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Chan, Rory; Stewart, Kirsten; Misirovs, Rashad; Lipworth, Brian

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Targeting Downstream Type 2 Cytokines or Upstream Epithelial Alarmins for Severe Asthma

Rory Chan, MBChB, Kirsten Stewart, MBChB, Rasads Misirovs, MBBS, and Brian J. Lipworth, MD *Dundee, United Kingdom*

Biologics, including omalizumab, mepolizumab, benralizumab, and dupilumab, targeting downstream IgE, cytokines IL-5, and IL-4/13, respectively, have shown promising effects in terms of reduction in annualized asthma exacerbation rates (AER), oral corticosteroid-sparing effects, improvements in forced expiratory volume in 1 second, and improved Asthma Control Questionnaire scores. However, despite these welcome advances, approximately 30% of patients with severe asthma receiving biologics tailored to their specific downstream type 2 biomarkers, including total IgE, peripheral blood eosinophils, and fractional exhaled nitric oxide, do not experience meaningful improvements in their AER. Instead of blocking downstream cytokines, targeting upstream epithelial alarmins, including IL-33, thymic stromal lymphopoietin, and IL-25, has been proposed to tackle the immunologic heterogeneity of asthma. This review article aims to pragmatically summarize the latest key clinical data on antialarmin therapies in severe asthma and put these findings into context with regard to currently available downstream cytokine blockers. **(J Allergy Clin Immunol Pract 2022;10:1497-505)**

Key words: *Antialarmins; Biologics; Brodalumab; Cytokines; Itepekimab; Severe asthma; Tezepelumab*

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

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

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In recent years, new therapeutic options have become available for patients with refractory severe asthma driven by type 2 (T2) inflammation.[1] Biologics including omalizumab, mepolizumab, benralizumab, and dupilumab targeting downstream IgE, cytokines IL-5, and IL-4/13, respectively, have shown promising effects in terms of reduction in annualized asthma exacerbation rates (AER), oral corticosteroid (OCS)-sparing effects, improvements in forced expiratory volume in 1 second (FEV_1), and Asthma Control Questionnaire (ACQ).[2]

However, despite these welcome advances, it is increasingly recognized that approximately 30% of patients with severe asthma receiving biologics tailored to their specific downstream T2 biomarkers including total IgE, peripheral blood eosinophils (PBE), and fractional exhaled nitric oxide (FeNO) do not experience meaningful improvements in their AER.[2] Super-responders to biologics are characterized as having no exacerbations and cessation of maintenance OCS accompanied by a large improvement in asthma control, comprising 2 or more times the minimal clinically important difference (MCID),[3,4] although in real life such cases are the exception. In contrast, a study of 250 patients with moderate-to-severe asthma receiving mepolizumab or reslizumab therapy revealed that 43% experienced a suboptimal treatment response with the latter being associated with daily OCS requirement, sinus disease, and late onset asthma.[5] Hence, there clearly remains an unmet need for many patients taking current biologics as monotherapy. Furthermore, although improvements in FEV_1 and ACQ are statistically significant in multicentre randomized controlled trials (RCTs), we should interpret these findings in the context that they do not exceed the MCID of 230 mL and 0.5 units, respectively.[6,7]

Instead of blocking downstream cytokines, targeting upstream epithelial alarmins including IL-33, thymic stromal lymphopoietin (TSLP), and IL-25 has been proposed to tackle the immunologic heterogeneity of asthma.[8] This review article aims to pragmatically summarize the latest key clinical data on antialarmin therapies in severe asthma and put these findings into context with regard to currently available downstream cytokine blockers (Table I). It is not meant to be an exhaustive systematic review nor will the aim be to discuss currently available downstream anticytokine therapies in detail as it has previously been published.[2] Furthermore, the scope of this review will not include a detailed discussion on omalizumab.

DOWNSTREAM TARGETING OF IL-4/5/13 PATHWAYS

In the United Kingdom, Europe, and USA, commonly used current licensed subcutaneously administered biologics that block downstream cytokines for the treatment of severe asthma include mepolizumab, benralizumab, and dupilumab, with intravenous

Abbreviations used

ACQ- Asthma Control Questionnaire
AER- Asthma exacerbation rate
AHR- Airway hyperresponsiveness
CI- Confidence interval
CIU- Chronic idiopathic urticaria
CRSwNP- Chronic rhinosinusitis with nasal polyps
FEF_{25-75}- Forced expiratory flow between 25 and 75% of forced vital capacity
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroid
LABA- Long-acting β-agonist
MCID- Minimal clinically important difference
OCS- Oral corticosteroid
PBE- Peripheral blood eosinophils
R5-R20- Difference between resistance at 5 and 20 Hz
RCT- Randomized controlled trial
SAD- Small airway dysfunction
T2- Type 2
TSLP- Thymic stromal lymphopoietin

