New and emerging drug treatments for severe asthma

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Abstract

Asthma is a common chronic inflammatory condition of the airways affecting over 300 million people worldwide. In 5-10% of cases it is severe, with disproportionate healthcare resource utilisation including costs associated with frequent exacerbations and the long-term health effects of systemic steroids. Characterisation of inflammatory pathways in severe asthma has led to development of targeted biological and small molecule therapies which aim to achieve disease control whilst minimising corticosteroid-associated morbidity. Herein we review currently licensed agents and those in development, and speculate how drug therapy for severe asthma might evolve and impact on clinical outcomes in the near future.

Introduction

Asthma is a common airways disease, affecting over 300 million people worldwide [1], characterised by fluctuating symptoms of wheeze, dyspnoea, chest tightness and cough, accompanied by variable airflow obstruction [2].

Current guidelines recommend that pharmacological therapy for uncontrolled disease is escalated in a step wise manner, without phenotypic differentiation, until a patient is classed to have severe asthma [2, 3]. Severe asthma is defined in those for whom 'guidelines suggested medication for Global Initiative for Asthma (GINA) steps 4-5 asthma (high dose inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABA) or leukotriene receptor antagonist (LTRA)/theophylline) or regular oral corticosteroids are required for ≥50% of the previous year to prevent it becoming uncontrolled or which remains uncontrolled despite this therapy'. Poor control exists in those who remain symptomatic, experience frequent or serious exacerbations or demonstrate reduction in lung physiology [4]. Non-adherence and co-morbidities are common reasons for suboptimal treatment response, and these should be assessed and managed before asthma is considered refractory [4].

Severe asthma affects 5-10% of the total asthma population [4], but accounts for a disproportionate amount of asthma spending [5, 6], including direct costs such as scheduled and unscheduled care visits and pharmacotherapy, and indirect costs due to time off work and early mortality. Many severe asthmatics require treatment with maintenance systemic corticosteroids or frequent short courses which are associated with significant morbidity [7]. Based on the burden to the individual asthma sufferer and healthcare services, severe asthma remains a significant unmet clinical need.

As our understanding of the immunopathology of severe asthma has progressed, drugs are increasingly more specific; typically targeting single cytokines or their receptors. The underlying disease heterogeneity indicates that responses to treatment are unsurprisingly variable and are both phenotype and outcome specific [8]. It is therefore important to determine the different domains of the disease; including clinical expression, inflammation, disordered airway physiology and airway remodelling or damage. Some of these domains are amenable to current treatment strategies and have been described as 'treatable traits' [9, 10]. This has clinical utility, but importantly will change if those aforementioned features that are currently not easily ameliorated become successfully managed with emerging treatments. Biomarkers are used to identify these responder phenotypes, which themselves might represent mechanistic pathways underlying the pathophysiology driving the disease (i.e. endotypes) [11].

In this article we present an overview of the pathophysiology of severe asthma, then use evidence from key clinical trials to discuss corresponding treatment options, and their impact upon different severe asthma phenotypes and specific clinical outcomes.

Pathophysiology

The pathophysiology of asthma is a consequence of complex host-environment interactions that occur over time and across the spatial scales of the disease, from gene to proteins through to tissue and organ, impacted upon by environmental exposure to allergens, pathogens (viruses, bacterial and fungi) and pollutants such as smoking and particulates. The current focus of asthma therapies is upon airway inflammation. The inflammatory endotype *type 2 (T2) immunity high* is well-described [12-14] and has been the major focus of pharmacotherapy.

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Beyond T2-mediated inflammation there is non-T2 inflammation [15, 16] e.g. elevated T1 and T17-immunity, and other important processes that can co-exist or occur independently of inflammation; namely airway hyperresponsiveness, airway remodelling, cough reflex hypersensitivity and recurrent infection. To date the features which are beyond T2-inflammation remain inadequately addressed by current therapies.

T2-mediated eosinophilic inflammation (Figure 1) is the most common inflammatory endotype, demonstrated in 80% of corticosteroid naïve and 50% of corticosteroroid treated patients [17, 18], and may be underestimated due to the suppressive effects of treatment [19]. In children and childhood-onset disease particularly, it is often associated with allergy [20], however it can exist independent of this [21]. In allergic asthma, dendritic cells stimulate T-helper 2 (Th2) cells in the presence of coactivators such as epithelial derived thymic stromal lymphopoetin (TSLP), with subsequent production of the characteristic T2 cytokines interleukin (IL)-4, IL5 and IL13. TSLP, along with the other epithelial 'alarmins' IL25 and IL33, activates type-2 innate lymphoid cells (ILC2) promoting T2 inflammation, and upregulating IL-5 and 13 (but not 4) in response to epithelial insult in non-allergic disease [22]. IL5 is an integral cytokine involved in recruitment, maturation and survival of eosinophils. IL4 and IL13 also facilitate eosinophil trafficking into tissue via upregulation of adhesion receptors on the vascular endothelium. Eosinophils are recruited to the lung mucosa under the influence of the chemokines acting via the CC-chemokine type 3 receptor and by activation of prostaglandin D2 type 2 receptor (DP2), also termed chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [23]. Importantly, DP2 is also expressed by T2-lymphocytes, ILC2 and mast cells [24-26]. Release of eosinophil products cause damage directly to the bronchial epithelium and may also cause bronchoconstriction through release of cysteinyl leukotrienes. IL4 promotes B cell production of immunoglobulin E (IgE) following

