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REVIEW

Targeting Eosinophils in Asthmatic Inflammation: Benefits and Drawbacks

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Abstract: Asthma is associated with eosinophilic airway inflammation which contributes to poor asthma outcomes in a subset of severe asthmatics. This review traces the scientific rationale as well as the clinical development of novel therapeutics to target either IL-5 or the IL-5α receptor to deplete eosinophils from the airway to improve asthma outcomes in severe asthma with eosinophilic airway inflammation. The importance of IL-5 to eosinophil growth, survival, and function was initially identified in mice, and has been confirmed in studies of human eosinophils. As both IL-5 and the IL-5α receptor were identified as therapeutic targets to deplete eosinophils in the airway in asthmatics, humanized IgG antibodies were developed to target either IL-5 or the IL-5α receptor in eosinophilic asthma. The current availability of three biologics that deplete eosinophils (mepolizumab, reslizumab, and benralizumab) has provided a novel therapeutic approach to treat severe asthma with eosinophilic inflammation not controlled by inhaled corticosteroids in combination with long acting bronchodilators. Two of these eosinophil targeted biologics (mepolizumab, reslizumab) target IL-5 an eosinophil growth factor, while the third eosinophil targeted biologic (benralizumab) targets the IL-5α receptor expressed by eosinophils. Each of these eosinophil targeted therapies significantly deplete eosinophils in the blood, sputum, and airway and are associated with a significant approximately 50% reduction in asthma exacerbations in most studies without significant side effects. In addition, selected studies have shown that eosinophil targeted biologics improve asthma symptom quality of life scores and lung function. At present, there are no direct head to head comparison studies to determine whether any of the three eosinophil targeted biologics has a better asthma outcome profile/safety profile. The development of eosinophil targeted biologics has been a significant advance in the treatment of severe asthma with eosinophilic inflammation.

Keywords: anti-IL-5 antibody, anti-IL-5 receptor antibody, asthma, mepolizumab, reslizumab, benralizumab

Introduction

Airway Inflammation and Asthma

Airway inflammation is a well recognized and cardinal feature of asthma.[1] Unraveling how the individual components of the airway inflammatory response contribute to the pathogenesis of asthma has been an important focus of investigators wishing to understand which of the component(s) of the inflammatory response are worth targeting to improve asthma outcomes. A variety of airway inflammatory cells have been implicated in the pathogenesis of asthma including eosinophils, CD4 cells, mast cells, neutrophils, dendritic cells, macrophages, as well as structural cells in the airway including airway smooth muscle, epithelium, and fibroblasts.[1] In this review, we focus on understanding the benefits and drawbacks of targeting only one of the components of the airway inflammatory response in asthma (ie eosinophils) to improve asthma outcomes.

Rationale for Targeting Eosinophils to Improve Asthma Outcomes

Eosinophilic inflammation is a key component of the airway inflammatory response in asthma, and increased numbers of circulating and airway eosinophils are accompanied by more frequent asthma exacerbations and declines in lung function.[2,3] Eosinophilic inflammation is present in approximately 50% of patients with asthma[2] and is associated with asthma severity, greater frequency of asthma exacerbations, and decreased lung function.[3] Additionally, poor asthma

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control is associated with progressive increases in sputum and blood eosinophil counts.[4] Thus, there is a need for novel therapies in severe asthma that target eosinophilic inflammation. Approximately 5% to 10% of asthmatics have severe asthma that is usually managed, but often incompletely controlled, with high-dose inhaled corticosteroids and long acting bronchodilators. Although severe asthmatics only comprise a small percentage of all asthmatics, severe asthmatics utilize approximately 50% of the total care costs of asthma which in the USA in 2014 was estimated to be approximately $37 billion due to the high cost of hospitalizations, ER visits, medications, and productivity loss.[5] As approximately 32% to 45% of severe asthmatics rely on either frequent oral corticosteroid bursts, or maintenance use of continuous oral corticosteroids because of poor asthma control,[6–8] it is important to develop non-corticosteroid therapies for severe asthma that are both effective and also avoid the side effects associated with chronic oral corticosteroid use.

The initial rationale for targeting eosinophils to improve asthma outcomes was based on several lines of evidence including the fact that a) eosinophils produce many pro-inflammatory mediators[9] that can contribute to the pathogenesis of asthma, b) large numbers of eosinophils have been identified in the airway in asthmatics which are associated with asthma exacerbations, decline in lung function, and poor asthma control,[2–4] and that c) depleting eosinophils in pre-clinical models of asthma improves asthma outcomes.[10] In this review, we provide greater detail about the sequence of studies that contributed to targeting the eosinophil in asthma, as well as the benefits and drawbacks of targeting the eosinophil that have been identified from these studies.

Biology of Eosinophils: Implications for the Pathogenesis of Asthma

Eosinophil Trafficking from Bone Marrow to the Lung in Asthma

Eosinophils are bone marrow derived granulocytes which traffic from the bone marrow to the lung in response to cytokine and chemokine signals. IL-5 is an eosinophil active cytokine which induces eosinophil differentiation and proliferation in the bone marrow.[9] Eosinophils express cell surface adhesion molecules (including L-selectin, β1 and β2 integrins) which allows the eosinophil to bind to adhesion counter-receptors expressed by endothelial cells lining the interior of inflamed blood vessels at sites of inflammation in the lung.[11] If there is no inflammation in the lung, endothelial cells lining the interior of blood vessels in the lung do not express induced adhesion molecules and eosinophils in the blood stream do not bind to endothelium in the lung and continue their flow in the circulation. However, if there is inflammation in the lung, mediators such as histamine or cytokines (TNFα, IL4, IL13) released from lung mast cells, macrophages, and/or other lung cells upregulate adhesion molecule expression by endothelium allowing eosinophils to adhere to adhesion molecules expressed by endothelial cells in the lung.[11] Eosinophils adherent to adhesion receptors such as VCAM-1 and ICAM-1 expressed by endothelial cells migrate into the airway in response to chemokines released by airway cells in particular airway epithelium. Eosinophils express α4β1 adhesion molecules, also known as VLA-4, which binds to its counterreceptor VCAM-1 expressed by endothelial cells.[11] As neutrophils do not express significant VLA-4, the eosinophil expression of VLA-4 allows for a VLA-4/VCAM-1 pathway that preferentially recruits eosinophils as opposed to neutrophils to the lung.[11] Eosinophils and neutrophils both express β2 integrins which bind to ICAM-1 expressed by endothelium allowing both eosinophils and neutrophils to utilize this β2 integrin and ICAM-1 pathway to enter the lung from the bloodstream. Eotaxin-1 is an example of prominent eosinophil specific chemoattractant, released by bronchial epithelium, which can direct migration of eosinophils from blood vessels in the airway to the bronchial epithelial cell mucosal surface along a chemokine gradient highest at the epithelium.

Eosinophil Pro-Inflammatory Mediators and Contribution to Asthma

The eosinophil expresses many pro-inflammatory mediators which can contribute to airway inflammation and airway hyperreactivity (AHR) in asthma including preformed cytoplasmic granule proteins (ie Major Basic Protein or MBP), newly released lipid mediators (ie Leukotriene C4 or LTC4), and newly transcribed cytokines (ie TNFα, IL5, GM-CSF, and multiple other cytokines).[9] Thus, eosinophils recruited to the lung have the potential to contribute to airway inflammation and airway hyperreactivity in asthma through a variety of their mediators that can contribute to airway inflammation and airway hyperreactivity. For example, MBP due to its extremely basic pH is toxic to airway epithelium and can denude areas of airway epithelium and contribute to AHR.[12] LTC4 is a potent contractor of airway smooth

muscle leading to bronchoconstriction. The ability of a therapeutic intervention to reduce eosinophilic inflammation in the airway would thus reduce levels of the multiple mediators each eosinophil is able to express and release.

Targeting IL-5 and the IL-5 Receptor α to Selectively Deplete Eosinophils in Asthma

As IL-5 is a lineage specific eosinophil growth and survival factor, IL-5 and its receptor[13] became a major focus of research into developing a therapy to deplete eosinophils that was both eosinophil specific (ie not targeting cell types other than eosinophils) and highly effective in depleting eosinophils (IL-5 is the key eosinophil growth factor). IL-5 has been detected by ELISA in BAL in spontaneously symptomatic asthmatics with airway eosinophilia,[14] as well as by in situ hybridization which detected IL-5 mRNA in BAL cells of asthmatics.[15] In asthma, IL-5 is generated by multiple cell types including CD4+ T lymphocytes, ILC2, mast cells, and eosinophils themselves.[15] Thus, targeting IL-5 would target the eosinophil indirectly by reducing levels of IL-5 produced predominantly by cell types other than eosinophils and thus depleting the amount of IL-5 available to bind to IL-5 receptors expressed by eosinophils and eosinophil progenitors and as a consequence influence eosinophil function (reduced eosinophil proliferation and survival).[16] Alternatively targeting the IL-5 Receptor (IL-5R) would target the eosinophil directly using an anti-IL-5R antibody which binds to the IL-5R α subunit on the eosinophil cell surface and blocks the ability of IL-5 to engage the IL-5R on eosinophils. The IL-5R is a heterodimer composed of two different subunits, including an IL-5 specific alpha (α) subunit and a common beta (β) subunit.[13] The IL-5R α subunit binds IL-5, and the β subunit is essential for signal transduction.[13] The IL-5Rα is a low affinity receptor, but dimerization with the β-chain produces a high affinity receptor. Unlike the α-chain, the β-chain does not bind IL-5, the β-chain is not specific to IL-5, as the IL-5R β subunit is also part of the receptors for IL-3 and GM-CSF. In addition, the IL-5R β subunit is not specific for eosinophils as it is expressed on practically all leukocytes. The IL-5Rα is thus a target to deplete eosinophils, for example by using monoclonal antibodies to the IL-5Rα that block IL-5 binding to the IL-5R.

Pre-Clinical Models and the Role of Eosinophils in Asthma

Pre-clinical models of asthma, in particular in the mouse, have demonstrated that IL-5 deficient mice do not develop airway eosinophilic inflammation, increased AHR, or airway remodeling in response to inhalation allergen challenge.[10] In addition, studies in non-human primates pretreated with anti-IL-5 and challenged with allergen demonstrate that they have reduced airway eosinophils and airway reactivity. These pre-clinical models, as well as studies of human asthmatics demonstrating increased levels of IL-5 and eosinophils in the airway in asthma,[14] provided support for investigating whether targeting IL-5 and eosinophils in human asthmatics would be equally as effective as pre-clinical models in reducing eosinophils and improving asthma outcomes.

Human Allergen Challenge Models of Asthma and the Role of Eosinophils

Human Endobronchial Allergen Challenge Late Phase Response and Eosinophils

Studies of endobronchial allergen challenge in mild asthmatics in which the allergen is delivered to a small airway via a bronchoscope have demonstrated that eosinophils are recruited to the airway during the late phase response, and that these airway eosinophils are activated to express cytokines including IL-5 and GM-CSF mRNA.[15] In contrast, peripheral blood eosinophils following allergen challenge did not express IL-5 and GM-CSF mRNA,[17] suggesting that eosinophils trafficking from the bone marrow to the lung were activated in the lung to express IL-5 and GM-CSF. At present, the physiologic stimulus that activates eosinophils to express cytokines and/or release mediators in the lung is unknown. Studies with anti-IL-5 administered before endobronchial allergen challenge have not yet been reported to determine whether anti-IL-5 blocks the late phase eosinophil response in the airway following endobronchial allergen challenge.

Human Inhalation Allergen Challenge: Effect of Anti-IL-5 on Late Phase Eosinophil Response

Inhalation allergen challenge can be used as a model to study the immediate response (approximately 10–30 minutes after allergen challenge) and the late phase response (approximately 4–8 hours after allergen challenge) in the lung in asthmatics. The immediate response is due to IgE mediated activation of mast cells and release of histamine and other mast cell derived mediators which occurs rapidly within minutes of allergen cross linking high affinity IgE receptors

(FcER1) on mast cells. The late phase response is associated with the presence of eosinophils in the airway and takes several hours to occur as eosinophils need time to traffic from the bone marrow to the blood stream to the lung. Pre-treatment prior to inhalation allergen challenge with a therapeutic intervention targeting eosinophils could thus potentially provide insight into whether the intervention could inhibit the late phase response and associated airway eosinophilia.