reslizumab being reserved for patients with higher body mass.[9-12] The National Institute for Health and Care Excellence and the Scottish Medicines Consortium have recently approved dupilumab only as second line for those who have previously failed on anti-IgE or anti-IL-5 therapies.[13,14] We have previously published a pragmatic review article examining factors that determine optimal choice of biologic therapy for patients including disease endotype, patient preference, and presence of concomitant T2 comorbidities.[2] All classes of biologics targeting IL-5 and IL-4/13 pathways have been shown in systematic and Cochrane reviews to improve exacerbation rates by approximately 60% to 70% as well as OCS-sparing effects amounting to an approximately 50% dose reduction.[15-17] Figure 1 depicts their effects on commonly measured T2 biomarkers in clinical practice. These main classes of cytokine blockers have also been shown to significantly improve FEV_1 and ACQ although these do not usually exceed MCID aside from super-responders.[16,18] In the phase 3 RCT involving benralizumab, the median difference reduction in OCS dose amounted to 50% compared with placebo, whereas for mepolizumab after 24 weeks there was a 50% median reduction in OCS dose.[19,20] Comparatively, the phase 3 trial studying dupilumab showed a slightly lesser OCS-sparing effect after 24 weeks with a 28% difference.[21] Another open-labeled real-life study (PONENTE) with benralizumab showed that 63% of patients were able to wean off OCS completely.[22]

TEZEPELUMAB (ANTI-TSLP)

TSLP is a key epithelial alarmin involved in binding of antigen-presenting cells in turn resulting in activation of downstream T2 inflammatory cytokines including IL-4, IL-5, and IL-13 (Figure 1).[23-25] In addition, TSLP is involved in interactions between airway epithelium and other immune cells that are not part of the T2 inflammatory process per se.[24] In allergic eosinophilic asthma, TSLP initiates pathways involving TH2 lymphocytes, basophils, and mast cells to generate airway eosinophilia. TSLP can also directly stimulate mast cells to produce T2 cytokines, whereas mast cells can produce significant amounts of TSLP from IgE cross-linking.[24]

Tezepelumab is a monoclonal antibody (IgG2λ) that specifically binds to the TSLP ligand in turn blocking receptor activation. In the phase 2b PATHWAY trial over 52 weeks, tezepelumab 210 mg every 4 weeks reduced the primary end point of overall AER by 71% (90% confidence interval [CI]: 54, 82).[26] Here significant reductions in AER were evident in patients with both T2 low and high disease using a threshold of PBE ≥250 or <250 cells/μL or FeNO <24 or ≥24 ppb. Furthermore, tezepelumab conferred reductions in PBE, FeNO, and total IgE compared with placebo inferring a broad-spectrum effect by attenuating downstream cytokine signaling including IL-4 (IgE), IL-13 (FeNO), and IL-5 (PBE) (Figure 1). However, reductions in PBE amounting to a mean fall of approximately 150 cells/μL from a mean baseline of 365 cells/μL are not as profound as those seen with anti-IL-5 agents.

In the subsequent phase 3 NAVIGATOR trial over 52 weeks, tezepelumab 210 mg significantly improved the primary end point resulting in an overall 56% (95% CI: 47, 63) reduction in AER. Tezepelumab also conferred significant mean improvements in key secondary end points including FEV_1 (130 mL), ACQ (−0.33), and Asthma Quality of Life Questionnaire (−0.34), although these were all less than their respective MCIDs.[27] As in the PATHWAY trial, there were decreased T2 biomarkers with mean falls amounting to 14 ppb in FeNO, 130 cells/μL in PBE, and 208 IU/mL in total IgE compared with placebo.

Of note, *post hoc* analysis of the primary end point in NAVIGATOR showed that AER were significantly reduced in the tezepelumab group to a greater degree in patients who had higher eosinophil counts.[27] For example, there was a 70% relative reduction in AER (95% CI: 60, 78) associated with baseline PBE ≥300 cells/μL compared with a 41% reduction (95% CI: 25, 54) with <300 cells/μL, which is a significant difference as indicated by CIs that do not overlap. Even in patients with PBE <150 cells/μL, there was a 39% (95% CI: 12, 68) reduction in AER. The same was observed in regard to non-overlapping CIs for AER with a 68% (95% CI: 58, 75) reduction for FeNO ≥25 ppb versus 32% (95% CI: 8, 49) for FeNO <25 ppb. For patients with T2 low asthma who had both PBE <300 cells/μL and FeNO <25 ppb, there were borderline significant reductions in AER compared with placebo amounting to 29% (CI: 0, 50). Intriguingly, for patients with PBE ≥300 cells/μL and FeNO <25 ppb, a 39% reduction in AER was observed (95% CI: −7, 65) although this was nonsignificant, which could be related to lower patient numbers in this particular subgroup analysis. The greatest reduction in AER was seen in those patients who had T2 high asthma with PBE ≥300/μL and FeNO ≥25 ppb where there was a 77% (95% CI: 67, 84) reduction. The wide CIs for T2 low patients indicate that in such cases there is considerable heterogeneity in response to tezepelumab, as compared with the much narrower CIs in T2 patients with a more homogeneous response. In other words, clinicians can expect a more predictable response to tezepelumab in those individuals with T2 high asthma.

