

Interleukin-5 Inhibitors for Severe Asthma: Rationale and Future Outlook

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Abstract In this review, we outline the pathophysiology of severe asthma and discuss the role of anti-interleukin (IL)-5 inhibitors for the treatment of asthma. Anti-IL-5 treatments have shown efficacy in reducing the rate of severe asthma attacks in eosinophilic asthma. We review the history of the development of these agents, lessons learnt about severe asthma along the way and key clinical trials supporting efficacy of the three anti-IL-5 treatments that are clinically available or undergoing clinical trials in asthma.

Key Points

Severe asthma attacks are responsible for a large amount of morbidity and healthcare spending.

Anti-interleukin (IL)-5 treatments significantly reduce the rate of severe exacerbations in eosinophilic asthma.

The peripheral blood eosinophil count is a robust, clinically accessible biomarker to predict response to anti-IL-5 treatment.

1 Introduction

Asthma is a common inflammatory condition of the airways that affects over 300 million people worldwide [1]. It is typically characterised by episodes of breathlessness, wheeze and cough due to an increased tendency of the airway to narrow (airway hyperresponsiveness), airway mucosal inflammation and increased airway mucus production. People with asthma are at risk of asthma attacks (also known as exacerbations), the most clinically important aspect of the disease which results in significant morbidity and mortality. Asthma attacks are characterised by worsening symptoms and airflow limitation, a diminished response to rescue bronchodilator treatment and a requirement for unscheduled healthcare utilisation and/or hospital admission. Asthma attacks still result in around 1200 deaths per year in the UK [2].

The clinical features of asthma have historically been thought to be due to a common underlying pathological process, with an implied homogenous, predictable response to a standard treatment regimen, escalated according to symptoms. It is, however, increasingly clear that asthma is a complex, heterogeneous condition with a number of clinically and pathologically distinct phenotypes and endotypes [3]. Until recently, there have been few novel therapies for asthma after the invention of the mainstays of asthma treatment—oral corticosteroids (OCSs) and inhaled bronchodilators in the 1950s, and inhaled corticosteroids (ICSs) in the 1960s. The first monoclonal antibody for respiratory disease was not in use until 2003 when omalizumab was licensed for the use in persistent, allergic asthma. The identification of eosinophilic airway inflammation as a recognisable, treatable trait that is linked to the risk of severe asthma attacks and has easily accessible biomarkers has been key to identifying and developing

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treatments that target this inflammatory pathway [4]. The most successful and studied treatments targeting eosinophilic inflammation are treatments that target the interleukin (IL)-5 pathway. In this review we outline the pathological processes in severe eosinophilic asthma and the current and emerging treatments targeting the key inflammatory IL-5 pathway.

2 Pathophysiology of Severe Asthma

The majority of people with asthma are well-controlled on inhaled treatments, but around 10% of people have severe asthma and require high-dose treatment to obtain control or remain uncontrolled despite treatment [5]. The most recent European Respiratory Society/American Thoracic Society (ERS/ATS) definition of severe asthma is shown in Table 1. Severe asthma is a complex clinical problem with regards to its diagnosis, treatment and the contribution of co-morbid factors, and is associated with a high level of morbidity (both disease and treatment related), healthcare utilisation and spending. Often the problem is that the diagnosis is incorrect, or that asthma is uncontrolled because of a failure to master the basics of asthma management including treatment adherence, inhaler technique and smoking cessation. Symptoms may also persist because of the presence of a co-morbid condition such as obesity and psychosocial issues. Because of the complexity of the condition, patients with severe asthma should be managed by an asthma specialist with access to detailed airway tests and a multi-disciplinary team that includes specialist nurses, physiotherapists and pharmacists.

Asthma had historically been classified as allergic ('extrinsic') or non-allergic ('intrinsic') based on the age of onset and the presence of clinically or pathologically detectable allergies. A developing knowledge of reliable

measurements of airways inflammation and the underlying inflammatory mechanisms has shown asthma to be a heterogeneous disease involving a number of inflammatory pathways, with no single pathology that is unique to the labels 'extrinsic' or 'intrinsic' asthma. An alternative classification of asthma based on underlying inflammation is a more clinically relevant categorisation since defining asthma by these inflammatory phenotypes can aid treatment decisions, with new and emerging treatments targeted at the underlying mechanistic pathways. Eosinophilic asthma is a distinct phenotype that has been identified both clinically using biomarkers and treatment responses [6–9] and by using unbiased multivariate cluster analysis in asthma populations [3, 10].

3 Role of Eosinophils and Interleukin (IL)-5 in Asthma

Inflammation in the airways is driven by two main pathophysiological themes, namely type-2-driven mechanisms resulting in eosinophilic inflammation and non-type-2 mechanisms such as the T helper (Th) 1 and Th17 pathways, often resulting in neutrophilic inflammation. Interactions between the bronchial epithelium and external factors are thought to be the driving force in producing airways inflammation. The known and potential underlying mechanisms resulting in type-2 inflammation are shown in Fig. 1.