Studies of anti-IL5 in reducing the late phase response to allergen inhalation challenge produced mixed results. For example, Leckie et al[18] performed a double-blind randomized placebo-controlled trial, in which a single intravenous infusion of humanized (IgG-k) monoclonal antibody to IL-5 (SB-240563) was given at doses of 2.5 mg/kg or 10 mg/kg to eight subjects in each group. Anti-IL-5 significantly reduced the sputum eosinophilia (12. 2%, placebo group vs 0.9% in the10 mg/kg anti-IL-5 group) and the blood eosinophilia that follows allergen challenge, but had no significant effect on the late asthmatic pulmonary function response, or on AHR to histamine. Thus, this study provided evidence that anti-IL-5 can significantly inhibit blood and sputum eosinophilia but anti-IL-5 did not inhibit AHR associated with the late phase response to inhalation allergen challenge. However, issues with the study design, including sample size and methodology, may have limited these conclusions.[19]

Effect of Anti-IL-5 on Blood Eosinophils in Asthma

Anti-IL-5 therapy has been associated with a very stable population of residual blood eosinophils that are not depleted.[20] Anti-IL-5 does not elicit any detectable transcriptional response in these residual blood eosinophils assessed by RNAseq in mepolizumab-treated severe eosinophilic asthmatics.[20] These results suggest that anti-IL5 spares residual blood eosinophils in severe eosinophilic asthma through an at present unknown mechanism. The residual blood eosinophils in severe eosinophilic asthma largely resemble blood eosinophils in healthy individuals not treated with anti-IL-5.[20] The limitations of this study[20] include the fact that levels of IL-5 receptors were not quantitated by FACS in the residual blood eosinophils to determine whether the lack of responsiveness of residual blood eosinophils to anti-IL-5 was related potentially to their low IL-5 receptor levels. In addition, this study[20] relied solely on eosinophil gene expression profiling for determining the effect of anti-IL-5 on residual eosinophil function, and thus this study[20] cannot exclude that anti-IL-5 could have effects on alternate residual blood eosinophil functions (ie adhesion, proliferation, release of granule mediators, LTC4 production, etc) not directly related to eosinophil gene expression.

Studies have also been performed on the effect of anti-IL-5 pathway biologics on recently described homeostatic (hEOs) and inflammatory (iEOs) eosinophil subsets designated as CD62L high hEOs or CD62L low iEOs.[21] Peripheral blood hEOs and iEOs were measured by flow cytometry assessment of surface CD62L protein in severe asthma patients treated with either mepolizumab or benralizumab.[21] Mepolizumab depleted iEOs, and also reduced circulating eosinophil viability, in severe asthma but preserved a residual population of circulatory hEOs.[21] These results are similar in some respects to another study describing persistence of residual blood eosinophis in severe asthmatics treated with mepolizumab.[20] In contrast, benralizumab (which targets the IL-5 receptor) depleted both iEOs and hEOs.[21] Higher iEO abundance and eosinophil viability were associated with poorer clinical outcomes following mepolizumab-treatment.[21] Whether monitoring circulating eosinophil phenotype and viability is useful to predict biologic treatment response to IL-5 targeted therapies in severe asthma requires further study.[21]

Initial Intervention Studies Targeting IL-5 in Asthma Disappoint

Early clinical studies investigating anti-IL-5 antibodies as therapy in unselected patients with asthma (ie, irrespective of eosinophil levels) demonstrated limited clinical efficacy.[19]

One initial clinical study with anti-IL-5 (SCH 55700) administered as a single dose intravenously was conducted in a small group of patients with difficult-to-manage asthma, all of whom were taking high doses of ICS and/or oral corticosteroids.[22] The study demonstrated that anti-IL-5 reduced blood eosinophils and, at one of the doses administered, had a small, but significant, transient benefit in improving FEV_1, but not in any of the other clinical outcomes.[22]

A few years later, the efficacy of anti-IL-5 (in this study mepolizumab) was investigated at two doses (250 mg or 750 mg IV at monthly intervals for three doses) in 362 patients with moderate to severe asthma with poor asthma control, a study that was adequately powered to find a clinically useful improvement in peak expiratory flow (PEF).[23]

Mepolizumab reduced blood and sputum eosinophils but did not improve PEF or any other clinical outcome renewing concerns from this and prior studies about whether eosinophils and IL-5 was an important target.[24] Interestingly, there was a trend for a decrease in asthma exacerbation rates in the mepolizumab 750-mg treatment group ($P = 0.065$),[23] as future studies that showed a positive effect of anti-IL-5 in asthma were powered on asthma exacerbations as the primary outcome. In addition, as this study in persistent asthma did not use eosinophil levels as an entry criteria,[23] future asthma studies modified entry criteria to include increased eosinophils.

Support for the Link Between Eosinophils and Asthma Exacerbations

Several studies have demonstrated that eosinophilic inflammation is present in the airway in asthma[14] and that the increased BAL eosinophils in symptomatic asthmatics is associated with increased IL-5 in BAL.[14] Increased sputum eosinophilia has been observed to develop several weeks before the onset of an asthma exacerbation, suggesting that eosinophils play a role in the development of the asthma exacerbation.[25] In addition, studies have demonstrated that an asthma treatment strategy directed at normalization of the induced sputum eosinophil count reduces asthma exacerbations and hospital admissions supporting the link between eosinophils and asthma exacerbations.[26] However, in this study[26] as the asthma treatment strategy included adjusting the dose of inhaled corticosteroids when sputum eosinophil counts increased, the inhaled corticosteroid treatment strategy could not only reduce sputum eosinophils but also other inflammatory cells and pathways associated with asthma exacerbations.

As it is easier to use blood eosinophil levels rather than sputum eosinophil levels to identify asthmatics with airway eosinophilia to enter into clinical trial with eosinophil targeted therapies studies have attempted to define blood eosinophil levels that would predict sputum eosinophilia. A study investigating the accuracy of using peripheral blood eosinophil levels in detecting sputum eosinophilia (≥3%) in different adult asthma phenotypes showed that blood eosinophil levels of $0.34–0.73\times10^9$ eosinophils/L had a 95% upper threshold specificity for predicting sputum eosinophilia, while a blood eosinophil level of $<0.09\times10^9$ eosinophils/L was associated with absence of airway eosinophilia in 92% of 336 asthmatics in the study.[27] Additional studies have shown that a cutoff of $>0.45\times10^9$ eosinophils/L for blood eosinophilia could usefully predict sputum eosinophilia (>2%) in 9/10 patients with severe asthma receiving high levels of treatment.[28] Peripheral blood eosinophil counts ≥400/μL are a risk factor for asthma exacerbations in the subsequent year.[29] Clinical trials with biologics targeting eosinophils have used a variety of peripheral blood eosinophil counts (eg 150, 300, or 400 eosinophils /μL) as entry criteria for severe asthmatics with eosinophilic inflammation. The lower the eosinophil blood count used as an entry criterion (ie 150 eosinophils/μL) the easier it will be to identify sufficient study subjects to enter the study. However, lower eosinophil blood counts do not correlate as well with increased sputum eosinophil counts and these studies may therefore be enrolling subjects without significant eosinophilic airway inflammation that would benefit from an eosinophil targeted biologic.

Clinical Trials of Anti-IL-5 or Anti-IL-5 Receptor α in Severe Eosinophilic Asthma Demonstrate Effectiveness

After the initial studies of anti-IL-5 disappointed in moderate to severe asthmatics with persistent symptoms despite ICS who were not enrolled based on eosinophil counts,[22,23] several large scale studies enrolled asthmatics based on eosinophil counts and used asthma exacerbations as the primary end point to demonstrate the significant effectiveness of anti-IL5 in asthma with eosinophilic inflammation. The following are the key studies with anti-IL-5 (mepolizumab or reslizumab) and the anti-IL-5 receptor α antibody (benralizumab) that demonstrate their effectiveness in asthma with eosinophilic inflammation and led to their regulatory approval (Table 1). The comparative asthma outcomes of these three biologics are summarized in Table 2.

Mepolizumab (Anti-IL-5)

Mepolizumab is a humanized IgG1 antibody which binds with high affinity to IL-5, preventing IL-5 binding to the α-unit of the IL-5 receptor, thereby inhibiting downstream IL5 Receptor signaling.

Table 1 Eosinophil Targeted Biologics

Biologic	Target	Severe Eosinophilic Asthma			CRSwNP[c]
		Route	Maintenance Dose	Age[b]	
Benralizumab	IL-5R	SC	30mg every 8 weeks[a]	≥ 6 years	Not currently FDA approved
Mepolizumab	IL-5	SC	300mg every 4 weeks	≥ 6 years	FDA approved ⩾18 years
Reslizumab	IL-5	IV	3 mg/kg every 4 weeks	≥18 years	Not currently FDA approved

Notes: [a]Benralizumab is administered 30mg every 4 weeks sc for the first three doses, and then switched to a maintenance dose of 30 mg every 8 weeks sc. [b]United States FDA approved age for administration of the biologic for severe eosinophilic asthma [c]United States FDA approved (or not approved) listed biologic for CRSwNP, with age for this indication listed.
Abbreviations: IL-5R, Interleukin-5 Receptor; IL-5, Interleukin-5; SC, subcutaneous; IV, intravenous; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; FDA, Food and Drug Administration.

Table 2 Asthma Outcomes in Phase 3 Studies of Eosinophil Targeted Biologics

Biologic	Phase 3 Study	Entry Eos	Asthma Outcomes		
			Asthma Exacerbations	FEV_1	ACQ, TASS, or SGRQ
Benralizumab	CALIMA[30]	* >300/μL	−33%^{q4}	+ 125 ml^{q4}	−0.12^{TASS}
		* ≥300/μL	−26%^{q8}	+ 116 ml^{q8}	−0.23^{TASS}
	SIROCCO[31]	*≥300/μL	$^{-5}$5%^{q4}	+106 ml^{q4}	−0.08^{TASS}
		*≥300/μL	$^{-4}$9%^{q8}	+159 ml^{q8}	−0.25^{TASS}
Mepolizumab	MENSA[32]	≥150/μL	−53%	+98 mL	−0.44^{ACQ5}
	MUSCA[33]	>150/μL	−58%	+120 mL	−7.70^{SGRQ}
Reslizumab	Study 1/2[34]	≥400/μl^{S1}	−50%^{S1}	+126 ml^{S1}	−0.26$^{ACQ7\text{-}S1}$
		>400/μl^{S2}	−41%^{S2}	+ 90 ml^{S2}	−0.24$^{ACQ7\text{-}S2}$
	Bjermer et al[35]	≥400/μL	** NR	+160mL	−0.35^{ACQ5}

Notes: Phase 3 Study lists study name with superscript number indicating reference number. As the Reslizumab Study 1/2 included results of two reslizumab studies in one publication,[34] the results of study 1 are listed with suprascript ^{S1} and the results of study 2 with suprascript^{S2}. For Benralizumab two dosing frequencies q4 weekly^{q4}, and q8 weekly^{q8} results are depicted with suprascripts. Entry Eos lists the number of peripheral blood eosinophils at entry into the study required for a study subject to be enrolled in that study. *This asterisk indicates that levels of blood eosinophils (Eos) were not a study subject entry requirement for the benralizumab studies. However, the primary end point and other results were analysed in placebo vs benralizumab treated subjects with blood eosinophil counts >300/ μL. Asthma Exacerbations are reported as the % reduction in the annual rate of asthma exacerbations. For benralizumab results of two dosing regimens q4 weekly, and q 8 weekly are depicted. **NR in the Asthma exacerbation column indicates not reported in that study. FEV_1 The mean difference in FEV_1 in mL compares the biologic therapy and placebo. ACQ is the Asthma Control Questionnaire which is reported as the improvement in the score comparing the biologic to the placebo group. ACQ5 or ACQ7 scores were recorded in different studies. For both ACQ5 and ACQ7, the minimal clinically important change for the patient is considered to be 0.50. SGRQ is the St. George's Respiratory Questionnaire score and is reported as the improvement in the score comparing the biologic to the placebo group. A 4 unit reduction in the total SGRQ score is generally accepted as the minimal clinically important difference for improvement in asthma. TASS is the total asthma symptom score a composite score with no minimally clinically important difference reported.[30,31] The suprascript TASS, ACQ 5, ACQ7, or SGRQ are included next to the improvement in score to indicate whether the result reported is TASS, ACQ5, ACQ7, or SGRQ.

Two companion studies published in 2009 in the NEJM by Haldar et al[36] and Nair et al[37] demonstrated the effectiveness of mepolizumab when asthmatics were enrolled based on having eosinophilic inflammation and the primary end point was the frequency of asthma exacerbations.

