5(rα) seems to be unrelated to FeNO levels in those patients with high PBE.

Although anti-IL4rα 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 ≥1,000/µl since it may also raise PBE levels. Hypereosinophilia was reported in 4.1% of patients receiving DUPI compared to 0.6% receiving placebo.[11] Although worsening clinical symptoms were only accompanied in 0.2% of overall patients with hypereosinophilia, one potential clinical challenge clinicians face is the next treatment decision for patients with rising PBE counts but improving asthma. Hence for patients with PBE ≥1,000/µl, our

MDT would suggest that until further long term safety data are available, anti-IL5(rα) seems to be the logical first line drug in such cases.

The best evidence for OCS sparing is with using anti-IL5(rα) or anti-IL4rα rather than anti-IgE. Since anti-IL4rα 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-IL5(rα) 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 (TEZE) [NCT03927157], a monoclonal antibody directed against thymic stromal lymphopoietin, which has shown promising exacerbation reductions in phase 2.[65] Since TEZE blocks signalling of the IL4, IL5 and IL13 pathways and suppresses PBE, FeNO and IgE, one might consider this to be the most broad spectrum of current biologics.

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Table 1: Effects of biologics on key patient outcomes and type 2 inflammatory biomarkers

MAb	Exac	FEV_1	ACQ/QoL	OCS sparing	PBE	IgE	FeNO
Anti-IL5	+++	+	+	++	+++	-	-
Anti-IL4rα	+++	++	+	++	-	++	++
Anti-IgE	++	+	+	+/-*	+	+/-#	+

*ACQ = asthma control questionnaire; Exac = exacerbations; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin type E; IL = interleukin; MAb = monoclonal antibody; PBE = peripheral blood eosinophils; QoL = quality of life; number of "+" symbols denotes degree of positive effect; *evidence for OCS sparing effect of Omalizumab is equivocal; ? = insufficient data; # Omalizumab paradoxically elevates bound total and specific IgE levels but reduces free IgE*

Figure 1 legend

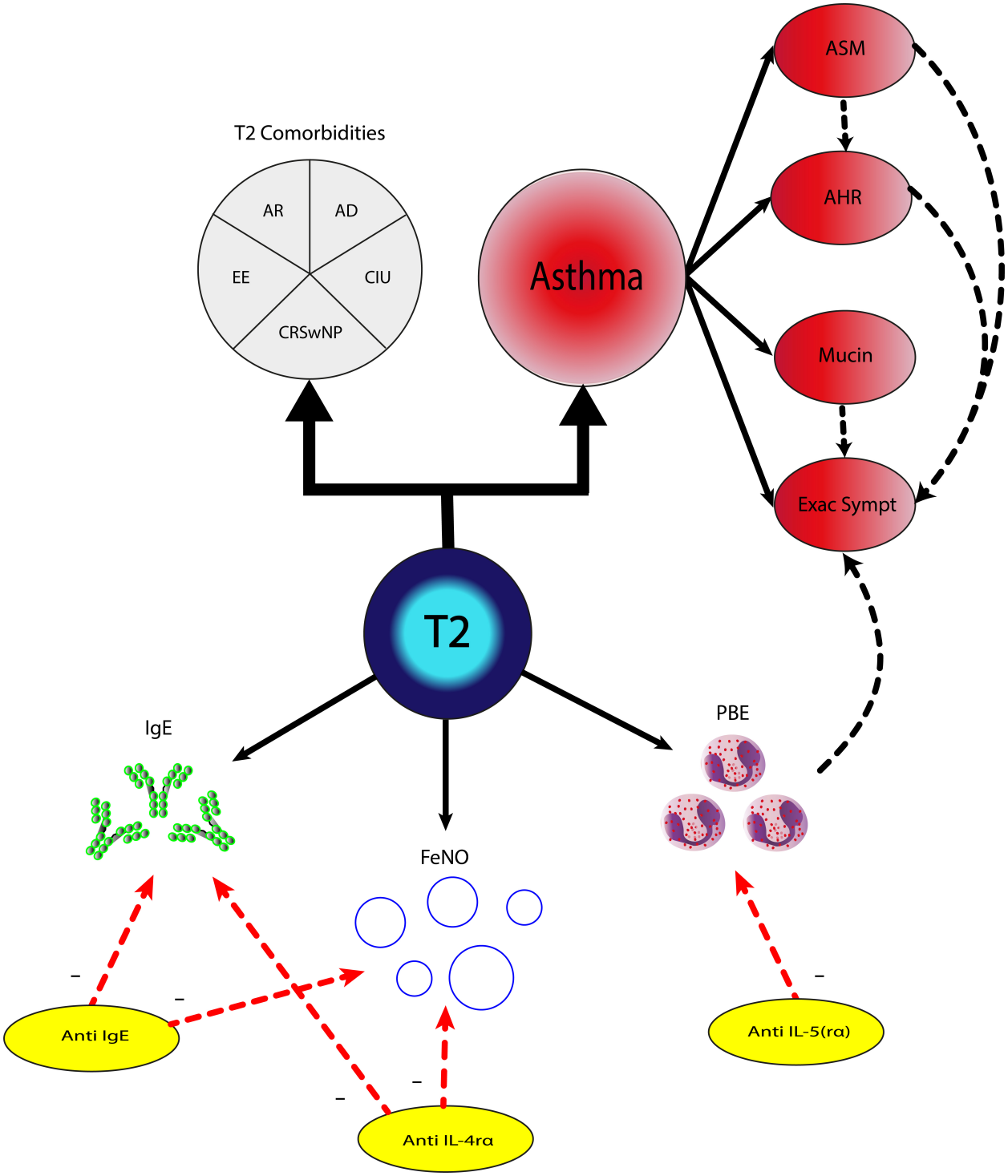
Activation of T2 inflammation elevates levels of IgE, FeNO and PBE. These biomarkers are targeted by various biological therapies as depicted. Relationship between T2 inflammation with asthma and relevant comorbidities shown. AD – atopic dermatitis; AHR – airway hyperresponsiveness; AR – allergic rhinitis; ASM – airway smooth muscle; CIU – chronic idiopathic urticaria; CRSwNP – chronic rhinosinusitis with nasal polyps; EE – eosinophilic esophagitis; Exac – exacerbations; FeNO – fractional exhaled nitric oxide; IgE – immunoglobulin type E; IL – interleukin; PBE – peripheral blood eosinophils; Sympt – symptoms; T2 – type 2 inflammation.