Eosinophils are potent granulocytic white blood cells that have a natural role in the innate immune response against helminth parasites, viruses and bacteria. They are also associated with allergic disease such as atopic dermatitis and atopy. Eosinophils make up a small fraction of the total blood white cell count, accounting for between 1 and 4% of the total count [11]. They are found in the

Table 1 European Respiratory Society/American Thoracic Society (ERS/ATS) definition of severe asthma 2014 [5]

Severe asthma is defined as:

Asthma that requires treatment with guideline-suggested medications for GINA steps 4–5 asthma (high-dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for >50% of the previous year to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy

Uncontrolled asthma is defined as at least one of the following:

Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)

Frequent severe exacerbations: ≥ 2 bursts of systemic CS (>3 days each) in the previous year

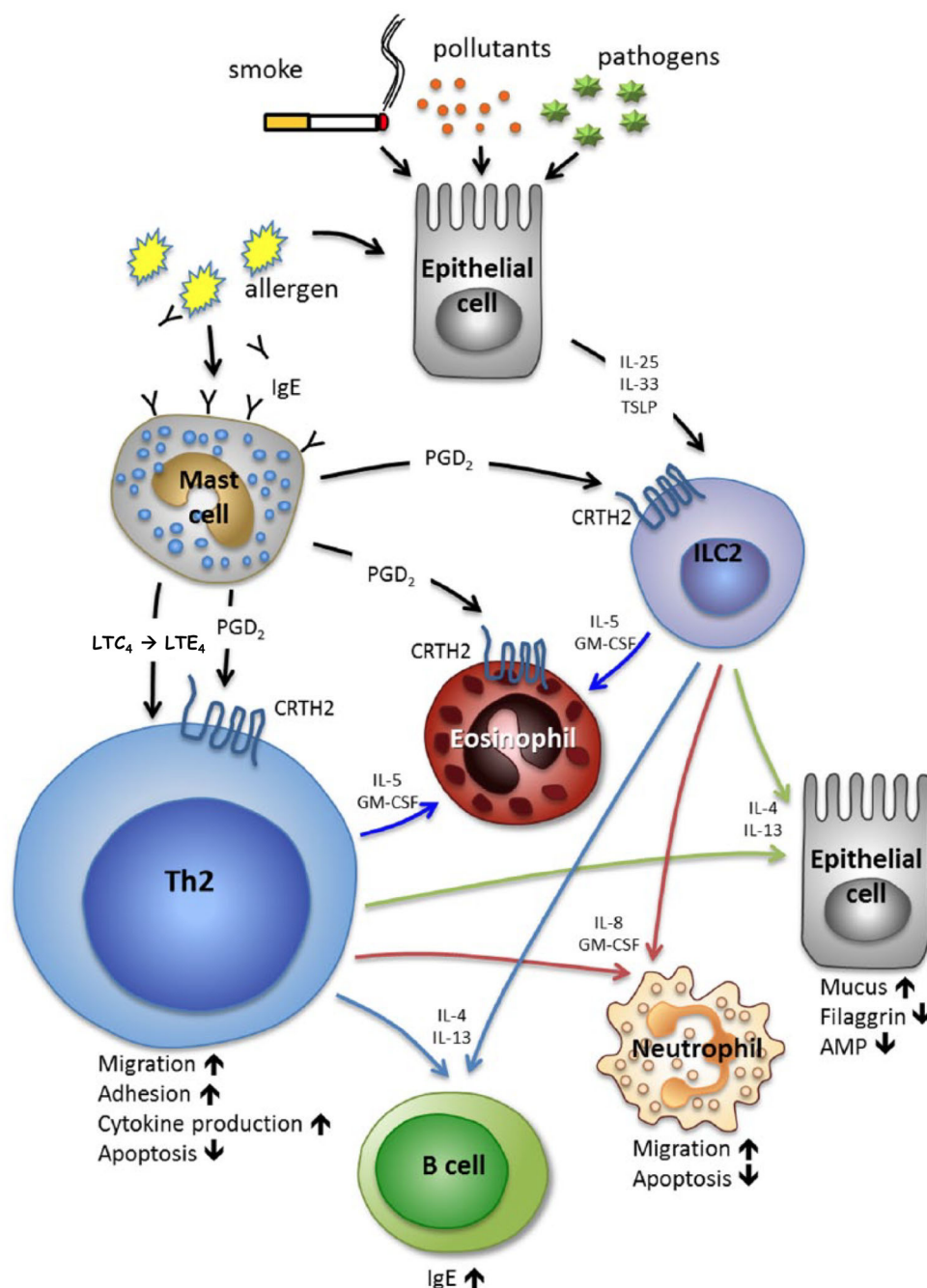
Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year

Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

ACQ Asthma Control Questionnaire, ACT Asthma Control Test, CS corticosteroids, FEV_1 forced expiratory volume in 1 s, FVC forced vital capacity, GINA Global Initiative for Asthma, ICU intensive care unit, LABA long-acting β_2 -agonists, NAEPP National Asthma Education and Prevention Program