B-cell class switching. IgE then binds with high affinity to mast cells, which following cross-linking by allergen results in degranulation with release of granule products, eicosanoids and cytokines which contribute to the overall inflammatory milieu and activation of the structural cells bronchial epithelium, mucous glands, goblet cells and airway smooth muscle. IL13 also increases the airway smooth muscle response and is involved in mucus hypersecretion [27]. Biomarkers of T2 inflammation which may be useful, alone or in combination, to predict response to treatments include sputum and blood eosinophils, exhaled nitric oxide (FeNO) and periostin [11].

T2 low inflammation is less well understood but is associated with later onset, non-atopic disease which is poorly responsive to corticosteroids [15]. Where inflammation is present it is typically neutrophilic in response to increased CXCR1/2 chemokines such as CXCL8. Activation of T1/T17 pathways or type 3 innate lymphoid cells have been implicated in T2 low disease [22] but the role of these pathways in asthma is unclear [28]. Indeed, T1/17 pathways are upregulated following suppression of T2 immunity, suggesting that a proportion of T2 low disease may be iatrogenic [29]. Some patients exhibit a pauci-granulocytic inflammatory profile, whereby there is no increase in airway granulocytes. This subgroup is associated with more benign disease with fewer exacerbations [30].

Airway hyperresponsiveness (AHR) is characterised by increased airway narrowing that can occur in response to direct or indirect stimuli. AHR is a consequence of heightened airway smooth muscle contractility and can occur independent of the inflammatory profile. Primary airway smooth muscle cultures from asthmatics demonstrate exaggerated contractility in part due to increased activation of nicotinamide adenine dinucleotide phosphate-oxidase 4 (NOX4) [31] expression with release of reactive oxygen species. *In vivo* mast cells are co-located to the

airway smooth muscle bundle and their number are associated with the degree of AHR [32]. In co-culture mast cells promote airway smooth muscle survival, activation and contractility via mast cell-derived IL-6 and 13, and stem cell factor [33, 34].

Airway remodelling reflects structural changes in the airway including ciliary dyskinesia, epithelial damage, goblet cell and mucous gland hyperplasia, sub-epithelial collagen deposition, increased myofibroblast and fibrocyte number, and airway smooth muscle hyperplasia and hypertrophy [32]. Increased airway smooth muscle mass is the strongest predictor of airflow limitation [35, 36] and is associated with computed tomography-derived airway narrowing [37]. Small airway obliteration is a consequence of airway wall remodelling, oedema secondary to increased vascularity, and mucus plugging. Importantly, airway remodelling can occur in childhood before evidence of airway inflammation, suggesting this is an important feature of asthma severity independent from rather than a consequence of chronic inflammation [38].

Recurrent infection is observed in severe asthmatics who have increased susceptibility to viral exacerbations [39, 40] and *S. pneumoniae* [41] lower respiratory tract infections. Persistent colonisation with bacteria, particularly proteobacteria such as *H. influenza* [42, 43] and fungi such as *A. fumigatus* [44], is a feature of some severe asthmatics and whether this is partly a consequence of corticosteroid therapy is unclear. Co-existent bronchiectasis is present in 40% of severe asthmatics [45] and this airway damage contributes to persistent colonisation and recurrent infection observed in severe asthma.

Cough reflex hypersensitivity is a feature of asthma. It is associated with airway inflammation and typically responds to corticosteroid therapy in the presence of T2-inflammation [46].

However, it can remain refractory and the predominant feature in some severe asthmatics. Therapies targeting the cough reflex in patients with chronic cough rather than specifically for asthma are under development and will not be discussed further in this review.

Treatment by pheno/endotype

T2 high disease

As above, T2 predominant disease is the most common inflammatory profile, and the focus of several treatments in development including biological agents and small molecules (Figure 1, table 1). We will consider agents licensed and in late phase trials.