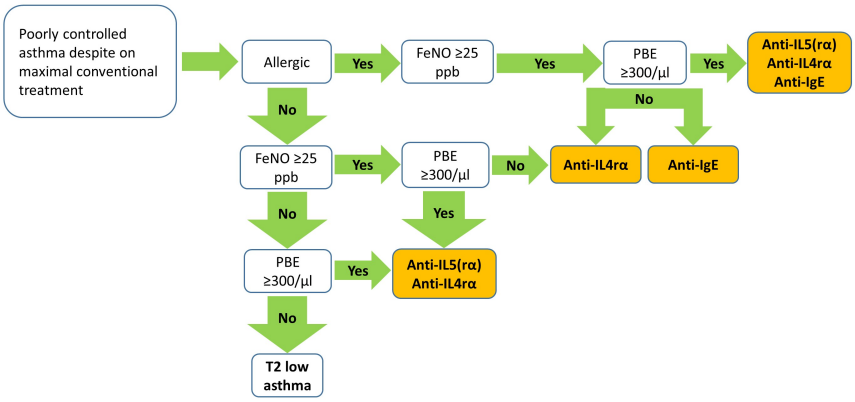
Figure 2 Legend

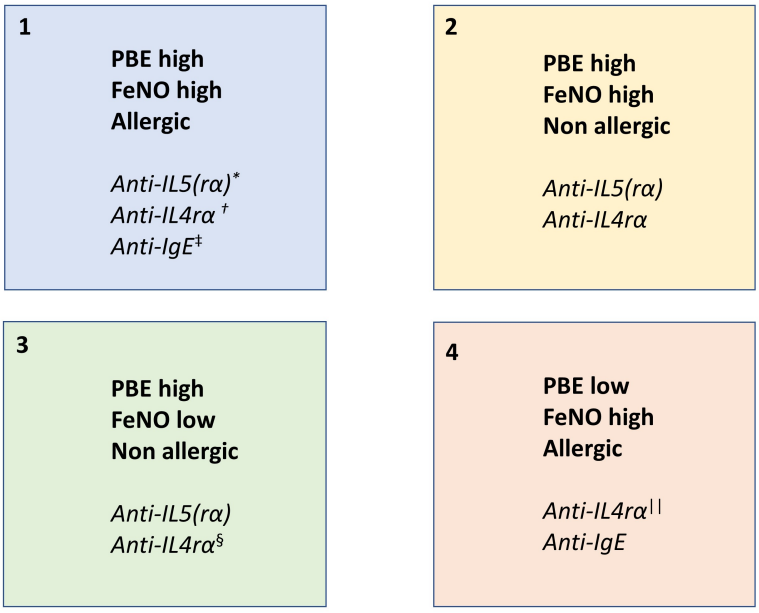
Proposed pragmatic clinical decision-making algorithm for the management of uncontrolled severe refractory T2 asthma in relation to the current available biologics. FeNO – fractional exhaled nitric oxide; IL – interleukin; µl – microlitre; PBE – peripheral blood eosinophils; ppb – parts per billion

Figure 3 Legend

Commonly occurring patterns of Type 2 inflammation in relation to choosing optimal biological therapy for severe uncontrolled asthma. Numbering corresponds to the various endotypes referred to in manuscript 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-IL5(rα) and anti-IL4rα if PBE ≥150/µL; || Anti-IL4rα preferred over anti-IgE due to greater exacerbation rate reduction. Anti-IL5(rα) preferred over anti-IL4rα for patients with endotypes 1, 2 and 3 if PBE ≥1,000/µl. PBE – peripheral blood eosinophils; FeNO – fractional exhaled nitric oxide.


T2 Comorbidities
AR
AD
EE
CIU
CRSwNP
Asthma
ASM
AHR
Mucin
Exac Sympt
T2
IgE
FeNO
PBE
Anti IgE
Anti IL-4rα
Anti IL-5(rα)


Poorly controlled asthma despite on maximal conventional treatment
Allergic
Yes
FeNO ≥25 ppb
Yes
PBE ≥300/µl
Yes
Anti-IL5(rα) Anti-IL4rα Anti-IgE
No
No
FeNO ≥25 ppb
Yes
PBE ≥300/µl
No
Anti-IL4rα
Anti-IgE
No
Yes
PBE ≥300/µl
Yes
Anti-IL5(rα) Anti-IL4rα
No
T2 low asthma


1
PBE high
FeNO high
Allergic
Anti-IL5(rα)*
Anti-IL4rα †
Anti-IgE‡
2
PBE high
FeNO high
Non allergic
Anti-IL5(rα)
Anti-IL4rα
3
PBE high
FeNO low
Non allergic
Anti-IL5(rα)
Anti-IL4rα§
4
PBE low
FeNO high
Allergic
Anti-IL4rα||
Anti-IgE