Fig. 1 Mechanisms of eosinophilic inflammation due to interactions of antigens and irritants at the air/epithelial layer interface. Antigens and irritants can induce eosinophilic inflammation via the IgE-mediated hypersensitivity pathway and also by IL-25- and IL-33-mediated activation of ILC2 cells. AMP antimicrobial peptide, CRTH2 chemokine receptor homologous molecule expressed on Th2 lymphocytes, GM-CSF granulocyte-macrophage-colony-stimulating factor, IgE immunoglobulin E, IL interleukin, ILC2 innate lymphoid cell type 2, LTC₄ leukotriene C₄, LTE₄ leukotriene E₄, PGD₂ prostaglandin D₂, Th2 T-helper type 2, TSLP thymic stromal lymphopoietin



circulation for only a number of hours after release from the bone marrow, where they mature, before migrating in to tissue where they can live for 2–5 days, although this may be extended depending on the tissue and the surrounding cytokines [12]. Tissue eosinophils account for 99% of the total body eosinophils.

Eosinophil granules contain four cationic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPX) and eosinophil-derived neurotoxin (EDN). Upon activation, degranulation

of eosinophils causes release of these cytotoxic proteins, as well as a host of pro-inflammatory cytokines such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8 and IL-13, lipid mediators including prostaglandins and leukotrienes, and reactive oxygen species [13]. This release causes local tissue damage and inflammation, as well as the recruitment of further inflammatory cells.

Eosinophils are found in increased numbers in the sputum, bronchial biopsies and peripheral blood samples of patients with type-2-mediated asthma [14–16]. The

underlying cause or trigger for this eosinophilic inflammation remains unclear; only 50% of type-2 asthma has a demonstrable allergic component. The presence of eosinophilic inflammation in the airways is associated with an increased risk of future exacerbations, increased medication use, increased symptoms and increased airway hyperresponsiveness [3, 14, 17, 18]. Eosinophilic inflammation is associated with a positive response to both inhaled and OCS-based anti-inflammatory treatment [7, 17, 19]. It has previously been difficult to identify those at highest risk of poor asthma outcomes due to eosinophilic inflammation, but recognition and measurement of biological markers specific to the underlying inflammatory process, such as the blood eosinophil count, sputum eosinophil count and fractional exhaled nitric oxide (FENO), has allowed us to phenotype patients according to their underlying pathology [20]. A summary of clinically accessible biomarkers with current and potential uses in defining type-2 high disease and predicting treatment responses is shown in Table 2.

IL-5 is the key cytokine in the development of eosinophilic inflammation. It is produced by a number of cells including CD4+ type-2 cells (Th2), CD8+ type-2 cells (Tc2), eosinophils, basophils, mast cells and innate lymphoid cells type-2 (ILC2) [13, 21–23]. IL-5 is involved in all stages from haematopoiesis in the bone marrow to promoting recruitment and maturation of eosinophils into the bloodstream and increasing eosinophil survival in tissues. IL-5 is also an important chemo-attractant, causing migration of eosinophils from the blood into the affected tissues. IL-5 works via the IL-5 receptor (IL-5R), which is composed of two subunits: the α subunit (IL-5R α) and the β subunit (IL-5R β). IL-5R α is found exclusively on eosinophils and basophils and is responsible for binding IL-5. The IL-5R β subunit does not directly bind IL-5, but is responsible for signal transduction. IL-5R β is found on most white blood cells [24].

4 Anti-IL-5 and Anti-IL-5 Receptor Treatments

Given the very selective and biologically relevant nature of cells that IL-5 works directly on, neutralising the action of IL-5, either by targeting IL-5 itself or the IL-5R, is an attractive target for the treatment of eosinophilic asthma. There are currently three monoclonal antibody therapies in clinical use or undergoing phase III clinical trials in humans. Mepolizumab and reslizumab target the IL-5R α binding domain of IL-5, whereas benralizumab targets the IL-5R itself [25].

4.1 Mepolizumab

Mepolizumab, the first anti-IL-5 treatment trialled in asthma, is a recombinant, humanised, IgG monoclonal antibody against IL-5. The first randomised controlled trial (RCT) of anti-IL-5 treatment in asthma investigated the effects of mepolizumab on the response to allergen challenge in patients with mild, allergic asthma. This trial showed dramatically reduced blood and sputum eosinophil counts in the 16 patients receiving mepolizumab compared with the eight patients that received placebo, but no improvements in airway hyperresponsiveness or the airway response to inhaled allergen [26]. A subsequent, larger RCT conducted to evaluate the safety and efficacy of mepolizumab in 362 patients with moderate asthma selected on the basis of persistent symptoms and impaired lung function showed again that blood eosinophil counts were significantly lowered by the drug. The clinical endpoints of lung function and quality of life were not significantly improved [27]. This disappointing result led some people to question whether eosinophilic inflammation played a fundamental role in asthma, as greatly reduced numbers of eosinophils in the blood and the sputum did not translate to improved symptoms or lung function [28]. However, patients with active eosinophilic