Currently licensed biological treatments

Anti IgE: Omalizumab

The first biological therapy approved for the treatment of asthma was the anti-IgE agent omalizumab. It is licensed for use in moderate-to-severe atopic asthma in patients aged 6 years and over, with proven aeroallergen sensitisation. Omalizumab reduces circulating IgE in the blood and interstitial space, and inhibits IgE binding to high and low affinity receptors on mast cells, basophils and dendritic cells, leading to receptor downregulation and reduced recruitment of inflammatory cells downstream. A Cochrane meta-analysis of omalizumab [47] as add-on therapy in moderate-to-severe asthma demonstrated a significant reduction in exacerbations in both stable disease and when used as a steroid sparing agent, however subgroup analysis of those with severe disease (including oral corticosteroid dependency) alone did not demonstrate a clear benefit, questioning its utility in this group. Serum IgE levels were not found to be predictive of a treatment response [48, 49], however, a post-hoc analysis showed that high levels of the T2 biomarkers FeNO, blood eosinophils and periostin, did identify those with a

greater benefit [50]. Clinical trials are ongoing to assess whether other biomarkers can identify a clear target population [51]. As yet there are no direct head-to-head comparisons between omalizumab and other biologic agents for use in T2 high disease.

Anti-IL5: Mepolizumab and Reslizumab

Mepolizumab is an anti-IL5 agent licenced for use as add-on therapy for severe eosinophilic asthma in patients aged 12 years or older. Initial studies assessing effect on airway physiology questioned mepolizumab's utility [52, 53], however, as studies progressed through phase 2, the focus of study primary outcomes narrowed to asthma exacerbation rates [54] and potential for oral corticosteroid reduction [55], highlighting the critical nature of appropriate trial design and patient selection. The randomised, double blind, placebo controlled DREAM trial [56] evaluated intravenous mepolizumab versus placebo in eosinophilic asthmatics with a history of recurrent severe exacerbations (at least 2 in the preceding 12 months) at doses of 75mg, 250mg and 750mg administered at 4 weekly intervals over a year. Clinically significant reductions in severe exacerbations were seen at all doses. Although reductions in sputum eosinophils were dose dependent, exacerbation reduction was similar across the treatment groups; the first trial to demonstrate therapeutic effect in the lower 75mg dose. Atopic status was not predictive of response, indicating a different treatment population compared to anti-IgE therapy. A subsequent trial [57] compared low dose intravenous mepolizumab to an equivalent subcutaneous dose in 576 exacerbating asthmatics with evidence of eosinophilia despite corticosteroid treatment. Exacerbation rates were reduced by 47% in both treatment groups. The SIRIUS trial [58] examined the steroid-sparing effect of subcutaneous mepolizumab over 20 weeks in 135 severe, eosinophilic asthmatics. Median reduction of oral corticosteroid dose was 50% in the treatment group compared to 0% in those receiving placebo; despite which a significant reduction in exacerbations were also reported. Phase 3b data [59]

focusing primarily on the impact of mepolizumab treatment on asthma related quality of life scores demonstrated that in 551 patients over a 24 week period, use of mepolizumab significantly improved St George's Respiratory Questionnaire (SGRQ) score with a treatment difference of -7.7 when compared to placebo (p<0.0001). Reduction in exacerbations were consistent with previous data. An un-blinded, observational follow up study by Haldar [60] demonstrated that treatment benefits are not sustained on withdrawal of treatment, with no significant reduction in exacerbation rates in the mepolizumab group versus placebo over the 12 months following treatment cessation. Studies support the blood eosinophil count as a simple and reliable biomarker of response, although there is considerable debate over the threshold indicative of a positive result.

Reslizumab is another anti-IL5 agent recently licensed for use as add-on maintenance therapy for adults with severe eosinophilic asthma. Following an initial study demonstrating good effect in patients with nasal polyposis [61], 2 parallel phase 3 trials were reported [62] which randomised 953 subjects on high dose asthma treatment with a history of exacerbations to 4-weekly reslizumab infusions versus placebo, with the primary outcome exacerbation rate over 52 weeks. Eosinophilia was defined as a blood eosinophil count >400 cells/μL. Exacerbations were defined as a new requirement for oral corticosteroids, a two-fold increase in current dose of oral or inhaled corticosteroid for at least 3 days, or asthma-related emergency treatment and were analysed as such dependent on physician assessment, 20% reduction in forced expiratory volume in 1 second (FEV1) or a 30% reduction in peak expiratory flow rate (PEFR) over 2 consecutive days. Exacerbation rates were reduced by rate ratio (RR) 0.5 in study 1 and 0.41 in study 2 (p<0.0001). Time to first exacerbation was increased in those receiving reslizumab and statistically significant improvements were seen in FEV1, asthma control scores and blood eosinophil counts. A secondary analysis by baseline treatment demonstrated the most

significant improvements in exacerbation rates and lung function in those at GINA step 5 [63]. As with the other licensed biologic agents, no direct comparisons exist but a subsequent trial has evaluated the effects of reslizumab in a small population of patients previously treated with mepolizumab for a minimum of 12 months [64]. 10 eosinophilic, oral corticosteroid dependent patients received 2 infusions of placebo followed by 4 infusions of reslizumab. Sputum and blood eosinophils were significantly reduced, associated with improvements in FEV1 (p=0.004) and Asthma Control Questionnaire (ACQ)-5 scores (p=0.006), with a greater reduction in sputum eosinophil count with reslizumab compared to mepolizumab. Providing space for regular infusion-based treatment may limit use in some clinical services at present, however trials of subcutaneous reslizumab are ongoing [65].