When inspecting data for AER in NAVIGATOR where T2 biomarkers were plotted as a continuous variable, it is evident that the slope is much steeper for increased AER with placebo compared with reduced AER with tezepelumab, this being the case for both PBE and FeNO. In contrast, the separation between regression lines remains constant across the range for total IgE, indicating that this is not a key determinant of response. For FEV_1

TABLE I. RCT data on effects of antialarmin therapy and downstream cytokine blockade on pulmonary function, asthma control, annualized exacerbation rate, type 2 biomarkers, and airway hyperresponsiveness for severe asthma patients compared with placebo

Biologic	Anti-IL-33	Anti-TSLP	Anti-IL-4rα	Anti-IL-5(rα)
FEV_1 (L)	↑	↑	↑	↑
FEF_{25-75} (L/s)	↑	N/A	↑	N/A
ACQ	↓	↓	↓	↓
AER	N/A	↓	↓	↓
PBE (cells/μL)	↓	↓	↑/↔	↓↓
FeNO (ppb)	↓	↓	↓	↔
Total IgE (IU/mL)	↓	↓	↓	↔
OCS sparing	N/A	↔	↓	↓
AHR	N/A	↓	N/A	N/A

ACQ, Asthma Control Questionnaire; *AER*, annualized exacerbation rate; *AHR*, airway hyperresponsiveness; *FeNO*, fractional exhaled nitric oxide; FEF_{25-75}, forced expiratory flow rate between 25% and 75% of full vital capacity; FEV_1, forced expiratory volume in 1 second; *N/A*, not applicable; *OCS*, oral corticosteroid; *PBE*, peripheral blood eosinophils; *RCT*, randomized controlled trial; *TSLP*, thymic stromal lympoietin.

the response was greater among those with PBE ≥300 cells/μL: 230 mL (95% CI: 150, 310) compared with PBE <150 cells/μL: 30 mL (95% CI: −70, 130), with non-overlapping CIs indicating a significant difference. Similar results occurred for ACQ: −0.50 (95% CI: −0.69, −0.31) versus −0.09 (−0.33, 0.16).

Taken together these results from phase 2/3 trials suggest that blocking the upstream alarmin TSLP with tezepelumab results in clinically meaningful improvements in asthma control in patients with T2 high asthma with regard to exacerbations, ACQ, and FEV_1. Tezepelumab also appears to confer lesser degrees of improvements in T2 low asthma in relation to exacerbation reductions but not for FEV_1 or ACQ, along with a more variable response. Nonetheless, it is notable that tezepelumab is the first biologic with at least some degree of activity in T2 low refractory severe asthma that is at present an unmet need. It would be helpful to have T2 low biomarkers that might be able to predict a better response with tezepelumab in preventing exacerbations.

Preliminary abstracted data from the phase 3 SOURCE trial[28] (NCT03406078) with subcutaneous tezepelumab 210 mg over 48 weeks in severe OCS-dependent asthma patients were disappointing in terms of showing an overall nonsignificant 22% (CI: −47, 31) reduction in the primary end point of OCS dose along with no signification reduction in AER: 31% (95% CI: −9, 56). *Post hoc* analysis in patients with baseline PBE ≥300 cells/μL revealed a 71% (CI: 14, 90) OCS dose reduction, with the wide CI indicating a variable response perhaps due to the inherent PBE suppressive effect of OCS. *Post hoc* analysis of OCS-dependent patients in NAVIGATOR observed a 28% (95% CI: −26, 59) reduction in AER indicating futility for tezepelumab, although in such patients there were improvements in FEV_1 of 270 mL (95% CI: 100, 440) and ACQ of −0.65 (95% CI: −1.08, −0.22), both of which exceeded MCIDs of 230 mL and 0.5 units.[29] Given the impressive overall results of NAVIGATOR and the known OCS-sparing effect of blocking downstream IL-4/13 signaling with dupilumab,[21] it is difficult to explain this anomaly with tezepelumab. A potential explanation for this phenomenon has been proposed as a 2-compartment model for T2 inflammation recently.[30] It is hypothesized that for a biologic to be OCS sparing, it must effectively regulate the systemic compartment of circulating eosinophils (anti-IL-5rα) or prevent eosinophils from escaping the vascular compartment (anti-IL-4rα). Tezepelumab reduces airway chemotactic pull mediated by IL-13 and measured using FeNO by a similar magnitude to dupilumab (Table II) albeit with suboptimal eosinophil suppression compared with anti-IL-5rα. Nonetheless both tezepelumab and dupilumab appear to confer similar clinical impacts on asthma control as AER, ACQ, and improved lung function as FEV_1 (Table II).

Another key part of the asthma disease phenotype is the presence of airway hyperresponsiveness (AHR), which can be measured by an indirect bronchial challenge using the osmotic agent mannitol. *Ex vivo* it has been shown that IL-13 is a key cytokine in mediating AHR that can be blocked by dupilumab.[32] The CASCADE phase 2 RCT in uncontrolled asthma investigating tezepelumab 210 mg every 4 weeks demonstrated a significant ($P = .03$) 1.15 doubling dose improvement in the secondary end point of mannitol AHR compared with placebo as well as significantly reducing the primary end point of airway biopsy eosinophils.[33] Meanwhile the UPSTREAM phase 2 RCT in patients with uncontrolled asthma using intravenous tezepelumab 700 mg found a mean 0.9 doubling dose difference in the primary outcome of mannitol AHR, which was not significant ($P = .06$), whereas airway biopsy and lavage eosinophils were both significantly suppressed.[34]

Tezepelumab is therefore unique among the currently available biologics in the sense that it significantly suppresses all 3 T2 biomarkers (PBE, total IgE, and FeNO) as well as attenuating AHR (Figure 1). The lack of apparent efficacy in OCS-dependent patients requires further investigation given the known OCS-sparing efficacy of anti-IL-5 and anti-IL-4rα agents.[19-21] In a sense tezepelumab could be considered to have similar efficacy to dupilumab in terms of IL-4/13 blockade through FeNO and IgE suppression but with the additional action of IL-5 blockade partially suppressing blood eosinophils. Thus, tezepelumab confers a theoretical advantage over dupilumab in terms of obviating escape of blood eosinophils.