Table 2 Biomarkers of eosinophilic inflammation

Biomarker	Association with treatment response	Invasiveness	Comments
FENO	Corticosteroids, anti-IL-13, anti-IL-4 and -13, anti-IgE	Non-invasive	Easy, quick, not specific, cheap, generally available
Serum IgE	Not associated	Minimal	Although recommended to be measured, there is no clear association between IgE as a biomarker and treatment responses or clinical outcome
Serum periostin	Anti-IL-13 ^a	Minimal	Effect shown with anti-IL-13; high costs and limited availability currently
Blood eosinophil count	Anti-IL-5 ^a , anti-IL-4/-13	Minimal	Generally available, high clinical impact, predicts anti-IL-5 response. Less clear predictor in anti-IL-4/-13 treatment
Sputum eosinophil count	Corticosteroids, anti-IL-5	Moderate	Specialist centres, tissue specific, time-consuming

FENO fractional exhaled nitric oxide, IgE immunoglobulin E, IL interleukin

^a Proven clinical efficacy in combination with this treatment

disease are at risk of exacerbations, so it is possible that mepolizumab would have a selective effect on this outcome. Moreover, treatment could only be expected to work in patients with active eosinophilic airway inflammation, which had not been a recruitment criteria in these earlier studies. This change in thinking led to the design of trials to investigate whether treatment with IL-5-targeted therapy reduced the frequency of severe asthma attacks in patients with severe eosinophilic asthma.

An RCT conducted to evaluate the effect of monthly intravenous dosing of mepolizumab or placebo on exacerbation rates over 1 year studied participants who had proven severe, eosinophilic asthma, defined as a sputum eosinophil count of $>3\%$ in the year leading up to recruitment. This trial involved 61 patients who took their regular medications in addition to the trial medications. Mepolizumab showed a 43% relative risk reduction of severe exacerbations and a modest improvement in asthma-specific quality-of-life scores [29]. Treatment with mepolizumab was associated with a marked reduction in the sputum and blood eosinophil counts, as seen in previous trials.

A further RCT of mepolizumab, also reported in 2009, compared monthly intravenous mepolizumab with placebo over 6 months in 20 participants with severe asthma and persistent sputum eosinophils who required OCS treatment, and had a phased withdrawal of OCSs during the trial period. This trial showed that mepolizumab reduced blood and sputum eosinophils and allowed OCSs to be reduced significantly compared with placebo. Improvements were also seen in the forced expiratory volume in 1 s (FEV_1). The patients taking mepolizumab treatment were able to reduce their OCS dose by a mean of 83.8% compared with 47.7% for those taking placebo [30]. This magnitude of corticosteroid reduction was much larger than seen in the only other monoclonal antibody available for asthma at the time, omalizumab. Steroid Reduction with Mepolizumab Study (SIRIUS) looked specifically at the reduction in need for OCS treatment [31]. It found that patients treated with mepolizumab were able to reduce their OCS dose by a median of 50% compared with no reduction for those taking placebo. The mepolizumab-treated group in this trial, despite lowering their corticosteroid dose, had a lower rate of exacerbations and an improved symptom score compared with the placebo group.

A much larger, multicentre RCT, the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial was designed to define the dose of mepolizumab and identify the optimum biomarker for predicting treatment response. It evaluated three doses of mepolizumab (75, 250 and 750 mg) delivered by monthly intravenous injection. Participants with severe eosinophilic asthma with a history of exacerbations were studied

($n = 621$). Eligible participants for the trial needed to demonstrate evidence of eosinophilic airway inflammation as reflected by one or more of the following: sputum eosinophils $>3\%$, blood eosinophils $>0.3 \times 10^9/L$, FENO >50 ppb and/or a prompt deterioration in asthma following a 25% reduction in corticosteroid treatment. This large study showed a large reduction in the number of severe exacerbations, with around a 50% reduction at all doses compared with placebo (Fig. 2) [32].

Significant reductions in the blood and sputum eosinophil count were seen and, whilst a dose-response relationship was seen for the latter, no such effect was seen for clinical outcomes and blood eosinophil reductions. Moreover, the study showed that the blood eosinophil count was more predictive of a response to mepolizumab treatment than any other measure, suggesting that the active treatment target is the circulating eosinophil (Fig. 3). The identification of a blood eosinophil level as a predictor of response to mepolizumab treatment is important as it is easily measurable across all hospitals, unlike induced sputum differential cell counts which require specialist expertise in obtaining and evaluating the sample.