Licensed agents: Safety and tolerability

Limited long term safety data exists for the newer agents however clinical trials suggest they are overall safe and well tolerated. Anaphylaxis can occur, although has been reported in small numbers and post dose monitoring is suggested in clinical practice. Concerns that omalizumab increases risk of malignancy have not been confirmed in a five year post-marketing study [66] and an increased severity of disease in the treatment population may have contributed to a higher incidence of cardio- and cerebrovascular events reported in patients receiving omalizumab [67]. The most frequently reported adverse effects associated with biologic agents are similar and include headaches, nasopharyngitis and upper respiratory tract infections.

Emerging treatments - beyond phase 2

Anti IL5R: Benralizumab

In contrast to the anti-IL5 agents described, benralizumab targets the α-subunit of the IL5 receptor expressed on eosinophils and basophils and may confer additional benefit through its

ability to stimulate active antibody-dependent cell mediated depletion of inflammatory cells and progenitors, compared to passive clearance of IL5 [68]. Phase 2 trials demonstrated reduced exacerbation rates in moderate to severe exacerbating eosinophilic asthmatics on a 4 to 8-weekly dosing schedule [69] which lead to the phase 3 trials CALIMA and SIROCCO [70, 71]. In CALIMA, 1306 patients with history of severe asthma on moderate to high dose treatment with history of at least 2 exacerbations in the preceding year received 30mg benralizumab subcutaneously 4 or 8-weekly or placebo. In patients with blood eosinophil counts >300 cells/µL, significant reductions in exacerbations were seen at both dosing regimens over the 48 week study period (Q4W RR 0.64, p=0.0018, Q8W RR 0.72, p=0.018). The cohort receiving treatment 8-weekly also demonstrated significant improvements in asthma symptom scores. SIROCCO included patients on high dose treatment with an otherwise similar design. Exacerbation rates were reduced (Q4W RR 0.55, p<0.0001, Q8W RR 0.49, p<0.0001) and significant improvements in lung function were seen. Nasopharyngitis was noted to be the most common adverse effect associated with treatment. Subanalyses have been completed using an eosinophil cut off of 150 cells/µL with statistically significant reductions in exacerbation rates also seen at this level [72], although higher blood eosinophils and more frequent exacerbations did predict greater improvements [73]. Oral glucocorticoid sparing effect was evaluated by Nair and colleagues [74] in 220 patients with oral glucocorticoid dependence and blood eosinophils >150 cells/µL. Patients were randomised to benralizumab 4 or 8-weekly or placebo with glucocorticoid dose reduced by 75% in those on treatment compared to 25% with placebo, and complete cessation achieved in approximately 50% on treatment. Despite steroid reduction, asthma control was maintained with a significant reduction in exacerbations and no deterioration in FEV1. A novel study of benralizumab administered in the emergency department in the setting of acute asthma exacerbation [75] demonstrated improved rates of recovery, however further work would be required to define

the use of biologics in this setting. Benralizumab is likely to obtain license for use in clinical practice in future and the less frequent, 8-weekly dosing schedule may be attractive when compared to other agents to improve adherence.

Anti-IL4R: Dupilumab

Dupilumab is a monoclonal antibody directed against the α-subunit of the IL4 receptor which inhibits both IL4 and IL13 signalling, an attractive target in view of the potential downstream effects of blocking both cytokine pathways. Phase 2a data from Wenzel et al. [76] demonstrated an impressive 87% reduction in exacerbations in asthmatics with blood eosinophils >300 cells/μL, however, maintenance medication in those receiving placebo was reduced over the trial duration, potentially enhancing the apparent effects. A phase 2b trial [77] randomised patients uncontrolled on medium-high dose therapy to 2 doses of subcutaneous dupilumab, 2 or 4-weekly versus placebo for 24 weeks. Primary outcome examined FEV1 change in the eosinophil high group, with significant improvement seen in all groups except those on the lower 4-weekly dosing schedule. Overall, improvements in lung function and an approximately 70% reduction in exacerbation rate was demonstrated irrespective of baseline eosinophil count, with most common adverse effects including upper respiratory tract infection and injection site reaction. Controller treatment was stable throughout the treatment phase. Preliminary reports from recent phase 3 trials [78] have demonstrated significant reduction in annual exacerbation rates, with effects increasing according to baseline blood eosinophil count (46% reduction overall, 60% in eosinophils >150 cells/μL, 67% in eosinophils >300 cells/μL, p<0.001). Pre-bronchodilator FEV1 at 12 weeks significantly improved in all groups with a 240ml improvement in those with eosinophils >300 cells/μL. In severe oral corticosteroid-dependent asthma dupilumab significantly reduced corticosteroid use, asthma attacks and improved lung function. These benefits were greater in those with higher baseline blood eosinophil counts,