Haldar et al (NEJM 2009)[36]

In this study of refractory eosinophilic asthma (sputum eosinophils >3%) and a history of recurrent severe asthma exacerbations, asthmatics received infusions of either 750 mg mepolizumab intravenously (29 subjects), or placebo (32 subjects) at monthly intervals for 1 year. The primary outcome measure was the number of severe asthma exacerbations per subject. Mepolizumab was associated with a significant 57% reduction in severe asthma exacerbations compared to placebo (2.0 mepolizumab vs 3.4 placebo, mean exacerbations per asthmatic), and with a significant 35% improvement in the Asthma Quality of Life Questionnaire (AQLQ) score. Mepolizumab significantly lowered eosinophil counts in the blood and sputum. Mepolizumab did not improve asthma symptoms, FEV_1 after bronchodilator use, or airway hyperresponsiveness.

Nair et al (NEJM 2009)[37]

This small study of 20 asthmatics examined the prednisone-sparing effect of mepolizumab in a subgroup of asthmatics who have sputum eosinophilia (>3%) and persistent airway symptoms despite continued treatment with oral prednisone. The primary outcomes of the study were asthma exacerbations and the mean reduction in the dose of prednisone as a percentage of the maximum possible reduction. Nine asthmatics received mepolizumab (five monthly IV infusions of 750 mg) and 11 asthmatics received placebo. The placebo group had significantly increased numbers of asthma exacerbations compared to the mepolizumab group (12 vs 1 asthma exacerbation) ($P = 0.002$). Nine of the asthma exacerbations in the placebo group were associated with sputum eosinophilia at the time of the asthma exacerbation, whereas only one patient who received mepolizumab had an asthma exacerbation, and this episode was not associated with sputum eosinophilia. Asthmatics who received mepolizumab were able to reduce their prednisone dose by approximately 83% as compared with approximately 47% in the placebo group ($P = 0.04$). The use of mepolizumab was associated with a significant decrease in the number of sputum and blood eosinophils.

DREAM Study (Pavord et al, Lancet 2012)[38]

The DREAM study (Dose Ranging Efficacy And safety with Mepolizumab) was a large multi-center study (81 centers) of 621 severe asthmatics which investigated whether mepolizumab reduced asthma exacerbations (the primary endpoint) in patients with a history of recurrent severe asthma exacerbations and signs of eosinophilic inflammation (sputum eosinophil >3% or blood eosinophils $>0.3\times10^9$ per L). Asthmatics received 13 intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or matched placebo infusions at 4-week intervals. The rate of clinically significant asthma exacerbations was 2.4 per patient per year in the placebo group. Mepolizumab significantly reduced the frequency of asthma exacerbations by 48% (75 mg mepolizumab), 39% (250 mg mepolizumab), and 52% (750 mg mepolizumab) compared to placebo. Mepolizumab reduced blood and sputum eosinophil counts and was well tolerated for 12 months. However, although mepolizumab significantly reduced asthma exacerbation rates mepolizumab had only small effects on FEV_1 and AQLQ and Asthma Control Questionnaire (ACQ) scores, which generally did not differ significantly from those reported with placebo.

Mepolizumab Large Scale Studies for FDA Approval in USA

In 2015, Mepolizumab was the first biologic targeting eosinophils that was approved in the USA as an add on treatment for severe eosinophilic asthma by the Food and Drug Administration. The approval was based on the results of large scale two Phase III studies which included the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma),[32] and the SIRIUS (Steroid Reduction with Mepolizumab Study)[39] clinical trials which are described next.

MENSA (Ortega et al, NEJM 2014)[32]

The MENSA study examined whether mepolizumab (75 mg IV or 100 mg subcutaneously compared to placebo) could reduce asthma exacerbations (the primary outcome) in 571 asthmatics with recurrent asthma exacerbations (at least two asthma exacerbations in the past year) and evidence of eosinophilic inflammation (peripheral blood eosinophil ≥150 cells/μL at screening, or ≥300 cells/μL during the previous year) despite high doses of inhaled glucocorticoids. Mepolizumab significantly reduced the rate of asthma exacerbations by approximately 47% in asthmatics receiving intravenous mepolizumab, and by approximately 53% in asthmatics receiving subcutaneous mepolizumab, as compared

with those receiving placebo. Mepolizumab therapy also resulted in improvements in secondary outcomes including an increase in FEV_1 of approximately 100 mL greater in patients receiving mepolizumab than in those receiving placebo, and improvements in both the 5-item Asthma Control Questionnaire (ACQ-5), and the St. George's Respiratory Questionnaire (SGRQ).

SIRIUS (Bel et al, NEJM 2014)[39]

The SIRIUS study (Steroid Reduction with Mepolizumab Study) compared the glucocorticoid-sparing effect of mepolizumab (100 mg subcutaneously every four weeks for five months, compared to placebo) in 135 severe eosinophilic asthma subjects (defined as in the MENSA study).[32] The primary outcome was the degree of reduction in the oral prednisone dose, a lack of asthma control during weeks 20 to 24, or withdrawal from treatment. The mean dose of oral prednisone at the start of the study was 12.5 mg in the mepolizumab group and 15 mg in the placebo group. Mepolizumab permitted a significant reduction from baseline in the prednisone dose of 50%, as compared with no reduction in the placebo group (P = 0.007). Despite a reduction in prednisone dose by asthmatics in the mepolizumab group, the mepolizumab group had a relative reduction of 32% in the annualized rate of asthma exacerbations (compared to placebo), and a significant reduction of 0.52 points with respect to asthma symptoms as measured on the Asthma Control Questionnaire 5 (in which the minimal clinically important difference is 0.5 points). Thus, mepolizumab had a significant glucocorticoid-sparing effect, without a deterioration in asthma control. However, although mepolizumab permitted a significant 50% reduction from baseline in the prednisone dose, this 50% reduction would equate to a mean reduction from the 12.5 mg prednisone baseline dose to a mean dose of 6.25 mg prednisone after 5 months of mepolizumab. It should be noted that more patients in the mepolizumab group than in the placebo group had a reduction of 90% to 100% in the oral prednisone dose (23% vs 11%) and a reduction of 70% to less than 90% (17% vs 8%). Thus, a subset of mepolizumab treated severe asthmatics (23%) were able to taper 90% to 100% of their oral prednisone dose.

Mepolizumab is Not FDA Approved to Reduce Oral Corticosteroids

Despite evidence of mepolizumab's ability to reduce oral corticosteroids in severe eosinophilic asthma,[37,39] mepolizumab is not currently FDA approved for this indication. Mepolizumab is approved by the FDA as add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype (Table 1).

MUSCA (Chupp et al, Lancet Resp Medicine 2017)[33]

The MUSCA study[33] aimed to examine the effect of mepolizumab in severe eosinophilic asthma on health-related quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) as the primary outcome. Mepolizumab (100 mg subcutaneous; n = 274 subjects) was compared to placebo (n = 277 subjects) every 4 weeks for 6 months. Asthmatics also had to have a history of at least two asthma exacerbations in the previous 12 months to enter the study, as well as evidence of eosinophilia (peripheral blood eosinophil >150 cells/μL at screening, or >300 cells/μL during the previous year). Mepolizumab therapy resulted in significant improvements in SGRQ total score (−15.6 mepolizumab vs −7.9 placebo), and also significantly reduced clinically significant asthma exacerbations by 58% compared to placebo.

Post-Hoc Analysis of DREAM and MENSA Demonstrate Close Relationship Between Baseline Blood Eosinophil Count and Response to Mepolizumab

A post-hoc analysis of the DREAM[38] and MENSA[32] studies showed a close relationship between baseline blood eosinophil counts and the clinical efficacy of mepolizumab.[40] The overall rate of asthma exacerbations with mepolizumab was reduced by 47% by combining the results of the two studies. When stratified for baseline eosinophil counts, the reduction in asthma exacerbations with mepolizumab increased progressively from 52% in asthmatics with a baseline blood eosinophil count of >150 eosinophils/μL, to 70% in patients with a baseline eosinophil count >500 eosinophils/μL. Baseline eosinophil counts of <150 eosinophils/μL predicted a poor response to mepolizumab, ie asthma exacerbations were reduced by only 26%.

Reslizumab (Anti-IL5)

Reslizumab is a humanized IgG4 monoclonal anti-IL5 antibody that was FDA approved in 2016 for the treatment of severe eosinophilic asthma based on results of studies by Castro et al[34,41,42] and Bjermer et al[35] whose results as well as other reslizumab studies[43] are described in greater detail below.

Castro et al (Am J Resp Crit Care Med, 2011)[41]

This study evaluated the effect of reslizumab, in patients with eosinophilic asthma (induced sputum eosinophils of >3%) that was poorly controlled with high-dose inhaled corticosteroid. The primary outcome measure was the difference in Asthma Control Questionnaire (ACQ) score from baseline to end of therapy (Week 15) between the reslizumab (3mg/kg IV) (n = 53) and placebo groups (n = 53). Reslizumab therapy resulted in a greater improvement in ACQ score than placebo with a −0.7 improvement in the reslizumab group and −0.3 in the placebo group (P = 0.054). Reslizumab also significantly improved FEV_1 by 180 mL as compared to a loss of 80 mL in FEV1 in the placebo group. Median percentage reductions from baseline in sputum eosinophils were 95% in the reslizumab group and 38% in the placebo group. Asthma exacerbations trended fewer in the reslizumab group (8%) compared to the placebo group (19%) (P = 0.083).

Castro et al (Lancet Resp Med, 2014)[42]

This phase 2b dose-ranging study assessed the efficacy and safety of subcutaneous reslizumab (2 mg, 20 mg, 100 mg, or placebo) in adults with uncontrolled eosinophilic asthma with two to six exacerbations in the past year. The primary endpoint was annual exacerbation rate in eosinophilic individuals after 1 year of follow-up. Severe eosinophilic asthmatics (n = 324) were randomly assigned to placebo (n = 80), or benralizumab 2 mg (n = 81), 20 mg (n = 81), or 100 mg (n = 82). In addition, 285 non-eosinophilic severe asthmatics received 100 mg benralizumab (n = 142) or placebo (n = 143). Study drugs were given as two subcutaneous injections every 4 weeks for the first three doses, then every 8 weeks, for 1 year. In severe asthmatics with eosinophilia, benralizumab 100 mg reduced asthma exacerbation rates by 41% compared to placebo, while benralizumab 2 mg and 20 mg did not reduce asthma exacerbation rates. Asthma exacerbation rates did not differ between benralizumab 100 mg and placebo for the non-eosinophilic participants.

Castro et al (Lancet Resp Med, 2015)[34]

Reslizumab was administered intravenously (3 mg/kg) every 4 weeks for one year in two phase III studies of inadequately controlled asthma with elevated blood eosinophil counts (≥400 eosinophils/μL), and the primary endpoint was the number of asthma exacerbations/year. Reslizumab significantly reduced the annual rate of asthma exacerbations by 50% in study 1 (n = 245 reslizumab; n = 244 placebo; recruited at 128 sites), and by 41% in study 2 (n = 232 reslizumab; n = 232 placebo; recruited at 104 sites), compared with placebo. Therapy with reslizumab also significantly improved FEV1 by 126 mL in study 1 and by 90 mL in study 2, which was associated with significant improvements in asthma quality of life measures including AQLQ, ACQ7, and Asthma Symptom Utility Index (ASUI) scores. Two of the 232 asthmatics (0.86%) assigned to the reslizumab group in study 2 had anaphylactic reactions. Both events were judged to be treatment-related, responded to standard treatment at the clinic site, and these patients were discontinued from the study. Both patients were negative for antidrug antibodies.

Bjermer et al (Chest, 2016)[35]

This phase 3 study investigated the efficacy and safety of reslizumab in asthmatics aged 12 to 75 years (n = 315) inadequately controlled by at least a medium-dose inhaled corticosteroid and with a blood eosinophil count ≥400 cells/μL. Asthmatics were randomized to receive reslizumab 0.3 or 3.0 mg/kg intravenously or placebo administered once every 4 weeks for 16 weeks (total four doses). The primary end point was change from baseline in pre-bronchodilator FEV_1 over 16 weeks. Reslizumab significantly improved the primary end-point FEV_1 with a 115 mL difference vs placebo (reslizumab 0.3 mg/kg) and a 160 mL difference (reslizumab vs placebo 3.0 mg/kg). Reslizumab improved scores on the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) vs placebo (greater effects seen with 3.0 mg/kg), but the minimally important difference was reached only for the AQLQ (reslizumab 3.0 mg/kg) but not on the ACQ. Asthma exacerbations were not recorded as an outcome in this study.

Overall, the 3.0-mg/kg dose of reslizumab provided greater improvements in asthma outcomes vs the 0.3-mg/kg dose, with comparable safety.