The finding that lower doses of mepolizumab were effective meant that subcutaneous administration was feasible as lower volumes of drug were required. The Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trial [33] used the key characteristic of the blood eosinophil count to identify eligible patients. Subjects needed to have a blood eosinophil count of $>0.15 \times 10^9/L$ at study entry, or $>0.3 \times 10^9/L$ in the past 12 months. This study used the lower dose of 75 mg intravenously compared with a subcutaneous dose of 100 mg and placebo. MENSA confirmed the results of previous trials, with a marked reduction in severe exacerbation rates and a clear relationship between clinical

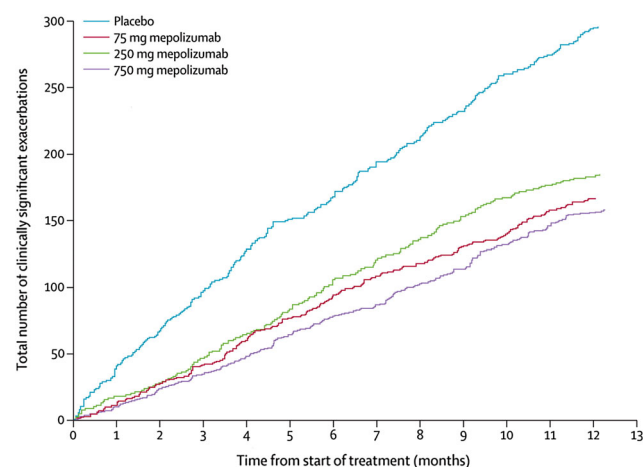


Fig. 2 Cumulative number of exacerbations in each treatment group—DREAM study, 2012 [25]. Significantly reduced exacerbation rate at all doses of mepolizumab

DREAM: Potential Predictor of Response

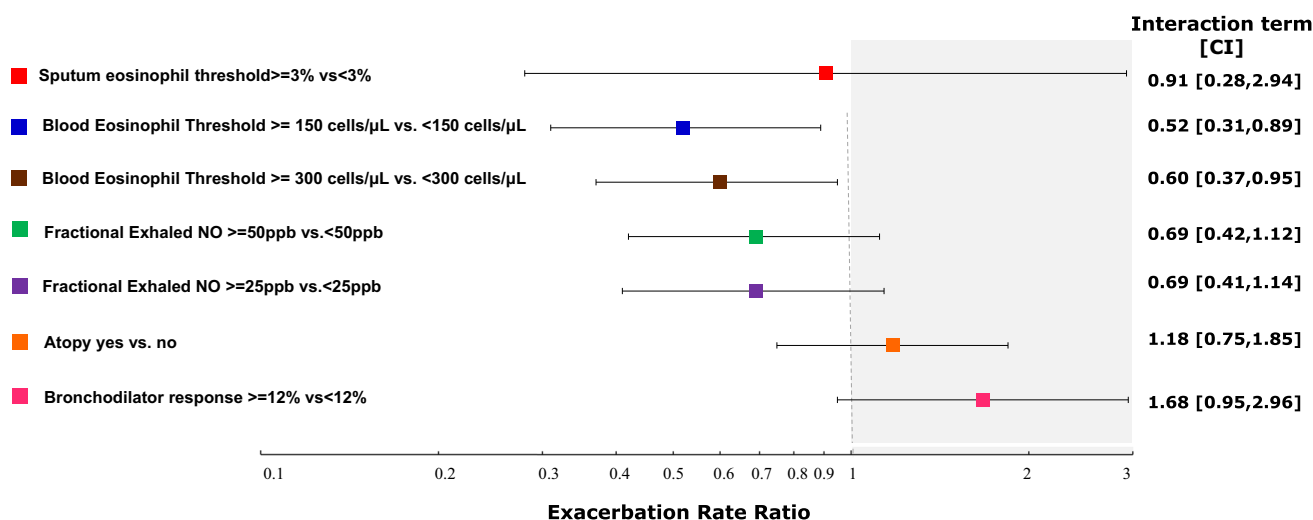


Fig. 3 DREAM: potential predictor of response. A post hoc analysis of exacerbation reduction ratios compared seven biomarkers above and below the listed threshold when measured at baseline Adapted

from GlaxoSmithKline data on file; electronic supplementary material accompanying Pavord et al. [32]. *CI* confidence interval, *NO* nitric oxide

benefit and baseline blood eosinophil count. Unlike in other studies, there was clear evidence of improvement in lung function and symptom scores, potentially reflecting better identification of a treatment-responsive population. Subgroup analysis showed a very large beneficial effect in the 30% of patients with a blood eosinophil levels of $> 0.5 \times 10^9/\text{L}$ (Fig. 4).

No difference was seen between subcutaneous and intravenous dosing [33]. The efficacy of subcutaneous dosing means that administering the drug is much simpler as it does not require the placement of an intravenous needle but can be given as a small injection under the skin.

Mepolizumab received approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2015 and the UK's National Institute for Health and Care Excellence (NICE) in 2017 and is now available for clinical use.