but importantly were also observed in the group as a whole with or without high eosinophil counts. Dupilumab has also demonstrated efficacy for treatment of atopic dermatitis and chronic sinusitis with nasal polyposis [79, 80]. Earlier studies of IL4 inhibition alone and more recently phase 3 studies of the anti-IL13 biologics lebrikizumab [81] and tralokinumab [82] have failed to meet their primary endpoints of exacerbation reduction, suggesting that the combined effect of inhibiting both IL-4 and 13 is necessary to observe sufficient clinical efficacy for this aspect of the disease. Interestingly in subjects with activated IL13 axis, as evidenced by biomarkers such as FeNO and blood periostin, there is a consistent improvement in lung function in subjects treated with anti-IL13 versus placebo which might be a consequence of direct effects of IL13 upon airway smooth muscle. Thus the benefits in lung function in response to dupilumab might be largely via inhibition of IL13 signalling.

Anti-DP2: Fevipiprant

DP2 represents an attractive target in asthma having been demonstrated to be involved in actions of multiple T2 effector cells in addition to eosinophils, including Th2 cells, ILC2s, and airway epithelial cells [23-26]. Elevated levels of DP2 are seen in broncho-alveolar lavage of asthmatics, with increased numbers of DP2 positive cells increasing in correlation with disease severity [83], highlighting potential as a therapeutic target. Fevipiprant, an oral anti-DP2 treatment, was trialled in moderate to severe asthmatics with evidence of sputum eosinophilia [84] in a single-centre, placebo-controlled randomised controlled trial. Significant improvements were seen in eosinophilic inflammation in both sputum and the bronchial submucosa over the 12-week study period. Fevipiprant also improved symptom control, quality of life and lung physiology compared to placebo. Importantly epithelial and mesenchymal cells express DP2, and fevipiprant also impacted on airway remodelling with improved epithelial integrity and, for the first time in any placebo-controlled drug trial, a reduction in airway

smooth muscle mass [85]. The impact on airway smooth muscle is a consequence of both a reduction in airway inflammation and a direct effect upon airway smooth muscle migration and activation. Outcomes of subsequent clinical trials are eagerly awaited.

Anti-TSLP: Tezepelumab

Thymic stromal lymphopoeitin is an epithelial-derived cytokine, released in response to environmental and pro-inflammatory stimuli with downstream effects on a number of cells including dendritic cells, T and B cells and ILC2s [86]. Levels are higher in asthmatics compared to healthy controls and correlate with disease severity [87, 88]. Tezepelumab is an IgG2 monoclonal antibody which binds to TSLP preventing interaction with the TSLP receptor complex, shown to inhibit early and late asthmatic responses and T2 biomarkers [89]. A phase 2 trial [90] investigated the effect of tezepelumab in moderate to severe, exacerbating asthmatics at 3 dose ranges. Significantly less exacerbations were seen at all doses (0.26, 0.19, 0.22 vs 0.67 in placebo group, $p<0.001$ in all) and was irrespective of eosinophil count or other T2 biomarkers, although substantial reductions in these measures were noted. Significant improvements in lung function were shown universally and persisted for the duration of the trial. Rates of adverse events were similar in placebo and treatment groups. 3 serious adverse events were deemed related to the trial agent; one case of pneumonia and stroke in the same patient receiving low dose treatment, and one case of Guillain-Barre syndrome in the medium dose group. These results confirm the significant role of epithelial cytokines in asthma pathogenesis and suggest that targeting upstream cytokine pathways may improve control across inflammatory profiles, representing a promising option for those with T2 disease but also possibly beyond T2-mediated inflammation.

Table 1: Biological agents for moderate-severe asthma: Results since 2010 of phase 3 programmes (or phase 2 trials for ongoing phase 3 programmes)