We are intrigued to know if locally acting inhaled anti-TSLP will prove to be as effective as systemic tezepelumab given that the former may not adequately address the systemic component of T2 inflammation or indeed be able to target the small airways. In a recent RCT, 12 weeks of therapy with the potent inhaled anti-TSLP CSJ117 was shown to reduce allergen-induced bronchoconstriction, sputum eosinophilia, and FeNO levels in mild allergic asthma patients compared with placebo.[35] The putative difference between inhaled and injected anti-TSLP is analogous to patients with refractory severe asthma despite using high-dose inhaled corticosteroid (ICS) who can then be adequately controlled by a small maintenance dose of OCS inferring a systemic component to refractory T2 inflammation.

ITEPEKIMAB (ANTI-IL-33)

IL-33 is an inducer of TH2 adaptive immunity and signals via the IL-1 receptor−related protein ST2 triggering the release of chemokines and cytokines that promote T2 inflammation.[36] Elevated levels of IL-33 messenger RNA produced by airway smooth muscle cells are detected from biopsies of patients with asthma compared with control subjects, especially those with severe asthma.[37] Along with IL-5, IL-33 is involved in the

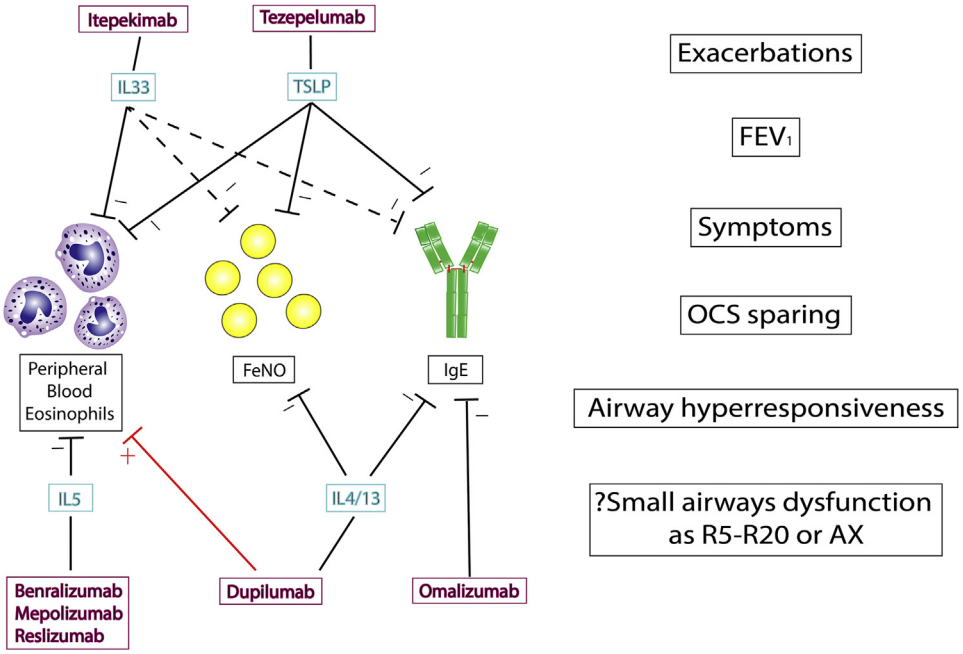

FIGURE 1. Effects of biologic and antialarmin therapies on upstream epithelial alarmins, downstream cytokines, and type 2 biomarkers in the context of key patient clinical outcome measures in severe asthma. Hypereosinophilia may be associated with dupilumab, whereas only tezepelumab has been shown to improve airway hyperresponsiveness. All biologics significantly improve ACQ and prebronchodilator FEV_1 and reduce OCS requiring exacerbations. Interrupted line refers to small but significant suppressive effect of itepekimab on FeNO and total IgE. *ACQ*, Asthma Control Questionnaire; *AX*, Area under reactance curve; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *OCS*, oral corticosteroid; *R5-R20*, difference between resistance at 5 and 20 Hz; *TSLP*, thymic stromal lympoietin.

production, activation, and survival of eosinophils and hence plays a key role in T2 high asthma.[38] Interestingly, dexamethasone fails to significantly dampen down TNFα-generated upregulation of IL-33 *ex vivo*.[37]