4.2 Reslizumab

Reslizumab is another humanised IgG antibody against IL-5, which is delivered via intravenous injection. An early trial of reslizumab in 106 subjects with severe eosinophilic asthma, as defined by sputum eosinophils of $\geq 3\%$, showed a reduction in sputum eosinophils and a small improvement in FEV_1 with treatment compared with placebo [34]. In two parallel phase III clinical trials in a total of 953 participants with poorly controlled, moderate–severe eosinophilic asthma, reslizumab at a dose of 3 mg/kg showed a similar effect to mepolizumab with a marked reduction in exacerbations of 50–59% [35], although patients did need to have a higher blood eosinophil count of $\geq 0.4 \times 10^9/\text{L}$ to enter the trial than in the mepolizumab trials. In contrast, a trial of reslizumab in 492 participants with uncontrolled asthma, but no selection criteria based on the presence of

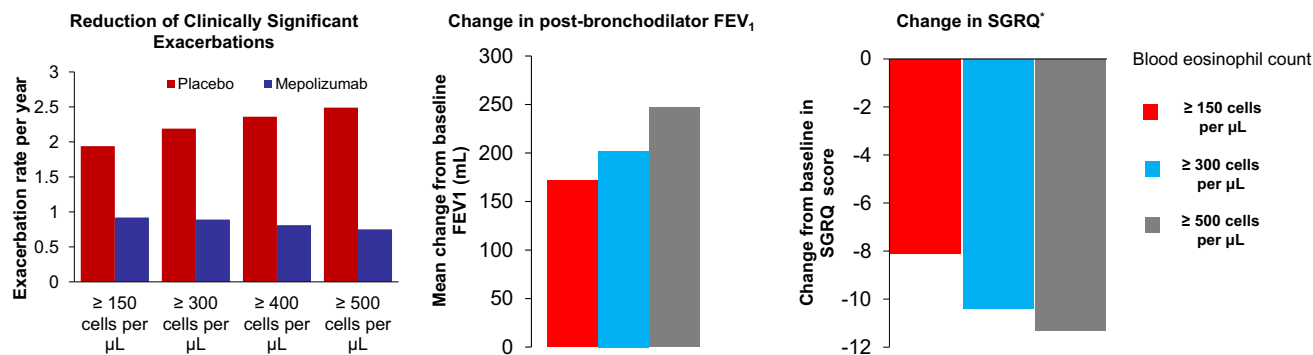


Fig. 4 Key MENSAs results by blood eosinophil count. Significant improvements in exacerbation frequency, FEV_1 and SGRQ with increasing blood eosinophil count. * increasing change shows

improved control. FEV_1 forced expiratory volume in 1 s, SGRQ St. Georges Respiratory Questionnaire

eosinophilic inflammation, showed no significant improvements in symptoms or lung function. Subgroup analysis showed improvements in the clinical outcome measures of asthma symptom control [Asthma Control Questionnaire (ACQ)], FEV₁ and rescue short-acting β_2 agonist use in participants with blood eosinophils $\geq 0.4 \times 10^9/\text{L}$ [36]. A 16-week trial of reslizumab in uncontrolled moderate and severe asthma patients with a blood eosinophil count of $\geq 0.4 \times 10^9/\text{L}$ showed that a dose of 3 mg/kg showed improvements in FEV₁ and symptom scores when compared with the lower dose of 0.3 mg/kg and placebo [37].

4.3 Benralizumab

Benralizumab is a humanised IgG antibody against the IL-5R α subunit of the IL-5R and inhibits proliferation of IL-5-dependant cell lines [38]. It is given as a subcutaneous injection. Benralizumab has shown efficacy in reducing exacerbations in participants with blood eosinophils $\geq 0.3 \times 10^9/\text{L}$ in a phase IIb dose-ranging study evaluating monthly subcutaneous dosing treatment for 1 year in 606 participants [39]. The largest studies of benralizumab to date were reported in October and November 2016. The SIROCCO trial randomised 1205 participants with severe asthma to receive placebo or benralizumab 30 mg every 4 or 8 weeks [40]. This study stratified subjects by their baseline eosinophil count of either above or below $0.3 \times 10^9/\text{L}$. The investigators found a 45–51% reduction in exacerbation rate in the eosinophilic group with both dosing regimens compared with a 17–30% reduction in the non-eosinophilic group. Lung function was also improved in the eosinophilic group for those receiving 8-weekly injections. The duplicate CALIMA trial with 1306 participants showed a 28–36% reduction in exacerbations for eosinophilic participants and an improvement in lung function with both dosing regimens [41].

Benralizumab has also shown increased eosinophil cell death via antibody-dependant, cell-mediated toxicity *in vitro* [42]. These mechanisms result in a rapid eosinopenia (low eosinophil count) following dosing with the drug and this was sustained for 8–12 weeks [43]. An RCT was conducted to evaluate whether a single dose of benralizumab given, alongside usual treatment, at the time of an acute asthma exacerbation reduced the occurrence of further exacerbations. The trial of 110 participants showed that in the 74 subjects receiving benralizumab, a single dose of benralizumab 0.3 or 1 mg/kg reduced the rate of exacerbations over the next 3 months by 49% [44]. This finding raises the possibility of using benralizumab as an add-on or alternative to usual treatment with OCSs for an asthma attack. Using benralizumab in place of OCSs may be logical, as it is likely that the main beneficial effect of

OCSs in treating an exacerbation is reducing circulating eosinophils. Further exacerbation trials are needed to answer this question.