Corren et al (Chest, 2016)[43]

This study was conducted in inadequately controlled asthmatics, unselected for baseline blood eosinophil counts, to determine the impact of baseline eosinophil levels on identifying the asthma population most likely to benefit clinically from reslizumab. The primary end point in this study was the change in FEV_1 from baseline to week 16, which differs from the primary end-point of asthma exacerbations frequently used in other studies of ant-IL-5. The mean change in the primary endpoint FEV_1 from baseline to week 16 was 255 mL in the reslizumab group and 187 mL in the placebo group, with a between-group difference of 68 mL which was not statistically significant ($P = 0.17$). The reslizumab group had small improvements in secondary outcomes such as quality of life measures (ACQ), and rescue SABA use. A post-hoc analysis of FEV_1 outcomes in response to reslizumab was performed comparing asthmatics with high blood eosinophil counts >400 eosinophils/μL (20% of the study population), and asthmatics with blood eosinophil counts of <400 eosinophil/μL at randomization (80% of the study population). Reslizumab had no effect on FEV_1 in those with eosinophil counts of <400 eosinophil/μL, but did improve FEV_1 in those with eosinophil counts >400 eosinophils/μL. Limitations of post-hoc analysis need to be understood in interpreting these results. Two out of 395 asthmatics in the reslizumab group (0.51%) had anaphylaxis (one was associated with reslizumab; one was related to ongoing allergen immunotherapy). For the reaction related to reslizumab, symptoms of wheezing, shortness of breath, and flushing occurred shortly after infusion, without hemodynamic compromise. The patient responded to epinephrine, salbutamol, antihistamine, and prednisone at the study site, and subsequently tested anti-drug antibody negative.

Additional Post-Hoc Studies of Reslizumab in Asthma

Several additional post-hoc analysis studies of reslizumab in asthma[44–46] have been performed from pooled analysis of study subjects enrolled in prior studies, rather than enrolling new study subjects. These studies using a post-hoc analysis of a subpopulation of patients with refractory asthma have reported on the long term safety and efficacy of reslizumab in patients with eosinophilic asthma,[44] the safety of reslizumab in uncontrolled asthma,[45] and the ability of reslizumab to reduce asthma exacerbation frequency, improve lung function, asthma control, and QoL versus placebo in patients with severe eosinophilic asthma with a high exacerbation rate before treatment.[46] Prospective studies of reslizumab are needed to confirm these study results obtained by post-hoc analysis of prior studies of reslizumab. Reslizumab is approved by the FDA as add-on maintenance treatment of adult patients aged 18 years and older with severe asthma and with an eosinophilic phenotype (Table 1).

Benralizumab (Anti-IL5 Receptor α)

Benralizumab targets the IL-5 Receptor α and thus differs from mepolizumab and reslizumab which target the cytokine IL-5 and not its receptor expressed by eosinophils. Benralizumab binds to the IL-5Rα subunit present on eosinophils (and also basophils) tagging eosinophils for antibody-dependent cell-mediated cytotoxicity via natural killer cell-induced apoptosis without the release of eosinophil pro-inflammatory mediators. Benralizumab is a humanized IgG1 monoclonal anti-IL5Rα antibody that was FDA approved in 2017 for the treatment of severe eosinophilic asthma based predominantly on results of phase 3 studies by Bleecker et al[31] Fitzgerald et al[30] and Nair et al[47] whose results are described in greater detail below.

SIROCCO (Bleecker et al, Lancet 2016)[31]

This phase 3 study investigated the safety and efficacy of benralizumab in patients with severe, uncontrolled asthma with eosinophilia (eosinophil counts >300 eosinophils/μL; or <300 eosinophils/μL). Asthmatics were randomly assigned (1:1:1) to benralizumab 30 mg subcutaneously every 4 weeks (Q4W) (n = 400), benralizumab 30 mg subcutaneously every 8 weeks (Q8W; first three doses every 4 weeks) (n = 398) or placebo Q4W (n = 407) for 48 weeks as add on to their standard treatment. The primary endpoint was annual asthma exacerbation rate comparing benralizumab versus

placebo. Benralizumab significantly reduced the annual asthma exacerbation rate by 55% (when given Q4W) and by 49% (when given Q8W) in asthmatics with peripheral blood eosinophil counts >300 eosinophils/μL. Asthmatics with blood eosinophil counts <300 eosinophils/μL had a smaller response to benralizumab in terms of reductions in asthma exacerbation rates ie in asthmatics with eosinophil counts <300 eosinophils/μL benralizumab reduced the annual asthma exacerbation rate by 30% (when given Q4W) and by 17% (when given Q8W). Thus, benralizumab was more effective in reducing asthma exacerbations in asthmatics with eosinophil counts >300 eosinophils/μL. Benralizumab also significantly improved the FEV_1 by 106 mL (when given Q4W) and by 159 mL (when given Q8W) in asthmatics with peripheral blood eosinophil counts ≥300 eosinophils/μL.

CALIMA (FitzGerald et al, Lancet, 2016)[30]

This phase 3 study investigated the safety and efficacy of benralizumab in patients with severe, uncontrolled asthma with eosinophilia (eosinophil counts >300 eosinophils/μL; or <300 eosinophils/μL) and a history of two or more asthma exacerbations in the previous year. The study design for investigating benralizumab in asthma by Fitzgerald et al[30] was similar to the study design of Bleecker et al.[31] Asthmatics were randomly assigned (1:1:1) to receive 56 weeks of benralizumab 30 mg every 4 weeks (Q4W) (n = 425), benralizumab 30 mg every 8 weeks (Q8W; first three doses 4 weeks apart) (n = 441), or placebo (all subcutaneous injection) (n = 440). The primary endpoint was annual asthma exacerbation rate comparing benralizumab versus placebo for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils >300 eosinophil/μL. Benralizumab significantly reduced the annual asthma exacerbation rate by 36% (when given Q4W) and by 28% (when given Q8W) in asthmatics with peripheral blood eosinophil counts >300 eosinophils/μL. Benralizumab also significantly improved pre-bronchodilator FEV_1 (Q4W and Q8W) and total asthma symptom score (Q8W only) in these asthmatics.

Despite similar trial designs and target eosinophilic asthma populations included in the primary analyses, reductions in asthma exacerbation rates were greater with benralizumab in the Bleecker et al SIROCCO study (55% reduction)[31] than in this FitzGerald et al CALIMA study (36% reduction).[30] An explanation for this difference in benralizumab efficacy between the two trials is not completely clear at this time.

Nair et al (NEJM, 2017)[47]

This study investigated whether benralizumab, was effective as an oral glucocorticoid-sparing therapy in severe eosinophilic asthmatics relying on oral glucocorticoids (median dose 10 mg prednisone or prednisolone for 6 months at trial entry) to manage severe asthma associated with eosinophilia (blood eosinophil >150 eosinophils/μL). The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Two benralizumab dosing regimens were investigated (30 mg subcutaneously either every 4 weeks n = 72, or every 8 weeks with the first three doses administered every 4 weeks n = 73) compared to placebo (n = 75). Both the two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ($P < 0.001$ for both comparisons). A total of 24 patients (33%) who received benralizumab every 4 weeks and 27 patients (37%) who received benralizumab every 8 weeks had a reduction of 90% or more from baseline in their final oral glucocorticoid dose, as compared with 9 patients (12%) who received placebo. Benralizumab allowed the tapering of oral glucocorticoids without increasing asthma exacerbations or reducing lung function.

Benralizumab is Not FDA Approved to Reduce Oral Corticosteroids

Despite evidence of benralizumab's ability to reduce oral corticosteroids,[47] it is not currently FDA approved for this indication. Benralizumab is approved by the FDA as add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype (Table 1).

Completeness of Eosinophil Depletion in Severe Asthma Using Eosinophil Targeted Therapies

There are currently no direct head to head comparison studies with the three eosinophil depleting agents in terms of showing their comparative completeness of eosinophil depletion and importantly whether this leads to better asthma

outcomes. In addition, studies of the relative completeness of eosinophil depletion in sputum or the airway would be more important to severe asthma than the relative completeness of eosinophil depletion in peripheral blood. The following information on the completeness of eosinophil depletion is obtained from studies of the individual eosinophil depleting agents. Caveats include that studies with each eosinophil depleting agent had different study protocols (ie different eligibility criteria, levels of eosinophils needed to enter study, timing of eosinophil counts, etc) which could influence the completeness of eosinophil depletion. However, until comparison studies are performed this is the data we have available.

Benralizumab

The pre-benralizumab median and IQR blood eosinophil levels in the >300 eosinophils/μL group were 450 eosinophils/μL [300–720] for Q4W benralizumab, and 440 eosinophils/μL [280–691] for Q8W benralizumab.[31] The IQR is defined as the difference between the 25th and 75th percentiles of the data, so values above the 75th percentile are not included in the IQR. Treatment of severe eosinophilic asthma with benralizumab reduced blood eosinophil counts in the >300 eosinophils/μL group significantly to a median of 0 eosinophils/μL (Interquartile range or IQR 0–10) by Week 4.[31] This blood eosinophil reduction in response to benralizumab was maintained to week 48.[31] Blood eosinophil levels in the placebo cohort remained similar between baseline and week 4. Blood eosinophil responses to benralizumab were similar for asthmatics with blood eosinophil counts less <300 eosinophils/μL.[31] Thus, in this study benralizumab showed a significant eosinophil depleting effect in the blood of >95% from week 4 to week 48.[31]

Mepolizumab

Mepolizumab decreased the blood eosinophil counts by week 4 and blood eosinophil counts reached a nadir around week 12 (with reductions of 83% in the intravenous group and 86% in the subcutaneous group), and the decreases were maintained during the study.[32,40] Baseline mean blood eosinophil counts were similar in the placebo (320 eosinophils/μL), IV mepolizumab (280 eosinophils/μL), and subcutaneous mepolizumab (290 eosinophils/μL) groups.

Reslizumab

Reslizumab decreased the blood eosinophil counts by week 4 and blood eosinophil counts reached a nadir around week 16 (with reductions of 84% in study 1 of reslizumab, and 94% in study 2 of reslizumab), and the decreases were maintained during the 52 week study.[45] Baseline mean blood eosinophil counts were similar in study 1 in the placebo (624 eosinophils/μL) and reslizumab groups (696 eosinophils/μL), as well as in study 2 in the placebo (688 eosinophils/μL) and reslizumab groups (610 eosinophils/μL). The baseline blood eosinophil counts are higher in this reslizumab study (610 and 696 eosinophils/μL) compared to studies described above for benralizumab (450 eosinophils/μL),[31] and mepolizumab (290 eosinophils/μL).[32]

Which Severe Asthmatics Benefit from Biologics ?

Responses to biologics appear to exist on a spectrum despite patients meeting similar eligibility criteria.[48] Studies in Denmark (n = 501 severe asthma),[49] Australia (n = 453 severe asthma),[50] and the UK (n = 1,111 severe asthma)[51] have relied on cross-sectional data collected at the time of biologic initiation to uncover why some severe asthmatics achieve remission on biologic therapy while others do not. One common feature in all three studies[48–50] which was associated with severe asthmatics achieving remission on biologic therapy was shorter duration of asthma. These studies suggest remission is currently achievable in approximately 20–30% of severe asthmatics on biologic therapy and that shorter asthma duration may be a key factor for attaining on-biologic remission.[48–51] Additional factors identified in some studies[51] that were associated with biologic therapy induced asthma remission include higher T2 biomarkers, male sex, lower body mass index and asthma symptoms at baseline.