In a phase 2 RCT, the anti-IL-33 monoclonal antibody itepekimab at a subcutaneous dose of 300 mg every 2 weeks was given alone, dupilumab 300 mg given alone, itepekimab and dupilumab administered as combination therapy, or placebo were evaluated in patients initially maintained on ICS/long-acting β-agonist (LABA) for the first 4 weeks, with LABA discontinued at week 4 and ICS tapered over 2 to 3 weeks starting at week 6. For the primary outcome of loss of asthma control after 12 weeks, itepekimab alone was associated with a 58% (95% CI: 12, 80) reduction compared with placebo and dupilumab alone, which was associated with a 67% (95% CI: 30, 85) reduction.[39] The combination of itepekimab and dupilumab had a 48% (95% CI: −6, 74) reduction that was not significant versus placebo and was no better than either drug alone. For secondary end points, mean improvements in FEV_1 of 0.14 L (95% CI: 0.01, 0.27) were seen with itepekimab alone and 0.16 L (95% CI: 0.03, 0.29) with dupilumab alone, which were both significant compared with placebo but less than MCID, whereas the combination was no better than placebo.[7] Improvements in ACQ were all statistically significant versus placebo for monotherapy and combination therapy but again were less than the MCID. Interestingly, PBE increased with dupilumab alone but not with combination or itepekimab alone, suggesting that itepekimab blocks downstream signaling of IL-5. Although improvements in control were generally greater in patients treated with dupilumab than with itepekimab especially in those with T2 high asthma, the study was not powered to detect such differences. Itepekimab alone reduced FeNO and IgE compared with placebo inferring interruption of IL-13 or IL-4 signaling although not to the same degree as the combination. In patients with PBE <300 cells/μL, no significant impact was seen on asthma control or FEV_1 with any of the randomized treatments, albeit with small patient numbers, in turn suggesting that itepekimab has no effect in T2 low disease.

BRODALUMAB (ANTI-IL-25)

IL-25, also known as IL-17E, is produced by bronchial epithelial cells and activates TH2 cells, basophils, eosinophils, and mast cells, thus perpetuating the T2 inflammation response in asthma.[40,41] It has been shown *ex vivo* that IL-25 is associated with angiogenesis and airway remodeling, both of which contribute to asthma severity.[42] IL-25 binds to the heterodimeric receptor complex composed of IL-17RA and IL-17RB.[43] TH17 cells predominantly exert their action by producing the IL-17 family of cytokines (IL-17A-17F), of which IL-17A and IL-25 (IL-17E) are thought to play pivotal roles in pulmonary inflammation through IL-17RA-containing heterodimeric receptor complexes expressed in airway smooth muscle cells.[43]

In a phase 2a RCT studying the anti-IL-17RA monoclonal antibody brodalumab, which blocks IL-17A, IL-17F, and IL-17E (IL-25), no improvements were observed in the primary end

TABLE II. Mean improvements in AER, FEV_1, FeNO, and asthma control with tezepelumab or dupilumab versus placebo from phase 3 trials

Phase III trial	Dupilumab liberty quest[31]	Tezepelumab navigator[27]
AER		
Baseline	2.09	2.11
Absolute Δ	0.98	1.18
% Δ	−47%	−56%
FEV_1 (L)		
Baseline	1.78	1.85
Absolute Δ	0.17	0.13
% Δ	9.6%	7.0%
FeNO (ppb)		
Baseline	35	44
Absolute Δ	−12.3	−13.8
% Δ	−35.1%	−31.4%
ACQ		
Baseline	2.8	2.8
Absolute Δ	−0.31	−0.33
% Δ	−11.1%	−11.8%

ACQ, Asthma Control Questionnaire; *AER*, annual exacerbation rate; *FEV_1*, forced expiratory volume in 1 second; *FeNO*, fractional exhaled nitric oxide.

point of ACQ after 12 weeks of treatment in patients with inadequately controlled moderate-to-severe asthma.[44] Any improvements in the secondary end point of FEV_1 also did not amount to statistical significance or a clinically meaningful response. In a subgroup analysis of patients with a mean bronchodilator response of 33% in the same study,[44] a significant ACQ improvement that exceeded MCID was shown with brodalumab 210 mg every 2 weeks. These findings are perhaps not entirely surprising due to the known complexity and heterogeneity in asthma pathophysiology. Consequently, further RCTs are required to assess the efficacy of anti-IL-25 blockade on other key outcomes such as AER and OCS dose reduction and its effect on FeNO, PBE, and IgE.

PROPOSED BIOLOGIC AND ANTIALARMIN FLOWCHART

On the basis of specific disease endotypes and current best available evidence, Figure 2 represents the T2 biomarker pivot in relation to FeNO and PBE and proposes a putative pragmatic clinical flowchart recommending optimal first- and second-line downstream cytokine blocker or upstream epithelial antialarmin options for the management of patients with severe refractory asthma. Of note, this flowchart refers to patients who are presently not taking OCS and is irrespective of allergic status. Thresholds of <300, 300-1000, and ≥1000 cells/μL are used to denote low, medium, and high PBE counts, respectively. The arbitrary cutoff of 1000 cells/μL was determined based on our clinical experience and that of others.[45] Indeed, in our Tayside specialist asthma clinic, a PBE count ≥1000 cells/μL would usually mandate testing for myeloperoxidase and proteinase 3 antibodies that if positive might suggest eosinophilic granulomatosis with polyangiitis.[46] Similarly, thresholds of <25, ≥25, and ≥50 ppb were used to represent low, medium, and high levels of FeNO according to current American Thoracic Society guidelines.[47]