Drug Target	Reference	Population	Dose/duration	Primary outcomes	Secondary outcomes
Mepolizumab Anti-IL5	Chupp LRM 2017 MUSCA Phase 3b[59]	Adults and children (>12 years), n = 556 ≥2 exacerbations in last year Background therapy: high dose inhaled corticosteroid plus additional controller(s) Pre-bronchodilator FEV1 < 80% in adults ≥ 18 years (<90% in 12-17 years) Blood eosinophils ≥300/µl in last 12 months or ≥150/µl at screening	100mg SC Q4W 24 weeks	SGRQ: ↓ score by 7.7 vs placebo	↓ exacerbation rate 42% ↑ FEV1 120ml
	Bel NEJM 2014 SIRIUS Phase 3[58]	Age range: 16-74 years, n = 135 Background therapy (5 to 35 mg/day of prednisone or its equivalent) for > 6 months Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	100mg SC Q4W 20 weeks	Oral corticosteroid use: ↓oral corticosteroid use (~50%)	↓ exacerbation rate ~32% ↓ ACQ (~0.52)
	Ortega NEJM 2014 MENSA Phase 3[57]	Adults and children (aged ≥12 years), n = 576 ≥2 exacerbations in last year Background therapy (≥880 µg/day fluticasone propionate equivalent) for >3 months and an additional controller Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	75mg IV Q4W or 100mg SC Q4W 32 weeks	Exacerbation rate: ↓ exacerbation rate ~50%	↑ FEV1 (100 mL) ↓ ACQ (~0.43), SGRQ (~7)
Reslizumab Anti-IL-5	Corren Chest 2016 Phase 3[91]	Adults and children (12 – 65 years), n = 492 ACQ ≥1·5 Background therapy (≥440 µg/day fluticasone propionate equivalent) for >1 month and an additional controller Bronchodilator response >12%	3mg/kg IV Q4W 16 weeks	FEV1 at week 16 ↔ FEV1	Eosinophil[High]: ↑ FEV1 (270 mL) ↓ ACQ (0.49) No benefits in eosinophil[Low] group
	Bjermer Chest 2016 Phase 3[92]	Adults and children (12 – 75 years), n = 315 ACQ ≥1·5 Background therapy (≥440 µg/day fluticasone propionate equivalent) for >1 month and an additional controller Blood eosinophil count ≥400 cells/µL	0.3mg/kg IV Q4W or 3mg/kg IV Q4W 16 weeks	FEV1 at week 16 in eosinophil[High]: ↑ FEV1 (~140 mL)	↓ ACQ (~0.3), ↑ AQLQ (~0.3)
	Castro LRM 2015 Phase 3[62]	Adults and children (12 – 75 years), n = 953 (study 1 n=489, study 2 n=464) ≥1 exacerbation in last year ACQ ≥1·5 Background therapy (≥440 µg/day fluticasone propionate equivalent) for >1 month and an additional controller	3mg/kg IV Q4W 52 weeks	Exacerbation rate (eosinophil[High] only recruited >400 cells/µL): ↓ exacerbation rate ~60-80%	↑ FEV1 (100 mL) ↓ ACQ (~0.25), ↑ AQLQ (~0.23)

		Bronchodilator response >12% Blood eosinophil count ≥400 cells/□L			
Benralizumab Anti-IL-5R	Nair NEJM 2017 ZONDA Phase 3[74]	Adults (18 – 75 years), n = 220 Background therapy (7.5 – 40mg/day prednisolone or its equivalent for > 6 months) Blood eosinophils ≥150 cells/µL at screening	30mg SC Q4W or Q8W 28 weeks	Oral corticosteroid use: ↓oral corticosteroid use (75%)	↓ exacerbation rate 55-70%
	Bleecker Lancet 2016 SIROCCO Phase 3[71]	Adults and children (12 – 75 years), n = 1205 ≥2 exacerbations in last year ACQ ≥1.5 Background therapy ICS plus LABA for ≥1 year before enrolment (high-dose ICS in adults and moderate-to-high in children) and another controller Pre-bronchodilator FEV1 <80% (adults), <90% (children), bronchodilator response >12%	30mg SC Q4W or Q8W 48 weeks	Exacerbation rate in eosinophil[High]: ↓exacerbation rate (~50%)	↑ FEV1 (110 mL) ↓ ACQ (~0.25), ↑ AQLQ (~0.25)
	Fitzgerald Lancet 2016 CALIMA Phase 3[70]	As per SIROCCO, n = 306	30mg SC Q4W or Q8W 56 weeks	Exacerbation rate in eosinophil[High]: ↓exacerbation rate (~30%)	↑ FEV1 (~120 mL) ↓ ACQ (~0.2), ↑ AQLQ (0.2)
Dupilumab Anti-IL4Rα	QUEST Phase 3[78]	Adults and children (≥12 years), n = 1902 Background therapy ≥250 mcg of fluticasone BD - 2000 mcg/day fluticasone and another controller	200mg SC Q2W or 300mg SC Q2W 52 weeks	Exacerbation rate: ↓ exacerbation rate 46% FEV1 at week 12: ↑ 130ml at 300mg dose	Rate of LOAC events/severe exacerbation events Time to LOAC event/ severe exacerbation event
	Wenzel Lancet 2016 Phase 2b[77]	Adults (≥18 years) ≥1 exacerbation in last year ACQ ≥ 1.5 Background therapy ≥500µg/day fluticasone proprionate equivalent + LABA for > 1 month Pre-bronchodilator FEV1 40-80%, bronchodilator response >12%	200mg SC Q2W or Q4W or 300mg Q2W or Q4W 24 weeks	FEV1 at week 12 in eosinophil[High]: ↑FEV1 (~210ml)	↓ exacerbation rate ~60-80% ↓ ACQ (~0.5) ↑ AQLQ (~0.6)
Fevipiprant Anti-DP2	Gonem LRM 2016 Phase 2[84]	Adults (≥18 years), n = 61 ≥1 exacerbation in last year or ACQ ≥1.5 Background therapy (low- to high-dose ICS) Sputum eosinophil count ≥2% at screening	225mg BD PO 12 weeks	↓ Sputum eosinophils	↑ FEV1 (160 mL) ↓ ACQ (0.56), ↑ AQLQ (0.59)
Tezepelumab Anti-TSLP	Corren NEJM 2017 Phase 2[90]	Adults (18-75 years), n = 584 ≥2 exacerbations requiring OCS or ≥ 1 severe exacerbation that led to hospitalization in last year ACQ≥1.5 Background therapy (250-500µg/day fluticasone + LABA) or high dose (>500µg/day fluticasone for > 6 months Pre-bronchodilator FEV1 40%-80%, bronchodilator response ≥12%, ≥200ml	70mg SC Q4W or 210mg SC Q4W or 280mg SC Q2W 52 weeks	Exacerbation rate: ↓exacerbation rate ~60-70%	↑FEV1 (~100-150ml) ↓ ACQ, ↑AQLQ at high dose