At present, there are no universally accepted definitions of how asthma phenotypes are defined and thus having well accepted standardized definitions of phenotypes would help to identify severe asthmatics who respond well to biologics.[52] At present, T2 high and T2 low biomarker phenotypes are frequently used to identify severe asthmatics who are likely to respond to anti-IL5 therapy.[52] The T2 biomarkers most commonly used to determine T2 high and T2 low phenotype include blood eosinophil levels and FeNO.[52] Although different studies use different definitions of levels

of blood eosinophils or FeNO that equate to T2 high, the ERS/ATS guidelines suggest a T2 cutoff of >150 eosinophils/ul as T2 high to guide anti-IL-5 initiation in adults with severe asthma and a history of severe and asthma exacerbations[52] (Table 3), while the ATS guidelines state that high FeNO levels (defined as ≥25 ppb in adults) are used to determine the T2 high status of a patient with severe asthma.[52] There are important caveats to just using these T2 high and T2 low biomarkers (BEC and FeNo) in isolation, as clinical phenotyping (ie age, age of asthma onset, allergic sensitization, obesity, etc) should be combined with biomarkers in determining an asthma phenotype.[52] In addition, phenotypes are not fixed and can change in response to environmental triggers (ie respiratory viral infections, tobacco smoke, air pollution).[52]

A retrospective study of the Danish Severe Asthma Register (n = 755) applied an unsupervised clustering method and sequencing analysis, identified three distinct trajectories of asthma disease progression in patients initiating biologic therapy.[53] Each of the identified asthma disease trajectories identified was associated with distinct asthma outcomes on biologic therapy with sudden onset severe asthma most likely to achieve remission (32%), compared to those with gradual onset (29%) and chronic severe asthma (17%).[53] The findings of all these studies highlight the potential importance of early intervention with biologics to prevent the long-term consequences of severe asthma.[48]

Long Term Response to Anti-IL-5

The long term responses to anti-IL-5 have been studied in severe asthmatics (n = 114) who had initiated an anti-IL-5 biologic (mepolizumab, reslizumab, benralizumab) 2 years earlier.[54] After 2-years of anti-IL-5 treatment, 14% of severe eosinophilic asthmatics were super responders, 69% partial responders, and 11% non-responders.[54] Super response was predicted by shorter asthma duration and higher FEV1 and tended to be associated with adult onset asthma, absence of nasal polyps, and lower body mass index.[54] After 2-years of anti-IL-5 therapy, the most common residual disease manifestations included impaired lung function (59%), uncontrolled sino-nasal disease (58%), and uncontrolled asthma symptoms (48%).[54]

Substituting One Eosinophil Depleting Agent for Another

In a single-center, single blind, placebo controlled study of 20 patients whose severe asthma was uncontrolled after ≥6 months of regular IL-5 targeted therapy (mepolizumab or reslizumab), treatment with an anti-IL-5Rα targeted therapy (benralizumab) significantly reduced sputum eosinophils (99.9%) and blood eosinophils (100%).[55] The inclusion criteria for this study included evidence of persistent sputum eosinophil counts ⩾3% (presence or absence free eosinophil granules) and an Asthma Control Questionnaire–5 (ACQ-5) score ⩾1.5. Approximately 71% of the severe asthmatics in the study were receiving prednisone at a median daily dose of 7.5 mg. Study subjects received monthly injections of the

Table 3 T_2 High Versus T_2 Low Asthma Biomarkers

T_2 Biomarkers	
T_2 High	**T_2 Low**
AEC ≥ 150/uL FeNO ≥ 25PPB	AEC < 150/uL FeNO < 25PPB

Notes: AEC: AEC is the "Absolute Eosinophil Count" in peripheral blood. ERS/ATS guidelines suggest an AEC T2 cutoff of ≥150 eosinophils/ul as T2 high to guide anti-IL-5 initiation in adults with severe asthma and a history of severe and asthma exacerbations.[52] FeNO: ATS guidelines state that high FeNO levels (defined as >25 ppb in adults) are used to determine the T2 high status of a patient with severe asthma.[52] ppb is parts per billion. Caveats: Clinical phenotyping (ie age, age of asthma onset, allergic sensitization, obesity, etc.,) should be combined with T2 biomarkers in determining asthma phenotype. In addition, phenotypes are not fixed and can change in response to environmental triggers (ie respiratory viral infections, tobacco smoke, air pollution).[52]

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study medication (Injection 1, 2, 6, 8 were placebo; benralizumab injection was administered at 3-, 4-, 5-, 7-, and 9-month visits, constituting five doses administered according to benralizumab dosing schedule). The primary study outcome was a significant reduction in sputum eosinophils at the end of treatment. Sixteen of the 20 severe asthmatics showed clinically relevant improvement in their asthma control (ACQ-5 score <1 and improvement of >0.5 points). Many severe asthmatics including the four who showed a poor response to treatment (ACQ-5 score >1.5) had CT evidence of mucus plugging and sinus disease. Thus, benralizumab can suppress sputum eosinophilia that is not suppressed by mepolizumab or reslizumab administered at the currently approved dosing regimens.

While this small study demonstrated interesting results, further large scale double blind studies are needed to determine whether switching from one eosinophil depleting agent targeting IL-5 to another agent targeting the IL-5Rα improves sputum eosinophilia and asthma control in severe asthmatics with sputum eosionophilia >3% as described in this single blind study.[55] In addition, the study population in this study is a subset of very severe asthmatics receiving prednisone at a median daily dose of 7.5 mg and whether similar results would be obtained with the much larger population of severe eosinophilic asthmatics not on daily prednisone requires further study. Finally, there are no studies investigating whether severe asthmatics not improving clinically on an anti-IL-5Rα targeted therapy (benralizumab) would improve clinically on an IL-5 targeted therapy (mepolizumab or reslizumab).

Kinetics of Eosinophil Depletion with Eosinophil Targeted Therapies

The rapid onset of depletion of blood and airway eosinophils with eosinophil depleting biologics may be important if these biologics are to be considered to be used as an alternative for prednisolone as a treatment of acute eosinophilic exacerbations of asthma. A small study therefore compared the rate of blood eosinophil depletion after administration of the first dose of either mepolizumab 100 mg subcutaneously (n = 6), benralizumab 30 mg subcutaneously (n=6), or prednisolone 30 mg (n = 6) in patients with severe eosinophilic asthma.[56] The primary outcome of this study was the time to reach a 50% reduction in blood eosinophil count after administration of either mepolizumab, benralizumab, or prednisolone. Inclusion criteria included a known diagnosis of severe asthma and baseline blood eosinophil count >300 eosinophils/μL. Baseline blood eosinophil counts were not significantly different between the groups. The mean time for the blood eosinophil level to decrease 50% from baseline was 25.8 +14.3 hours on mepolizumab, 1.7 ± 0.7 hours on benralizumab, and 2.5 ± 0.3 hours on prednisolone ($P < 0.001$ for both benralizumab and prednisolone compared with mepolizumab; $P = 0.874$ between prednisolone and benralizumab). A blood eosinophil count ≤100 cells/μL was achieved by 4 hours in 5/6 participants treated with benralizumab and 5/6 treated with prednisolone. In contrast 0/6 mepolizumab treated subjects had ≤100 cells/μL by 4 hours with only by 1/6 patient mepolizumab treated subjects had ≤100 cells/μL by 96 hours. Thus, benralizumab in this study depleted peripheral blood eosinophils at a similar rate to prednisolone during the first 24 hours after treatment. The speed and magnitude of the depletion were much greater than mepolizumab.[56] Future studies demonstrating a similar outcome on sputum eosinophils as with blood eosinophils will be important in understanding whether benralizumab is likely equivalent to prednisolone in the treatment of acute eosinophilic exacerbations of asthma. Mepolizumab and benralizumab have similar efficacy and safety in the longer-term treatment of severe eosinophilic asthma suggesting that the difference in the speed of onset is not relevant to the chronic use of these therapies.

Effect of Eosinophil Targeted Therapies on Airway Remodeling in Asthma

Studies in mouse models of allergen induced chronic asthma have demonstrated that IL-5 deficient mice have significantly reduced levels of eosinophilic airway inflammation, eosinophils expressing TGFβ1, and reduced features of airway remodeling including reduced peribronchial fibrosis, reduced thickness of the peribronchial smooth muscle layer, and reduced mucus.[10] The importance of TGFβ1 to these observations is suggested from studies of SMAD3 deficient mice (that are unable to mediate TGFβ1 signaling) that also have reduced levels of airway remodeling in the allergen induced chronic asthma mouse model.[57] Studies in mild asthmatics treated with anti-IL-5 have extended these murine findings to human asthmatics by showing that anti-IL-5 reduces levels of BAL eosinophils expressing TGFβ1 as well as levels of extracellular matrix proteins associated with airway remodeling.[58]

Effect of Anti-IL-5 on Co-Morbidities: Nasal Polyps

Mepolizumab and Nasal Polyps (SYNAPSE Study; Han et al, Lancet Resp Med 2021)[59]

Mepolizumab has an FDA approved indication for nasal polyps in patients 18 years and older based on large scale phase 3 studies including the study of Han et al.[59] Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) affects approximately 2–4% of the general population, and long-term use of systemic corticosteroids in such patients is associated with adverse effects. Approximately 20%–60% of patients with nasal polyps have associated asthma.[60] The aim of the SYNAPSE study (a randomised, double-blind, placebo-controlled, phase 3 study) was to assess the efficacy and safety of mepolizumab in adults with recurrent, refractory severe bilateral CRSwNP. Eligible patients had refractory, severe, bilateral nasal polyp symptoms (nasal obstruction symptom visual analogue scale [VAS] score of >5), were eligible for repeat nasal surgery despite standard of care treatment, and had to have at least one nasal surgery in the past 10 years. Patients received either 100 mg mepolizumab (n = 206) or placebo (n = 201) subcutaneously every 4 weeks for 52 weeks, as well as standard of care (mometasone furoate intranasal spray, nasal saline irrigations, systemic corticosteroids and/or antibiotics). The co-primary endpoints were total endoscopic nasal polyp score, and mean nasal obstruction VAS score. In patients with CRSwNP mepolizumab significantly improved both endoscopic nasal polyp size as well as nasal obstruction VAS score compared to placebo.[59] These findings suggest that mepolizumab provides an effective add-on treatment option to standard of care in CRSwNP with continued nasal polyps and symptoms.

Benralizumab and Nasal Polyps (OSTRO, Bachert et al, J Allergy Clin Immunol 2022)[61]

The OSTRO phase 3 study investigated the efficacy and safety of benralizumab for treating CRSwNP.[61] Patients with severe CRSwNP who were symptomatic despite treatment with intranasal corticosteroids and who had a history of systemic corticosteroid (SCS) use and/or surgery for nasal polyps (NP) were randomized to either benralizumab 30 mg (n = 207) or placebo (n = 206) for 40 weeks. Co-primary end points were change in Nasal Polyp Score (NPS) and Nasal blockage score. Benralizumab significantly improved NPS and nasal blockage score compared to placebo at week 40 ($P \leq 0.005$), and reduced difficulty with sense of smell. However, there were no improvements in Sinonasal Outcome Test 22 (SNOT 22) score, time to first NP surgery, and/or corticosteroid use for NP. Benralizumab is currently as of May 2025 not FDA approved for the treatment of CRSwNP and in 2022 the FDA asked Astra Zenica for additional clinical information for the FDA to reconsider their decision.

Reslizumab and Nasal Polyps

There are currently no published large scale phase 3 studies of reslizumab in CRSwNP and reslizumab as of May 2025 is not FDA approved to treat CRSwNP.

Which Biologic to Chose to Target Eosinophils in Asthma?

As there are no direct head-to-head comparator trials of different eosinophil targeted biologics in severe eosinophilic asthma, it is not possible to provide a strong evidence based choice of which of the three currently available eosinophil targeted biologic to choose in severe eosinophilic asthma. All three eosinophil targeted biologics appear to be equally effective in the treatment of severe eosinophilic asthma and have a similar excellent safety profile. Each are FDA approved for the treatment of severe eosinophilic asthma based on large scale phase 3 clinical trials. Some considerations in choosing one of the three eosinophil targeted biologics include if the individual with severe eosinophilic asthma also had a comorbidity such as CRSwNP as currently only mepolizumab has FDA approval for treatment of CRSwNP. Patients may also express a preference for subcutaneously administered therapy (mepolizumab, benralizumab) as these can be administered at home as compared to intravenous administered eosinophil targeted therapies (reslizumab) which require clinic visits. In addition, the frequency of administration of eosinophil targeted therapies is either every 4 weeks (mepolizumab, reslizumab), or alternatively initially every 4 weeks and then every 8 weeks on maintenance (benralizumab) can influence patient choices. The pediatric age of the individual may also influence the choice as reslizumab is not FDA approved in pediatric patients and is currently only approved in ages 18 years and older (Table 1). Mepolizumab is approved for ages >6 years, whereas benralizumab is approved for ages >12 years (Table 1). Boxed prescribing warnings in the FDA package insert may also influence the choice of eosinophil targeted biologic. For example, reslizumab has

a boxed prescribing warning indicating that anaphylaxis occurred with reslizumab infusion in 0.3% of patients in placebo-controlled studies, and that patients should be observed for an appropriate period of time after reslizumab IV infusion. Although the risk of anaphylaxis with reslizumab is very small, it can influence very risk averse patients if there is an alternate option without this warning.

Target Eosinophils or Alternate Pathways in Asthma?