The recommendations stratified by high, medium, and low levels of PBE and FeNO are based on the following considerations. First, in patients with moderate PBE together with moderate or high FeNO, either anti-IL-5(rα) or anti-IL-4rα could potentially be used as first line as both have been shown to be effective in T2 high disease.[2] Secondly, those patients with high PBE (irrespective of FeNO) have predominantly IL-5-driven disease and therefore should receive anti-IL-5(rα) as first line.[48] In a real-life setting, the clinical effectiveness of mepolizumab and benralizumab was independent of the baseline FeNO level in severe eosinophilic asthma.[49] Although dupilumab has been shown to be more effective in those with either PBE ≥300 cells/μL or FeNO ≥50 ppb,[31] there is a putative concern regarding the risk of inducing hypereosinophilia due to IL-5 escape, and therefore some caution should perhaps be exercised when prescribing this in patients with pre-existing hypereosinophilia or that which could be masked by prior anti-IL-5 or OCS treatment. Having said that, it remains unclear if such escape of PBE is clinically relevant if as suggested blocking IL-13 signaling results in suppression of tissue eosinophils.[50] Thirdly, patients with low PBE and raised FeNO have predominantly IL-13-driven disease and therefore anti-IL-4rα would be considered first choice. Lastly, similar to the second group, those patients with medium PBE and low FeNO should initially be trialed on anti-IL-5(rα) therapy. Although dupilumab is more effective in patients with PBE ≥300 cells/μL, one might perhaps consider using it as second line in this group due to low FeNO.

Where might anti-TSLP fit into this pathway given its broad-spectrum effects on inhibiting downstream signaling of IL-4/5/13? One possibility is that tezepelumab could be used wherever dupilumab is indicated especially in patients with high FeNO given that it exhibits similar inhibitory effects on downstream IL-4/13 signaling. However, as tezepelumab appears to obviate potential concomitant eosinophil escape, it might be preferable to dupilumab in those patients with high PBE. Notably, we would not advocate tezepelumab as a first-line alternative to anti-IL-5 in patients with high PBE and low FeNO as it appears to only partially attenuate downstream IL-5 signaling. Tezepelumab is presently also the only biologic to work in T2 low disease and therefore would be the optimal choice for such patients, albeit bearing in mind the likelihood of a more variable response.

Although we appreciate that Figure 2 is somewhat speculative in the absence of head-to-head trials, this is based on clinical experience and current best available evidence. Our current Scottish guidelines support patients with severe asthma with PBE ≥150 cells/μL receiving anti-IL-5 therapy[51] although we would personally only consider ≥300 cells/μL as truly eosinophilic while at the same time predictive of a more meaningful clinical response.[52] One can also debate whether flowcharts offering 3 or 4 first-line options may be of questionable use to the practicing clinician. In a sense it is rather intellectually naive to believe that a single biologic can be used to achieve optimal control aside from occasional super-responders. In real life, use of biologic combinations is likely to be prohibitive from a cost perspective until further data from RCTs become available. Ultimately, head-to-head trials are required to answer the important question of which antialarmin or combination of biologics is best suited to which patient.

FURTHER CLINICAL CONSIDERATIONS

In phase 3 trials of biologics including antialarmins, all drugs have been shown to significantly reduce exacerbations and