A summary of the key anti-IL-5 trials and their subjects are shown in Table 3.

5 Discussion

In combination, these trials have shown that anti-IL-5 treatment is effective at reducing the risk of severe asthma exacerbations when used in patients with active eosinophilic asthma as shown by sputum or blood eosinophils. These large trials support the view that anti-IL-5 treatments are well-tolerated with an acceptable safety profile. The longer-term effects of anti-IL-5 treatment and its subsequent depletion of eosinophils is subject to ongoing study. Eosinophils may have a role in cancer rejection, including the activation of macrophages affecting the tumour vascularisation [45].

Currently, asthma guidelines do not recommend measuring markers of eosinophilic inflammation [46]. We suggest that, with the emergence of inflammation-targeted therapies, understanding and defining the inflammatory phenotype is key in deciding which treatments to offer in severe asthma. Induced sputum testing gives a direct reflection of the inflammatory processes in the airway but is time-consuming and requires technical expertise both in obtaining and processing the sample [20]. The blood eosinophil count and FENO are very accessible, minimally invasive biomarkers that predict eosinophilic airways inflammation to a good degree and could be measured routinely. The blood eosinophil count appears to be the best predictor of response to anti-IL-5 treatment [47].

Whilst the reduction in future severe asthma exacerbations is a very clinically important endpoint, anti-IL-5 treatment may have other specific uses in asthma. Mepolizumab has been shown to allow a reduction in the OCS dose, high doses of which are a cause of significant treatment-related morbidity, with no worsening of asthma control [31]. The corticosteroid-sparing effect of the other IL-5 treatments should be explored. There may be a role for the use of benralizumab in the treatment of acute eosinophilic asthma attacks [44], either as an adjunct to OCSs, which are currently the mainstay of treatment of severe asthma attacks, or in place of them as the main benefit from OCSs seems to be the eosinophil-depleting effect, which is achieved rapidly with benralizumab.

The future uses of anti-IL-5 treatment may be personalised depending on the patient history and clinical situation, i.e. whether it is for the treatment of an acute exacerbation or for the prevention of future exacerbations.

Table 3 Key trials of anti-interleukin-5/anti-interleukin-5 receptor therapy in asthma

Study, year	Drug	Study population	No. of subjects	Dose	Mean blood eosinophils ($\times 10^9$ cells/L)	Study period	Outcomes vs. placebo
Leckie et al. [26], 2000	Mepolizumab	Mild allergic asthma	24	Single-dose IV	0.38	16 weeks	Lowered blood and sputum eosinophils <i>No effect on late airway response to allergy or histamine</i>
Flood-Page et al. [27], 2007	Mepolizumab	Moderate ICS treated asthma	362	250 or 750 mg IV, 4-weekly	0.37	20 weeks	Lowered blood and sputum eosinophils <i>No significant differences in lung function, symptoms or SABA use</i> Possible trend towards lower exacerbation rate in treatment groups
Halder et al. [29], 2009	Mepolizumab	Refractory, eosinophilic (sputum $\geq 3\%$ eosinophils) asthma with at least 2 courses of OCS in the preceding 12 months	61	750 mg IV 4-weekly	0.34 ^a	12 months	Lowered blood and sputum eosinophils <i>43% relative risk reduction for severe exacerbations</i> Improved asthma quality of life scores (AQLQ) No significant differences in lung function
Pavord et al. [32], 2012	Mepolizumab	Refractory, eosinophilic (sputum $\geq 3\%$ eosinophils or blood eosinophils $\geq 0.3 \times 10^9/L$ or FENO ≥ 50 ppb) asthma with at least 2 courses of OCS in the preceding 12 months	621	75, 250 or 750 mg IV 4-weekly	0.25 ^a	12 months	<i>48–52% reduction in severe exacerbations</i> <i>Rate of reduction in exacerbations varied according to the baseline blood eosinophil count</i> Lowered blood and sputum eosinophils No significant differences in lung function or symptom scores
Ortega et al. [33], 2014	Mepolizumab	Severe asthma with blood eosinophils $\geq 0.15 \times 10^9/L$ at screening or $>0.3 \times 10^9/L$ in the preceding 12 months	576	100 mg SC or 75 mg IV 4-weekly	0.30 ^a	40 weeks	<i>Similar efficacy of subcutaneous and intravenous dosing</i> Lowered blood eosinophils Small improvement in FEV ₁ and improvement in QOL scores
Bel et al. [31], 2014	Mepolizumab	Severe asthma with blood eosinophils $\geq 0.15 \times 10^9/L$ at screening or $>0.3 \times 10^9/L$ in the preceding year AND OCS use for at least 6 months	135	100 mg SC 4-weekly	0.24 ^a	32 weeks	<i>Median reduction of 50% of OCS dose compared with no reduction in placebo arm</i> Reduced annualised exacerbation rate: 1.4 vs. 2.1 Lowered blood eosinophils No significant change in lung function
Castro et al. [34], 2011	Reslizumab	Severe eosinophilic (sputum eosinophils $\geq 3\%$) asthma	106	3 mg/kg IV 4-weekly	0.5 ^b	15 weeks	<i>Reduction in sputum eosinophils</i> Small improvement in FEV ₁ Possible trend towards improved symptom scores, more marked in subjects with nasal polyps
Castro et al. [35], 2015	Reslizumab	Moderate-severe, uncontrolled asthma (ACQ) with blood eosinophils $\geq 0.4 \times 10^9/L$ in screening period	953	3 mg/kg IV 4-weekly	0.65	15 months	<i>50–59% reduction in asthma exacerbations</i> Small improvements in FEV ₁ and asthma symptom and control scores Reduction in blood eosinophils