There are currently six FDA approved biologic therapies for severe persistent asthma that target different pathways (eosinophil and non-eosinophil pathways) in an attempt to reduce asthma exacerbations, improve asthma symptom control, improve lung function, and potentially decrease oral corticosteroid use (ie anti-IgE;[62] dupilumab targeting the IL-4Rα;[63] tezepelumab targeting TSLP;[64] and the three eosinophil targeted biologics). No information is currently available from randomized controlled clinical trials in severe asthma to compare any of the 6 available biologic therapies head-to-head in asthma. Thus, in the absence of such studies, the selection of a specific biologic agent for severe asthma should be individualized by utilizing a profile of clinical features including comorbid conditions that could also be controlled by that biologic (ie CRSwNP), biomarker status (eosinophils, FeNO, IgE), corticosteroid dependence (dupilumab is the only biologic with FDA indication for corticosteroid dependent asthma),[65–70] patient preference (IV vs sc medication), and side effect profile.[71]

The following specific asthma clinical circumstances warrant consideration of the selection of particular biologics:

a. **Severe asthma with oral corticosteroid dependence**: Dupilumab is the only biologic with FDA approval for corticosteroid dependent asthma (irrespective of biomarker status).[65] Mepolizumab[37,39] and benralizumab[47] have also shown corticosteroid sparing effects for severe eosinophilic asthma but do not have FDA approval for this indication.
b. **Severe asthma without evidence of elevated type 2 biomarkers**: Tezepelumab is the only biologic therapy with FDA approval for severe persistent asthma with and without evidence of elevated type-2 biomarkers.[67]
c. **Asthma and CRSwNP**: There are three biologics with FDA approval for treatment of nasal polyposis and asthma (mepolizumab,[68] dupilumab,[65] anti-IgE[66]). No direct head to head comparator studies have been performed of these three FDA approved biologics for treatment of nasal polyposis and asthma. A post-hoc indirect comparator study suggested that dupilumab had the biggest impact on patient-reported outcome measures compared to mepolizumab or omalizumab.[72] However, there are significant limitations to post-hoc indirect comparator studies, and thus direct prospective head to head comparator studies are needed to make firm objective conclusions.
d. **Severe Asthma: Biologic Improvement in Lung Function-Indirect Comparison**: Indirect comparison suggests that dupilumab and tezepelumab appear to provide the best improvement in lung function and the highest reduction in asthma exacerbation risk compared to placebo.[73] However, until prospective head to head biologic comparison studies are performed with all 6 current biologics in severe asthmatics these indirect conclusions are not yet substantiated by conclusive evidence.

Use of Historical Blood Eosinophil and Sputum Eosinophil Counts to Define Severe Eosinophilic Asthma

A one time eosinophil blood count may not accurately reflect the true underlying eosinophil phenotype in severe asthma as levels of eosinophilic inflammation are variable over time, and oral corticosteroid therapy can suppress eosinophilic inflammation.[74] A ten year retrospective study of 235 biologic therapy naïve severe asthmatics in the WATCH cohort demonstrated that approximately 40% were blood eosinophilic (>300 eosinophils/μL) at WATCH enrollment whilst an additional approximately 43% who were not eosinophilic at enrollment demonstrated eosinophilia at least once during the previous decade.[74] Thus, historical eosinophil blood counts may identify severe asthmatics with previous but not current eosinophilia which may be related to changes in asthma therapy and/or other factors. Further studies are needed to determine whether severe asthmatics with previous, but not current eosinophilia, respond as well to eosinophil target biologics as severe asthmatics with current eosinophilia.

Three Component Definition of T2 High Status in Severe Asthma (Eosinophils; FeNO; Clinical)

Using a three factor multicomponent definition of T2 high status that included eosinophilic blood inflammation (>150 eosinophils/μL), as well as two additional components (FeNO ≥ 20; maintenance oral corticosteroid use and/or clinically allergen driven asthma), 93% of 388 biologic naïve severe asthmatics were identified as T2 high.[75] Interestingly, of the 7% of severe asthmatics identified as T2 low by this definition, 75% of them had raised peripheral blood eosinophils within the preceding 10 years which left only 1.8% of severe asthmatics who had never had a T2 signal.[75] As there are 6 biologics that can target T2 high asthma, the ability to identify the vast majority of severe asthmatics as T2 high using a three component definition improves the ability to identify severe asthmatics who may benefit from a T2 directed therapy but does not identify the specific biologic that is likely to be best.

Evaluating and Treating an Asthma Exacerbation While on Mepolizumab

The MEX study[76] which investigated the inflammatory phenotype and physiological characteristics of asthma exacerbations events in severe eosinophilic asthma treated with mepolizumab have demonstrated that asthma exacerbations on mepolizumab have two distinct phenotypes, which can largely be differentiated by using FeNO. Non-eosinophilic asthma exacerbations which are likely driven by infection are associated with a low FeNO and high C-reactive protein concentration, whereas eosinophilic asthma exacerbations are FeNO high.[76] A FeNO measurement of <20 ppb demonstrated a 100% positive predictive value for predicting non-eosinophilic, infectious asthma exacerbations.[76] As oral prednisolone has extensive additional biologic and anti-inflammatory effects in patients taking mepolizumab, prednisolone use should be considered in high FeNO mepolizumab associated asthma attacks.[77,78] Whether low Feno asthma exacerbations in the setting of anti-IL-5 therapy benefit from prednisolone require further study.[77,78] The results of the MEX study[76] challenge the routine use of oral corticosteroids for the treatment of all asthma exacerbation events on mepolizumab, as well as the switching of biological therapies for treatment failure without profiling the inflammatory phenotype of ongoing asthma exacerbations.

Future Directions: Ultra Long Acting Anti-IL-5

Depemokimab is an ultra-long-acting anti-IL-5 with enhanced binding affinity for IL-5 that may enable effective 6-month dosing intervals.[79] In two phase 3A placebo-controlled replicate trials, the efficacy and safety of depemokimab was examined in patients with severe eosinophilic asthma (≥300 eosinophils/μL in the previous 12 months, or ≥150 eosinophils/μL at screening) and a history of asthma exacerbations.[79] Asthmatics were randomly assigned to receive either depemokimab (100 mg subcutaneously) (n = 502) or placebo (n = 260) at weeks 0 and 26, plus standard care. The primary end point was the annualized rate of asthma exacerbations at 52 weeks which was reduced by approximately 59% with depemokimab (mean exacerbation rate 0.46) compared to placebo (mean exacerbation rate 1.11). This study of depokinumab[79] was placebo controlled but did not have an active short acting anti-IL-5 comparator administered every month such as mepolizumab to determine whether depokinumab every 6 months was as effective as mepolizumab every month. The mean number of asthma exacerbations in the placebo group in this depokinumab study was only 1.1 which is a small number of annual exacerbations. Nevertheless, patients will likely prefer a twice yearly anti-IL-5 therapy if it is equally effective as a monthly IL-5 therapy especially if it can be administered at home.

Targeting Eosinophils in Asthma: Drawbacks

How Often Do We Have a Clinical Remission to an Eosinophil Targeted Biologic in Severe Asthma?

If a therapy is not effective or minimally effective in severe asthma that would be a significant drawback. Several studies have shown that biologics only induce clinical remission in approximately 20% to 40% of severe asthmatics with no substantial differences in efficacy across the different classes of biologics.[80–86] Asthma characteristics associated with a suboptimal or lack of response to an asthma biologic include a high asthma exacerbation rate, longer asthma duration, greater oral corticosteroid requirements, and relatively impaired lung function (which may may be associated with airway

remodeling).[87] However, our current method of biomarker endotyping of eosinophilic asthma (based on blood eosinophils or sputum eosinophils) is not sufficiently rigorous to differentiate between IL-5 driven causes of eosinophilic inflammation (which will respond to an IL-5 targeted therapy) and non-IL-5 driven causes of eosinophilic inflammation (which will not respond to an IL-5 targeted therapy).

Nolasco et al[80] have proposed that the response to mepolizumab may have either the desired outcome (ie clinical remission occurring in approximately 20%-40% of severe asthmatics treated with mepolizumab), or an inadequate or lack of response to mepolizumab (in approximately 60%–80% of severe asthmatics). A significant clinical asthma remission response with mepolizumab occurred in 20%–40% of severe asthmatics treated with mepolizumab whose response included a significant reduction in sputum eosinophils, asthma exacerbations, asthma symptoms, and improvement in lung function.[80] This mepolizumab responsive subset is likely due to IL-5 being the primary cytokine contributing to the pathogenesis of asthma in this subset of mepolizumab treated patients, and the dose of mepolizumab being sufficient to neutralize all the IL-5 in the airways.[80] A second subset of asthmatics treated with mepolizumab (mepolizumab partially responsive subset) may have continued asthma symptoms and eosinophilic asthma exacerbations, which may occur when the standard dose of mepolizumab is inadequate to neutralize the very high levels of IL-5 in the airway and is thus ineffective in reducing high eosinophil numbers in the airway.[80] This partially responsive mepolizumab subset may need either higher doses of anti-IL-5, or switching to an anti-IL-5Rα agent, that may allow more complete depletion of sputum eosinophils, which may improve treatment outcomes in such asthmatics.[80] A third subset of asthmatics treated with mepolizumab (mepolizumab unresponsive subset) may have continued asthma symptoms because their eosinophilic asthma is not due to IL-5 but due to other non-IL-5 mechanistic pathways such as IL-4/IL-13, TSLP, IL-33, mast cells, ILC2, or other pathways.[80] These studies underscore the need to develop additional validated biomarkers for specific cytokines (ie IL-5, IL-4/IL-13, TSLP, IL-33, eotaxin-1, RANTEs, etc), and cell types (mast cells; ILC2 which are IL-13^+ IL-5^+) that may be contributing to the pathogenesis of asthma in partially responsive and unresponsive eosinophilic asthmatics. Additionally, it is also possible that a remodeled airway with structural changes of airway wall fibrosis and smooth muscle hypertrophy (or hyperplasia) may also show poor treatment response to an anti-IL-5 biologic as suggested in studies examining mepolizumab responses in an Australian registry of mepolizumab treatment for severe asthma which described three different responses to mepolizumab when monitored over a 12 month period.[88]

What Happens When Eosinophil Directed Therapies are Discontinued?

Studies in severe eosinophilic asthma have demonstrated that subjects who discontinued mepolizumab experienced significant increases in blood eosinophils, asthma symptoms, and number of asthma exacerbations within 3 to 6 months after the last dose of mepolizumab.[89] Thus, a potential minor drawback to eosinophil targeted therapies is that they do not induce long term remission off of therapy and in this aspect are similar to other therapies used for the treatment of severe asthma such as inhaled or oral corticosteroids, and biologics that do not target eosinophils.

FDA Approved Biologics for Eosinophilic Asthma are Well Tolerated

Biologics that are FDA approved for targeting eosinophils in the treatment of asthma are generally well-tolerated. Meta-analysis of randomized controlled trials that assessed the efficacy of biologics approved to treat eosinophilic asthma have generally been associated with fewer adverse effects than the control subjects including serious adverse events and deaths.[90] The most common adverse effects noted with biologics used to treat asthma are generally minor and common to all agents, and include nasopharyngitis, upper respiratory infection, and reactions at the injection site.[68–70] However, there are a few very rare potential side effects and warnings from the FDA regarding specific biologics that we discuss in greater detail below.

Very Low Incidence of Herpes Zoster

Opportunistic infection occurred in approximately 4%–7% of patients receiving mepolizumab (n = 339) in two 52 week open-label extension trials for severe eosinophilic asthma.[91] Herpes zoster was the most common of these infections (n = 11),[91] with one episode of herpes zoster considered serious[91,] and all other episodes resolved despite the continuation of

mepolizumab.[91] Mepolizumab's FDA approved package insert recommends consideration of vaccination prior to starting therapy if appropriate.[68]

Benralizumab therapy in eosinophilic asthma had no increased risk of infection, and there were no reported helminth infections.[30,31,47,92] There was one reported case of herpes zoster associated with benralizumab.[30] Subsequently in 2019, a case report described a 61-year-old asthmatic who developed disseminated herpes zoster after initiation of benralizumab.[92] Benralizumab 1- and 5-year extension trials did not demonstrate an increased risk of herpes zoster infection.[93,94] There are no published contraindications or FDA recommendations regarding herpes zoster vaccination for benralizumab.