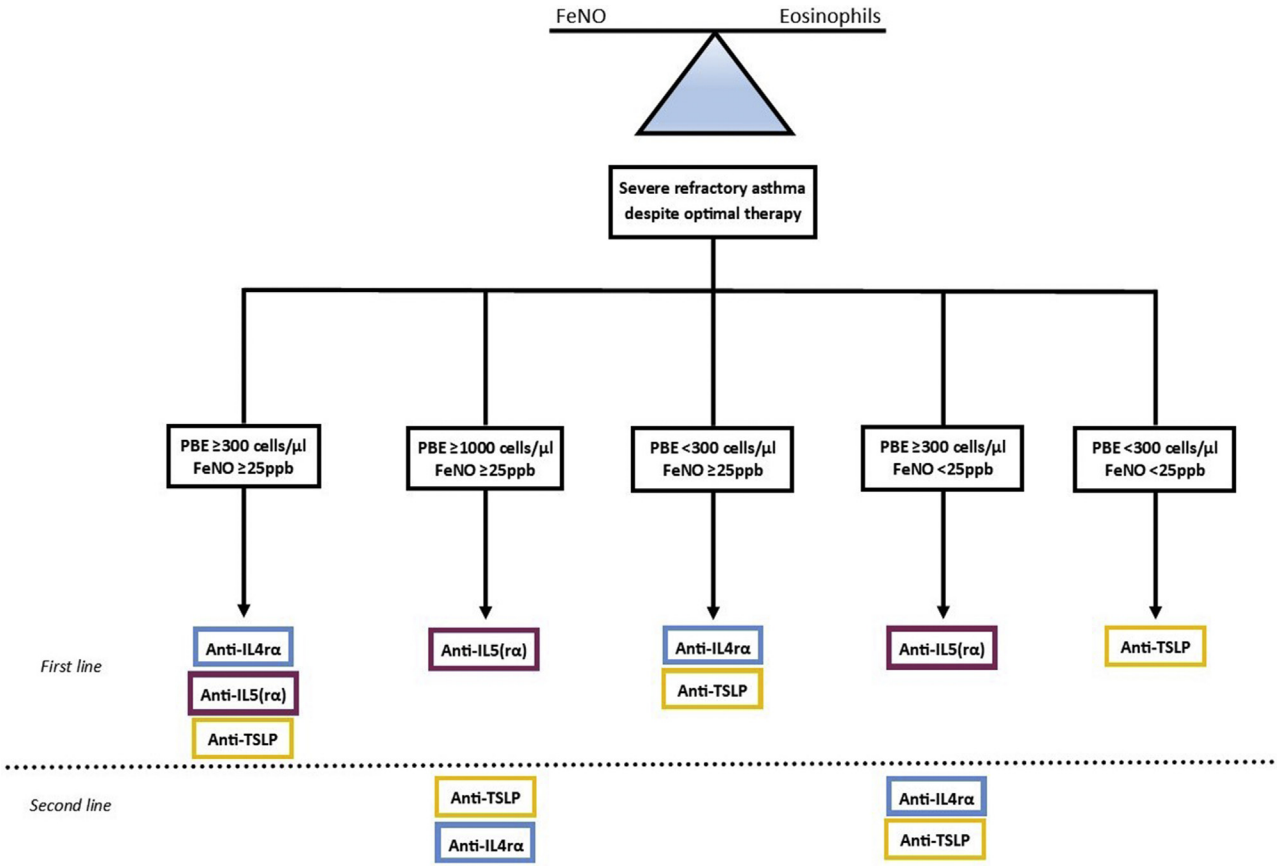

FIGURE 2. Type 2 biomarker pivot in regard to FeNO and blood eosinophils depicting the proposed clinical flowchart in severe refractory asthma despite optimal inhaled and oral therapies. Putative recommendations on first- and second-line biologics are shown according to specific disease endotypes irrespective of allergy status in patients not taking oral corticosteroids. In patients who have peripheral blood eosinophil (PBE) counts ≥300 cells/μL and FeNO ≥25 ppb, theoretically either anti-IL-4rα, anti-IL-5(rα), or anti-TSLP could be considered first line, although in patients with FeNO ≥50 ppb, indicating persistent IL-13 escape, anti-IL-5(rα) might become relatively less effective. FeNO ≥50 ppb would in turn predict a better response to anti-IL-4rα or anti-TSLP. Anti-IL-4rα may occasionally be associated with hypereosinophilia especially in patients with baseline PBE ≥1000 cells/μL, whereas anti-TSLP suppresses PBE albeit to a lesser degree than anti-IL-5(rα). *FeNO*, Fractional exhaled nitric oxide; *TSLP*, thymic stromal lympoietin.

improve FEV_1. Although downstream cytokine blockers have OCS-sparing effects, thus far anti-TSLP does not. Downstream cytokine blockers and anti-TSLP are all more effective in T2 high patients with raised PBE, whereas drugs that block IL-13 signaling including dupilumab and tezepelumab are more effective in patients with raised FeNO. Because of the unlikelihood of head-to-head biologic trials in the near future, we performed a brief indirect treatment comparison of dupilumab versus tezepelumab using phase 3 clinical trial data[27,31] with regard to lung function, asthma control, and FeNO (Table II). Absolute percentage improvements in FEV_1, FeNO, ACQ, and AER were largely comparable for either therapy calculated from a similar baseline. However, we appreciate that such comparisons, although intriguing, are often crude and should perhaps be interpreted with some caution.

Improvements in ACQ are significant across all biologics including antialarmins, and although questionnaires are subjective and influenced by patient expectations, perceptions, and comorbidities, their inclusion is vital for patient-and-clinician and interdisciplinary shared decision-making.

It is known that small airway dysfunction (SAD) is associated with poor asthma control, a higher AER, and more severe airway hyperresponsiveness.[53,54] However, the effect of biologic therapy on SAD has not been well characterized. Itepekimab has been shown to significantly improve forced mid expiratory flow rate (forced expiratory flow between 25 and 75% of forced vital capacity [FEF_{25-75}]) by 0.17 L/s (95% CI: 0.01, 0.33) compared with placebo in patients with severe asthma, whereas in the same study, dupilumab improved FEF_{25-75} by 0.19 L/s (95% CI: 0.03, 0.35) compared with placebo.[39] However, these improvements did not exceed the biological variability value of 0.21 L/s for FEF_{25-75} in severe asthma.[55] One real-life retrospective study showed that biologic therapy with mepolizumab or omalizumab improves FEF_{25-75} in severe asthmatics and that the difference in impulse oscillometry as resistance heterogeneity between 5 and 20 Hz (R5-R20) also significantly improved with biologic therapy in those with baseline R5-R20 ≥ 0.08 kPa/L/s,[56] in conjunction with significant improvements in asthma exacerbations and ACQ.[57] Another real-life study revealed significant improvements in FEF_{25-75} after 24 weeks of benralizumab therapy in allergic

patients with severe eosinophilic asthma.[58] Clearly, further prospective placebo-controlled studies powered *a priori* in patients who exhibit abnormal small airway function at baseline are required, powered on outcomes such as respiratory oscillometry or perhaps nitrogen washout.