T2 low inflammation

There are few established treatment options for T2 low disease, the burden of which is subject to debate, once the suppressive effects of corticosteroids on T2 high disease are accounted for. A number of anti-inflammatory agents directed against neutrophilic inflammation are no longer in development having shown inconsistent clinical benefit and concerning adverse effects, including anti-TNF (tissue necrosis factor) [93-97], anti-CXCR2 [98] and the anti-IL17 agent brodalumab [99]. A trial of anti-IL23 is ongoing and results are awaited [100]. Targeting mast cells with the tyrosine kinase inhibitor imatanib improved AHR [101] (as previously shown with anti-TNFα) supporting the view that this aspect of disease is responsive to therapy, but due to poor tolerability and known adverse events these therapies are not being developed further for asthma.

Antimicrobials

Macrolide antibiotics have demonstrated efficacy in reducing acute exacerbations of COPD [102] and bronchiectasis [103], although whether the benefit is entirely via its antibiotic properties or in concert with its anti-inflammatory effects is uncertain. A 2013 study by Brusselle and colleagues [104] demonstrated a reduction in exacerbations in a subgroup of non-eosinophilic asthmatics (characterised by low blood eosinophils and FeNO without sputum analysis) treated with low dose azithromycin, suggesting a possible role in patients selected by a T2 low phenotype. A more recent trial [105] of 420 moderate to severe asthmatics, randomised to 500mg azithromycin thrice weekly or placebo met the primary outcome of overall reduction in moderate to severe exacerbations (1.07 per patient year on azithromycin vs 1.86 for placebo group, IRR 0.59), with benefit demonstrated in both eosinophilic and non-eosinophilic subjects on subgroup analysis. Increased numbers of macrolide resistant organisms were noted on surveillance cultures across the trial period and there is a general

recognition that this issue represents a significant barrier to widespread uptake of long term antimicrobial therapy in airways disease. Current guidelines do not recommend macrolide use in severe asthma [4]. Fungal sensitisation is an important consideration in treatment refractory asthma, previously reported to be present in up to 50% of cases [106]. Anti-fungal treatment is recommended in allergic bronchopulmonary aspergillosis [4], however, trials in severe asthma with fungal sensitisation not meeting criteria for ABPA have failed to demonstrate a consistent benefit [107].

Discussion

The ultimate goals of asthma therapy are prevention of disease onset, inducing total remission whilst continuing therapy without treatment-related adverse events, or cure. To date the new and emerging therapies discussed above have not been tested to address their impact on asthma prevention, and have neither led to cure nor total remission. Some have demonstrated benefits on asthma symptoms, control and health status with positive impacts on future risk of exacerbations, lung function impairment and reduction in adverse events from current therapy, in particular oral corticosteroids. These benefits have resulted in new licensed therapies for asthma and provided new insights on asthma pathogenesis and the relationship between the underlying pathobiology and clinical expression.

Clinically it will be important to make choices as to which biologic to select for which patient. Although studies have helped to define responder groups, head-to-head trials will be required to further define responder characteristics. Notwithstanding the need for these data, the choice of biologic will also be driven pragmatically by local and national rules for access to licensed therapies.

Targeting eosinophilic inflammation has been successful with three biologics in phase 3 reducing severe exacerbations. The magnitude of reduction in exacerbations was related to the degree of eosinophilic inflammation with reductions in the region of 50% in the blood eosinophil high groups. Improvements in lung function and symptoms were also related to baseline blood eosinophil counts, but the effects on these outcomes were more modest. For the two anti-IL5 biologics (mepolizumab and benralizumab) that explored corticosteroid sparing effects there were consistent reductions in oral corticosteroid dose. Interestingly, reductions in exacerbations were at least comparable if not greater following anti-IL4Rα, with greater improvements in lung function and symptoms than observed with anti-IL5. Effects of anti-IL13 are less than anti-IL4Rα in terms of exacerbation reduction whereas both improve lung function, perhaps via direct effects upon airway smooth muscle. Whether the reduction in exacerbations attributed to anti-IL4Rα are due to an impact upon airway eosinophilic inflammation and whether this effect is different than anti-IL13 is unknown. Importantly, targeting IL4Rα and IL13 increases blood eosinophil counts, possibly due to effects upon eosinophil adhesion to the endothelium [108].