Table 3 continued

Study, year	Drug	Study population	No. of subjects	Dose	Mean blood eosinophils ($\times 10^9$ cells/L)	Study period	Outcomes vs. placebo
Corren et al. [36], 2016	Reslizumab	Moderate-severe, uncontrolled (ACQ) asthma	492	3 mg/kg IV 4-weekly	0.28	28 weeks	No significant difference in FEV_1 or ACQ Subgroup analysis showed improvements in FEV_1 , ACQ and rescue SABA use in subjects with blood eosinophils $\geq 0.4 \times 10^9/L$
Castro et al. [39], 2014	Benralizumab	Moderate-severe uncontrolled (ACQ) asthma with 2-6 courses of OCS in the preceding 12 months	606	2, 20 or 100 mg SC 4-weekly	0.56—eosinophilic subgroup 0.18—non-eosinophilic subgroup	12 months	41% reduction in asthma exacerbations in the eosinophilic subgroup receiving the 100 mg dose 20 and 100 mg doses reduced exacerbations in individuals with blood eosinophils $\geq 0.3 \times 10^9/L$ Small improvement in FEV_1 in eosinophilic subgroup
Nowak et al. [44], 2015	Benralizumab	Acute asthma exacerbation requiring ED assessment with 1 previous exacerbation in the preceding 12 months	110	0.3 or 1 mg/kg SC once	0.25	24 weeks	Reduced asthma exacerbation rates by 49% and exacerbations resulting in hospitalization by 60% Reduced blood eosinophils No difference in FEV_1 or ACQ
FitzGerald et al. [41], 2016	Benralizumab	Moderate-severe asthma with at least 2 courses of OCS in the last 12 months	1306	30 mg SC 4- or 8-weekly	0.36	56 weeks	28–36% reduction in exacerbation rate with either dosing regimen in subjects with blood eosinophils $\geq 0.3 \times 10^9/L$ Small improvements in FEV_1 with both doses Improvement in asthma symptom scores with both doses
Bleecker et al. [40], 2016	Benralizumab	Moderate-severe asthma with at least 2 courses of OCS in the last 12 months	1205	30 mg SC 4- or 8-weekly	0.37	48 weeks	45–51% reduction in exacerbation rate with either dosing regimen in subjects with blood eosinophils $\geq 0.3 \times 10^9/L$ Small improvements in FEV_1 with both doses Improvement in asthma symptom scores with 8-weekly dosing

All of the trials were randomised, double-blind, placebo-controlled trials in subjects with asthma. Selected outcomes shown in *italics*

ACQ Asthma Control Questionnaire, AQLQ asthma quality of life questionnaire, ED emergency department, FENO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 sec, IV intravenous, OCS oral corticosteroid, QOL quality of life, SABA short-acting β_2 -agonist, SC subcutaneous

^a Geometric mean

^b Median

Questions, however, remain about the use of anti-IL-5 treatments in asthma. It is not known what happens to the pattern of inflammation or to asthma control when treatments are withdrawn—do they go back to baseline, or is there a lasting effect? Data from the post-treatment follow-up period of a mepolizumab study suggests that blood eosinophils and exacerbation frequency increase back to baseline over 6 months following stopping treatment [48]. Further studies are needed to explore this post-treatment period. Another area of uncertainty is around the type, and management, of asthma attacks for subjects on anti-IL-5 therapy—as blood eosinophils are quickly and fully depleted by anti-IL-5 therapy, are asthma attacks while receiving therapy different in nature to those before therapy, and should they still be treated with eosinophil-depleting corticosteroid therapy? Close examination of these asthma attacks, with appropriate inflammatory phenotyping, that occur whilst on treatment with anti-IL-5 will help answer these questions.

6 Conclusion

Therapies targeting the IL-5 pathway in eosinophilic asthma markedly reduce the risk of severe asthma attacks. The peripheral blood eosinophil count, a widely accessible biomarker, is the best predictor of response to anti-IL-5 treatment and should be used to select patients to offer these treatments to. Current, ongoing studies will help further refine the role of anti-IL-5 treatment in eosinophilic asthma, both in preventing asthma attacks and as a possible treatment for them.

Compliance with Ethical Standards

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