There is emerging interest in the effect of biologic therapy on T2 comorbidities including chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic oesophagitis, chronic idiopathic urticaria (CIU), and atopic dermatitis.[59-62] One perhaps would expect a so-called higher burden of T2 inflammation in patients with concomitant T2 comorbidities. One retrospective study showed that patients with concomitant moderate-to-severe asthma with CRSwNP had higher circulating levels of FeNO and PBE compared with those with asthma alone.[63] Benralizumab is more effective in patients with asthma and CRSwNP than patients with asthma alone although this might be due to the presence of higher PBE in such patients.[52] All biologics currently used for the treatment of asthma are efficacious in CRSwNP although at present when using indirect treatment comparisons dupilumab seems to be the most effective.[64,65] Studies demonstrating similar associations with other combinations of T2 conditions would be of interest as further characterization of the disease endotype could help clinicians choose optimal biologic therapy. We look forward to the results of large ongoing clinical trials investigating the effects of tezepelumab on CRSwNP (NCT04851964) and CIU (NCT04833855).

Currently, there is an unfortunate lack of trial data concerning head-to-head biologic comparisons, but we anticipate the results of the PREDICTUMAB trial (NCT03476109) studying the magnitude and prediction of omalizumab versus mepolizumab response in adult patients with severe asthma.

Another pertinent area is the identification of factors that separate biologic super-responders from suboptimal or non-responders. For example, in large RCTs, the odds ratios (95% CI) for mepolizumab and benralizumab to reduce OCS requirement by 100% were 1.67 (0.49, 5.75) and 4.19 (1.58, 11.12), respectively.[19,20] We would especially like to see RCTs looking at combination therapy on AER, for example, comparing benralizumab plus dupilumab (ie, co-benradupilumab) versus respective monotherapy in patients with both high PBE and FeNO who are not controlled on either drug alone, to examine whether blocking all 3 downstream cytokines together confers additivity of response. This would test the hypothesis as to whether eosinophil escape via IL-5 or FeNO escape via IL-13 is pertinent in regard to achieving optimal control. For example, in our severe asthma clinic, we often see patients who reduce their AER from say 6 to 2 on antiI-IL-5 in the presence of eosinophil suppression but persistent FeNO elevation. Obviously, the cost of such combination therapy would in many countries be prohibitive although this might be counterbalanced by improved quality of life and in particular time off work. Although TSLP blockade might conceivably achieve attenuated signaling of IL-4/5/13, it should be borne in mind that eosinophil suppression with tezepelumab is much less effective compared with anti-IL-5. Hence, for patients with high PBE $\geq$1000 cells/μL, one might prefer to start off using anti-IL-5. Moreover, there is a paucity of data regarding the effects of biologics on AHR except for tezepelumab. Therefore, we look forward to the results with benralizumab (EudraCT number 2019-003763-22) and dupilumab (EudraCT number 2021-005593-25) powered on mannitol AHR in patients with uncontrolled severe asthma.

Hypereosinophilia with systemic manifestations is a potential concern when commencing patients on dupilumab therapy as reflected by the manufacturer's prescribing information.[45,66] In rare circumstances, anti-IL-4rα therapy has been associated with sudden deterioration of asthma, eosinophilic tissue infiltration, and eosinophilic granulomatosis with polyangiitis-like symptoms.[67] This is especially precarious if pre-existing hypereosinophilia has been masked beforehand by OCS or anti-IL-5 therapy, and this therefore would be a further argument for considering combined dupilumab and benralizumab or indeed tezepelumab alone for such patients. We are particularly intrigued to find out whether the observed improvements in AER, FEV_1, and ACQ with current monotherapy phase 3 data would be additive for combination biologic therapy. Although one might expect this to be the case, we are reminded that phase 3 data looking at combination therapy with the eosinophil suppressor itepekimab along with dupilumab were not superior to either drug alone compared with placebo in regard to loss of asthma control, FEV_1, or ACQ.[39]

More data are required on airway tissue biopsy and sputum cells especially eosinophils given the preliminary negative results of the EXPEDITION trial (NCT02573233) showing no impact of dupilumab versus placebo on airway inflammatory cells, especially as the UPSTREAM trial with tezepelumab showed a reduction of airway eosinophils. In this regard, benralizumab has also been shown in a phase 1 RCT to significantly reduce airway mucosal/submucosal eosinophils.[68]

In conclusion, although the underlying disease endotype is undoubtedly a crucial part of the immunological puzzle of asthma that requires solving, there are likely other currently unknown factors also at play. For example, if eosinophilic inflammation is the main driver of asthma exacerbations, can eosinophil depletion rather than suppression fully explain why switching from anti-IL-5 to anti-IL-5rα therapy significantly improve FEV_1, asthma control, and OCS dose requirement in suboptimal responders to the former?[69,70] Although head-to-head biologic trials are unlikely in the near future, we would be especially keen to see key patient outcomes along with safety data in response to combination biologic therapy.

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