The consistent reduction in exacerbations in all therapies that reduce eosinophilic inflammation suggest that other therapies that ameliorate eosinophilic inflammation in development including fevipiprant in phase 3 [109], the GATA-3 DNAzyme awaiting phase 2b [110] and dexpramipexole in phase 2a [111], are likely to reduce exacerbations and could represent important future pre-biologics if well-tolerated. Corticosteroid resistance or relative insensitivity is also a possible mechanism for inadequate response to corticosteroid therapy[4]. Targeting corticosteroid resistance has been of therapeutic interest for many years, but therapies have not moved into late phase development in part due to toxicity. Some such as

inhaled phosphatidylinositol 3-kinase delta (PI3K) inhibitors are in early phase development[112].

Cytokines upstream of T2 inflammation such as TSLP and possibly IL33 might have greater benefits than targeting individual T2 cytokines or their receptors. Indeed the anti-TSLP phase 2 study suggested greater benefits in terms of exacerbation reduction, symptoms and lung function improvements than previously observed with other biologics. Anti-TSLP also reduced blood eosinophil counts. Whether this can be replicated in a more severe population in later phase studies will be important. Anti-IL33 is currently in phase 2a studies in asthma [113] and whether this intervention also has broad efficacy is eagerly awaited.

Recently licensed biologics for asthma have underscored the importance of precision medicine with the need to both identify a biologically responsive group and a tractable outcome such as eosinophilic inflammation in severe asthma with frequent exacerbations. This dogma becomes undermined if newer treatments have a broader efficacy for which precision medicine becomes less important. The broad spectrum efficacy observed in phase 2 for anti-TSLP with respect to symptoms, lung function and exacerbations, with these benefits independent of eosinophilic inflammation, begins to challenge our view on precision medicine. It will be important in later phase trials of anti-TSLP to determine the mechanisms of action and magnitude of effects beyond the predicted benefits in eosinophilic disease as this will determine whether this could become a therapy for a wider asthma population, including possibly those with T2 low disease. Interestingly TSLP is also important in allergic sensitisation [114], which tantalisingly might mean this intervention could in the future influence disease onset and possibly prevent disease.

Some features of airway remodelling, such as thickening of the lamina reticularis, are reduced by corticosteroids but other features such as epithelial damage and increased airway smooth muscle mass are resistant to standard therapy [115]. Fevipiprant promotes epithelial repair and is the only drug intervention to demonstrate a reduction in airway smooth muscle mass suggesting it might impact on disease progression by reversing some of the features of airway remodelling. Whether other therapies implicated in epithelial function such as the biologics targeting the alarmins TSLP and IL33 impact on airway remodelling need to be explored in future bronchoscopic studies.

It is likely that despite the successes described above some patients will still have persistent poorly controlled disease. Whether this is due to co-morbidities, poor adherence or non-T2 disease refractory to all the above strategies remains uncertain. It is possible that antibiotics or perhaps alternative strategies to normalise the airway microbiome might have an important role in the future beyond the current use of macrolide antibiotics. This would need to have minimal or no further impact on the increasing burden of anti-microbial resistance. Whether targeting non-T2 mediated inflammation such as IL17/23 pathways also remains to be determined.

Current and emerging therapies are therefore moving towards partial remission of established disease. However, we need to raise expectations of total control as well as prevention and cure. In the short term this will require a reassessment of what is disease remission in terms of maintaining control and eliminating future risk. Recent success of therapies make this ambition more realistic than previously considered and will help to develop new strategies to define success and failure of interventions, thus helping to determine stopping and switching rules in the clinic and for shaping future head-to-head studies of new therapies. Prevention and cure remain more challenging goals, but positioning of these new therapies in earlier disease,

especially in children, will help us to understand their role in disease onset and early progression.

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Figure Legend

Figure 1. Biologics and emerging small molecule therapies for severe asthma licensed or in phase 3; their targets in the immunopathology of the disease and clinical impact. ↑ improve, ↓ attenuate, ↔ no effect, ? awaiting data, or not studied and ↑↓ variable reports. *Dupilumab studies included non-atopic subjects in phase 2 and 3. Effects in non-atopic were not reported in phase 2 but phase 3 full report is awaited. IL, interleukin; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoeitin; DP2/PGD2, prostaglandin D2; R, receptor; RBM, reticular basement membrane.