Reslizumab: Very Low Risk of Anaphylaxis/Hypersensitivity Reaction

Reslizumab is an IV administered biologic and features a boxed warning by the FDA for anaphylaxis.[69] A pooled analysis of 6 clinical trials with 1,028 reslizumab treated asthmatics revealed three cases of anaphylaxis occurred with reslizumab administration (0.3%).[45] All episodes of anaphylaxis occurred shortly after initiating or completing the infusion, and all affected patients were successfully managed with standard anaphylaxis therapies.[45] In an open-label extension trial, no cases of anaphylaxis were reported among 1,051 patients who received reslizumab.[44] The FDA package insert recommends observation after reslizumab infusion for "an appropriate period of time."[69]

Benralizumab: Hypersensitivity Reactions

In placebo-controlled trials of benralizumab hypersensitivity reactions to benralizumab (primarily urticarial rash) were reported in approximately 1%–3% of asthmatics.[30,31,47] Anaphylaxis to benralizumab did not occur in randomized, controlled, double-blind studies among patients receiving benralizumab. However, anaphylaxis to benralizumab was reported in one patient in the open-label extension trial of 1,576 benralizumab treated asthmatics.[95]

Eosinophils and Risk of Parasitic Infections

While eosinophils are associated with several parasitic infections and are effective at killing parasites in vitro, their role in clearing parasites in humans in vivo is complex and not fully understood.[96] In vitro, eosinophils kill various helminth and protozoan parasites in laboratory settings, often in the presence of antibodies or complement.[96] The precise role of eosinophils in clearing parasites in vivo in humans is less clear. While eosinophils are known to be attracted to parasitic infections, their role in killing adult parasites is not as well-established as their ability to kill larval stages.[96] Studies also suggest that eosinophils are not always essential for clearing parasitic infections, and other immune cells like neutrophils and T cells can also play important roles. The use of eosinophil depleting agents has led to some information regarding the risk of parasitic infection in eosinophil depleted patients (who may or may not have been exposed to parasites, and who were not specifically monitored with tests for parasitic infection). For example, there were no reported helminth infections or opportunistic infections in a 24-month open-label extension trial of reslizumab.[45]

Eosinophils and Risk of Malignant Neoplasms

As eosinophils are associated with malignant neoplasms studies with eosinophil depleting agents have also focused on understanding whether eosinophil depleting agents are associated with an increased risk of malignancies. Although, eosinophils infiltrate multiple tumors their role in influencing tumor growth either positively or negatively in vivo is not known.[97] Eosinophils are capable of releasing unique granule proteins that can potentially kill tumor cells.[97] Alternatively, eosinophils can secrete pro-angiogenic and matrix-remodeling soluble mediators that could promote tumor growth.[97] As eosinophils infiltrate tumors, the potential impact of eosinopenia induced by benralizumab on the risk of malignancy has been raised.[95] However, there is insufficient evidence to suggest an increased risk of malignancy among patients receiving benralizumab. In a 1-year open-label extension study of benralizumab, new malignancy occurred in 1% of asthmatics, and one case was felt by the investigator to be related to benralizumab.[92] This asthmatic had a history of prostatic hypertrophy and elevated prostate-specific antigen and developed prostate cancer 3 days after the second dose of benralizumab.[92,95] A subsequent 5-year extension study of benralizumab did not demonstrate an

increased risk of malignancy compared to placebo. Malignancy was reported in 3 (0.7%) of patients receiving benralizumab compared to 1 (0.5%) of patients receiving placebo.[93]

Risks of Eosinophil Targeted Biologics in Pregnancy

As many asthmatics are in their child bearing years, consideration needs to be given as to whether therapies targeting either IL-5 or the IL-5 Receptor α are safe to use in pregnancy. Mepolizumab, reslizumab, and benralizumab are IgG monoclonal antibodies that transport across the placenta in a linear fashion as pregnancy progresses.[98–100] Thus, their potential effects on a fetus are likely to be greater during the second and third trimester. In non-human primate studies, no evidence of fetal harm has been observed with eosinophil targeted therapies.[99] For example, in pregnant non-human primates, administration of mepolizumab (9-fold the maximum recommended human dose)[68] or benralizumab (310-fold of the maximum recommended human dose)[70] elicited no maternal or fetal adverse effect up to 9 months after birth. No such data are available for reslizumab.[69] No signal of harm in human pregnancy and breastfeeding has yet been published for mepolizumab, benralizumab, or reslizumab.[98–100] Although the absence of a signal of harm in pregnancy for IL-5/IL-5Rα targeted therapies thus far is reassuring, as with all therapies administered in pregnancy the pros/cons of administering the therapy should be discussed with the patient. There are currently ongoing pregnancy exposure registries for mepolizumab, and benralizumab, but no registry for reslizumab.[101] However, the value of the registry is dependent upon information related to pregnancy outcomes on biologics (good and bad) being voluntarily provided to the registry.

Eosinophil Targeted Therapies Open Label Extension Studies of Safety

Limitations of the Interpretation of Safety and Efficacy in Open Label Extension Studies

While long term open label studies of mepolizumab,[102] reslizumab,[44,45] and benralizumab[93] provide useful information on long term safety and efficacy, the absence of a placebo control group and the lack of blinding are a significant limitation of such study designs.[103] The lack of a placebo-controlled arm means it is difficult to make robust clinical interpretations regarding any follow up treatment-related outcomes.[98,103] Patient recruitment to extension studies are also biased toward recruitment of those who responded to therapy, and to those without AEs, as those with AEs may discontinue and not be included in extension studies.[98,103] These factors may bias and positively affect the long term treatment safety and efficacy outcomes.[98,103] Finally, in extension studies if the use of background asthma therapies are not systematically checked during the extension study and are at the investigator's discretion whether to increase background asthma therapies, this approach may influence the results of efficacy outcomes.[98,103] In addition, any changes in bronchodilator therapy may affect the lung function results.[98,103]

Decreased Adherence to Inhaled Corticosteroids in a Subset of Asthmatics While on Biologic

A subset of asthmatics receiving biologic therapy demonstrate decreasing adherence to inhaled corticosteroids (ICS) treatment. It is therefore essential to check ICS adherence[104] while an asthmatic is on a biologic, as mepolizumab associated nonadherence to ICS predicts a poor clinical response.[105] Benralizumab in the SHAMAL trial[106] demonstrated that asthmatics controlled on benralizumab can have meaningful reductions in ICS dose while maintaining their asthma control. However, benralizumab was associated with a decline in FEV_1 in a subset of asthmatics who decreased their ICS dose to as-needed budesonide-formoterol[106.] No significant decrease in FEV_1 was noted in asthmatics on benralizumab receiving low-to-moderate dose ICS therapy. Thus, it is important to ensure that asthmatics receiving biologics adhere to taking at least a low to moderate dose of ICS.

Conclusion

Human IL-5 was initially cloned in 1987[107] and its functional ability to regulate eosinophil proliferation in mice[13,16] and humans[13,16,107] led to subsequent studies demonstrating that IL-5 was present in the airway of asthmatics[14] and that inhibiting IL-5 in the mouse prevented allergen induced eosiniophilic airway inflammation, airway hyperreactivity, and

airway remodeling.[10] These and other pre-clinical studies provided the impetus for the development by pharma of biologics targeting IL-5 and the IL-5Rα. The trials and tribulations of bringing an IL-5 targeted therapy to the clinic[19] were underscored by the lack of response in initial studies which did not focus on requiring an entry criteria of eosinophilic inflammation in severe asthmatics, or an end point of asthma exacerbations which were later shown to be essential in demonstrating the effectiveness of IL-5 targeted therapies in severe asthma. FDA approval for the first IL-5 targeted therapy occurred in 2015,[68] approximately 28 years after the initial discovery of human IL-5 underscoring the length of time taken for these IL-5 targeted biologics to reach the clinic. IL-5 and IL-5Rα targeted therapies have been an important advance in the treatment of severe asthmatics with eosinophilic inflammation. Side effects are infrequent and generally mild. However, as only approximately 20% to 40% of severe asthmatics with eosinophilic inflammation respond significantly to IL-5 and IL-5Rα targeted therapies it is important to correctly choose those severe asthmatics with eosinophilic inflammation who are most likely to respond to IL-5 and IL-5Rα targeted therapies by improving our ability to measure the specific biologic target biomarkers (ie IL-5 in the case of anti-IL-5 therapy), as well as by making sure that the dose of the biologic being used is optimal for an individual asthmatic, and by investigating whether an alternate non-IL-5 pathway is mediating eosinophilic airway inflammation if there is no response to IL-5 and IL-5Rα targeted therapies.

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References

1. Broide DH. Immunologic and inflammatory mechanisms that drive asthma progression to remodeling. *J Allergy Clin Immunol*. 2008;121(3):560–570. doi:10.1016/j.jaci.2008.01.031
2. Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. *Immunol Allergy Clin North Am*. 2007;27(4):623–632. doi:10.1016/j.iac.2007.09.003
3. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med*. 2015;3(11):849–858. doi:10.1016/S2213-2600(15)00367-7
4. Belda J, Parameswaran K, Lemière C, Kamada D, O'Byrne PM, Hargreave FE. Predictors of loss of asthma control induced by corticosteroid withdrawal. *Can Respir J*. 2006;13(3):129–133. doi:10.1155/2006/189127
5. Kamble S, Bharmal M. Incremental direct expenditure of treating asthma in the United States. *J Asthma*. 2009;46(1):73–80. doi:10.1080/02770900802503107
6. Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol*. 2010;125(3):600–608. doi:10.1016/j.jaci.2009.11.033
7. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the national heart, lung, and blood institute's severe asthma research program. *J Allergy Clin Immunol*. 2007;119(2):405–413. doi:10.1016/j.jaci.2006.11.639
8. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308–1321. doi:10.1183/13993003.00779-2015
9. Arnold IC, Munitz A. Spatial adaptation of eosinophils and their emerging roles in homeostasis, infection and disease. *Nat Rev Immunol*. 2024;24(12):858–877. doi:10.1038/s41577-024-01048-y
10. Cho JY, Miller M, Baek KJ, et al. Inhibition of airway remodeling in IL-5-deficient mice. *J Clin Invest*. 2004;113(4):551–560. doi:10.1172/JCI19133
11. Broide D. Fast flowing eosinophils: signals for stopping and stepping out of blood vessels. *Am J Respir Cell Mol Biol*. 2002;26(6):637–640. doi:10.1165/ajrcmb.26.6.f240
12. Gundel RH, Letts LG, Gleich GJ. Human eosinophil major basic protein induces airway constriction and airway hyperresponsiveness in primates. *J Clin Invest*. 1991;87(4):1470–1473. doi:10.1172/JCI115155
13. Takatsu K. Interleukin-5 and IL-5 receptor in health and diseases. *Proc Jpn Acad Ser B Phys Biol Sci*. 2011;87(8):463–485. doi:10.2183/pjab.87.463
14. Sur S, Gleich GJ, Swanson MC, Bartemes KR, Broide DH. Eosinophilic inflammation is associated with elevation of interleukin-5 in the airways of patients with spontaneous symptomatic asthma. *J Allergy Clin Immunol*. 1995;96(5):661–668. doi:10.1016/S0091-6749(95)70265-2
15. Broide DH, Paine MM, Firestein GS. Eosinophils express interleukin 5 and granulocyte macrophage-colony-stimulating factor mRNA at sites of allergic inflammation in asthmatics. *J Clin Invest*. 1992;90(4):1414–1424. doi:10.1172/JCI116008
16. Willebrand R, Voehringer D. Regulation of eosinophil development and survival. *Curr Opin Hematol*. 2017;24(1):9–15. doi:10.1097/MOH.0000000000000293
17. Sullivan S, Broide DH. Compartmentalization of eosinophil granulocyte-macrophage colony-stimulating factor expression in patients with asthma. *J Allergy Clin Immunol*. 1996;97(4):966–976. doi:10.1016/S0091-6749(96)80072-8

18. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet*. 2000;356(9248):2144–2148. doi:10.1016/S0140-6736(00)03496-6
19. O'Byrne PM, Inman MD, Parameswaran K. The trials and tribulations of IL-5, eosinophils, and allergic asthma. *J Allergy Clin Immunol*. 2001;108(4):503–508. doi:10.1067/mai.2001.119149
20. Van Hulst G, Jorssen J, Jacobs N, et al. Anti-IL5 mepolizumab minimally influences residual blood eosinophils in severe asthma. *Eur Respir J*. 2022;59(3):2100935. doi:10.1183/13993003.00935-2021
21. Fricker M, Harrington J, Hiles SA, Gibson PG. Mepolizumab depletes inflammatory but preserves homeostatic eosinophils in severe asthma. *Allergy*. 2024;79(11):3118–3128. doi:10.1111/all.16267
22. Kips JC, O'Connor BJ, Langley SJ, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med*. 2003;167(12):1655–1659. doi:10.1164/rccm.200206-525OC
23. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med*. 2007;176(11):1062–1071. doi:10.1164/rccm.200701-085OC
24. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med*. 2003;167(2):199–204. doi:10.1164/rccm.200208-789OC
25. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med*. 2000;161(1):64–72. doi:10.1164/ajrccm.161.1.9809100
26. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*. 2002;360(9347):1715–1721. doi:10.1016/S0140-6736(02)11679-5
27. Westerhof GA, Korevaar DA, Amelink M, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J*. 2015;46(3):688–696. doi:10.1183/09031936.00012415
28. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. *J Allergy Clin Immunol*. 2015;135(3):822–824. doi:10.1016/j.jaci.2014.09.034
29. Zeiger RS, Schatz M, Li Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract*. 2014;2(6):741–750. doi:10.1016/j.jaip.2014.06.005
30. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388 (10056):2128–2141. doi:10.1016/S0140-6736(16)31322-8
31. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388 (10056):2115–2127. doi:10.1016/S0140-6736(16)31324-1
32. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371 (13):1198–1207. doi:10.1056/NEJMoa1403290
33. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390–400. doi:10.1016/S2213-2600(17)30125-X
34. Castro M, Zangrilli J, Wechsler ME. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355–366. doi:10.1016/S2213-2600(15)00042-9
35. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789–798. doi:10.1016/j.chest.2016.03.032
36. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360 (10):973–984. doi:10.1056/NEJMoa0808991
37. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360 (10):985–993. doi:10.1056/NEJMoa0805435
38. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651–659. doi:10.1016/S0140-6736(12)60988-X
39. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371 (13):1189–1197. doi:10.1056/NEJMoa1403291
40. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549–556. doi:10.1016/S2213-2600(16)30031-5
41. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184(10):1125–1132. doi:10.1164/rccm.201103-0396OC
42. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med*. 2014;2(11):879–890. doi:10.1016/S2213-2600(14)70201-2
43. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799–810. doi:10.1016/j.chest.2016.03.018
44. Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2017;5(6):1572–1581. doi:10.1016/j.jaip.2017.08.024
45. Virchow JC, Katial R, Brusselle GG, et al. Safety of Reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from 6 trials. *J Allergy Clin Immunol Pract*. 2020;8(2):540–548. doi:10.1016/j.jaip.2019.07.038
46. Wechsler ME, Hickey L, Garin M, Chauhan A. Efficacy of reslizumab treatment in exacerbation-prone patients with severe eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2020;8(10):3434–3442. doi:10.1016/j.jaip.2020.06.009
47. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448–2458. doi:10.1056/NEJMoa1703501

48. Yang F, Bossios A. Who really responds to asthma biologics? The clue lies in the journey before treatment. *Eur Respir J*. 2025;65(4):2500044. doi:10.1183/13993003.00044-2025
49. Hansen S, Søndergaard MB, von Bülow A, et al. Clinical response and remission in patients with severe asthma treated with biologic therapies. *Chest*. 2024;165(2):253–266. doi:10.1016/j.chest.2023.10.046
50. Thomas D, McDonald VM, Stevens S, et al. Biologics (mepolizumab and omalizumab) induced remission in severe asthma patients). *Allergy*. 2024;79(2):384–392. doi:10.1111/all.15867
51. McDowell PJ, McDowell R, Busby J, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. *Eur Respir J*. 2023;62(6):2300819. doi:10.1183/13993003.00819-2023
52. Bourdin A, Brusselle G, Couillard S, et al. Phenotyping of severe asthma in the era of broad- acting anti-asthma biologics. *J Allergy Clin Immunol in Practice*. 2024;12(4):809–823. doi:10.1016/j.jaip.2024.01.023
53. Soendergaard MB, Hjortdahl F, Hansen S, et al. Pre-biologic disease trajectories are associated with morbidity burden and biologic treatment response in severe asthma. *Eur Respir J*. 2025;65(4):2401497. doi:10.1183/13993003.01497-2024
54. Eger K, Kroes JA, Brinke AT, Bel EH. Long-term therapy response to anti-IL-5 biologics in severe asthma-a real-like evaluation. *J Allergy Clin Immunol Pract*. 2021;9(3):1194–1200. doi:10.1016/j.jaip.2020.10.010
55. Mukherjee M, Huang C, Venegas-Garrido C, et al. Benralizumab normalizes sputum eosinophilia in severe asthma uncontrolled by anti-IL5 antibodies: a single-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med*. 2023;208(12):1330–1335. doi:10.1164/rccm.202308-1413LE
56. Moran AM, Ramakrishnan S, Borg CA, et al. Blood eosinophil depletion with mepolizumab, benralizumab, and prednisolone in eosinophilic asthma. *Am J Respir Crit Care Med*. 2020;202(9):1314–1316. doi:10.1164/rccm.202003-0729LE
57. Le AV, Cho JY, Miller M, McElwain S, Golgotiu K, Broide DH. Inhibition of allergen-induced airway remodeling in Smad 3-deficient mice. *J Immunol*. 2007;178(11):7310–7316. doi:10.4049/jimmunol.178.11.7310
58. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003;112(7):1029–1036. doi:10.1172/JCI17974
59. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141–1153. doi:10.1016/S2213-2600(21)00097-7
60. Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. *J Asthma Allergy*. 2016;9:45–53. doi:10.2147/JAA.S86251
61. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2022;149(4):1309–1317. doi:10.1016/j.jaci.2021.08.030
62. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol*. 2003;111(1):87–90. doi:10.1067/mai.2003.49
63. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475–2485. doi:10.1056/NEJMoa1804093
64. Menzies-Gow A, Wechsler ME, Brightling CE, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. *Lancet Respir Med*. 2023;11(5):425–438. doi:10.1016/S2213-2600(22)00492-1
65. *Dupilumab (Package Insert)*. Cambridge, MA: Sanofi and Regeneron Pharmaceuticals I; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761055s057lbl.pdf.
66. *Omalizumab (Package Insert)*. San Francisco, CA: Genentech; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf.
67. *Tezepelumab-ekko (package insert)*. Gaithersburg, MD: AstraZeneca; 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761224s001lbl.pdf.
68. US Food and Drug Administration (FDA). Highlights of prescribing information: nucala® (mepolizumab) US food and drug administration website. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125526s004lbl.pdf. Accessed August 18, 2025.
69. US Food and Drug Administration (FDA). Highlights of prescribing information: cinqair® (reslizumab) US Food and Drug Administration website. 2016. Available from: https://www.accessdata.fda.gov/spl/data/c3617953-03c5-4746-bfdb-e731faf705d7/c3617953-03c5-4746-bfdb-e731faf705d7.xml. Accessed August 18, 2025.
70. US Food and Drug Administration (FDA). Highlights of prescribing information: fasenra® (benralizumab) US Food and Drug Administration website. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761070Orig1s020correctedlbl.pdf. Accessed August 18, 2025.
71. Salciccioli JD, Israel E. Asthma biologics: lung function, steroid-dependence, and exacerbations. *Immunol Allergy Clin North Am*. 2024;44(4):693–708. doi:10.1016/j.iac.2024.08.002
72. Peters AT, Han JK, Hellings P, et al. Indirect treatment comparison of biologics in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2021;9(6):2461–2471. doi:10.1016/j.jaip.2021.01.031
73. Couillard S, Jackson DJ, Pavord ID, Wechsler ME. Choosing the right biologic for the right patient with severe asthma. *Chest*. 2025;167(2):330–342. doi:10.1016/j.chest.2024.08.045
74. Azim A, Newell C, Barber C, et al. Clinical evaluation of type 2 disease status in a real-world population of difficult to manage asthma using historic electronic healthcare records of blood eosinophil counts. *Clin Exp Allergy*. 2021;51(6):811–820. doi:10.1111/cea.13841
75. Rupani H, Kyyaly MA, Azim A, et al. Comprehensive characterization of difficult-to-treat asthma reveals near absence of T2-low status. *J Allergy Clin Immunol in Pract*. 2023;11(9):2812–2821. doi:10.1016/j.jaip.2023.05.028
76. McDowell PJ, Diver S, Yang F, et al. The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med*. 2021;9(10):1174–1184. doi:10.1016/S2213-2600(21)00004-7
77. Howell I, Mahdi M, Bafadhel M, et al. Recovery of breakthrough asthma attacks treated with oral steroids while on monoclonal antibody therapy: protocol for a prospective observational study (BOOST). *JMIR Res Protoc*. 2023;12:e46741.

78. Howell I, Yang F, Brown V, et al. Anti-inflammatory effects of oral prednisolone at stable state in people treated with mepolizumab: a proteomic and bulk transcriptomics analysis. *medRxiv*. 2024;24302812.
79. Jackson DJ, Wechsler ME, Jackson DJ, et al. Twice-yearly depemokimab in severe asthma with an eosinophilic phenotype. *N Engl J Med*. 2024;391(24):2337–2349. doi:10.1056/NEJMoa2406673
80. Nolasco S, Mukherjee M, Nair P. Trajectories of responses to mepolizumab in severe asthma. *Eur Respir J*. 2025;65(1):2402023. doi:10.1183/13993003.02023-2024
81. Perez-de-Llano L, Scelo G, Tran TN, et al. Exploring definitions and predictors of severe asthma clinical remission after biologic treatment in adults. *Am J Respir Crit Care Med*. 2024;210(7):869–880. doi:10.1164/rccm.202311-2192OC
82. Crimi C, Nolasco S, Noto A, et al. Long-term clinical and sustained REMIssion in severe eosinophilic asthma treated with mepolizumab: the REMI-M study. *J Allergy Clin Immunol Pract*. 2024;12(12):3315–3327. doi:10.1016/j.jaip.2024.08.033
83. Pelaia C, Crimi C, Benfante A, et al. Sustained remission induced by 2 years of treatment with benralizumab in patients with severe eosinophilic asthma and nasal polyposis. *Respirology*. 2024;29(10):869–879. doi:10.1111/resp.14767
84. Wechsler ME, Brusselle G, Virchow JC, et al. Clinical response and on-treatment clinical remission with tezepelumab in a broad population of patients with severe, uncontrolled asthma: results over 2 years from the NAVIGATOR and DESTINATION studies. *Eur Respir J*. 2024;64(6):2400316. doi:10.1183/13993003.00316-2024
85. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol*. 2019;143(5):1742–1751. doi:10.1016/j.jaci.2018.09.033
86. Pavord ID, Rabe KF, Israel E, et al. Dupilumab induces long-term on-treatment clinical remission in patients with type 2 asthma. *J Allergy Clin Immunol Pract*. 2025;13(1):132–142. doi:10.1016/j.jaip.2024.10.009
87. Varricchi G, Ferri S, Pepys J, et al. Biologics and airway remodeling in severe asthma. *Allergy*. 2022;77(12):3538–3552. doi:10.1111/all.15473
88. Hamada Y, Thomas D, Harvey ES, et al. Distinct trajectories of treatment response to mepolizumab toward remission in patients with severe eosinophilic asthma. *Eur Respir J*. 2025;65(1):2400782. doi:10.1183/13993003.00782-2024
89. Moore WC, Kornmann O, Humbert M, et al. Stopping versus continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study). *Eur Respir J*. 2021;59(1):2100396. doi:10.1183/13993003.00396-2021
90. Kyriakopoulos C, Gogali A, Markozannes G, Kostikas K. Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials. *Eur Respir Rev*. 2024;33(172):230238. doi:10.1183/16000617.0238-2023
91. Khurana S, Brusselle GG, Bel EH, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study. *Clin Ther*. 2019;41(10):2041–2056. doi:10.1016/j.clinthera.2019.07.007
92. Busse WW, Bleecker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019;7(1):46–59. doi:10.1016/S2213-2600(18)30406-5
93. Korn S, Bourdin A, Chupp G, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. *J Allergy Clin Immunol Pract*. 2021;9(12):4381–4392. doi:10.1016/j.jaip.2021.07.058
94. Chow TG, Oppenheimer J, Joshi SR. A review of adverse reactions to biologics used in allergy-immunology practice. *J Allergy Clin Immunol Pract*. 2022;10(12):3075–3086. doi:10.1016/j.jaip.2022.09.020
95. Jackson DJ, Korn S, Mathur SK, et al. Safety of eosinophil-depleting therapy for severe, eosinophilic asthma: focus on benralizumab. *Drug Saf*. 2020;43(5):409–425. doi:10.1007/s40264-020-00926-3
96. Klion AD, Nutman TB. The role of eosinophils in host defense against helminth parasites. *J Allergy Clin Immunol*. 2004;113(1):30–37. doi:10.1016/j.jaci.2003.10.050
97. Grisaru-Tal S, Itan M, Klion AD, Munitz A. A new dawn for eosinophils in the tumor microenvironment. *Nat Rev Cancer*. 2020;20(10):594–607. doi:10.1038/s41568-020-0283-9
98. Sitek A, Chiarella SE, Pongdee T. Adverse effects of biologics used to treat asthma. *Ther Adv Respir Dis*. 2025;19:17534666251319175. doi:10.1177/17534666251319175
99. Schatz M, Krishnan JA, Chambers C. Implications of changes in U.S. Food and drug administration prescribing information regarding the safety and use of asthma biologics during pregnancy. *Ann Am Thorac Soc*. 2018;15(10):1131–1136. doi:10.1513/AnnalsATS.201806-400PP
100. Shakuntulla F, Chiarella SE. Safety of biologics for atopic diseases during pregnancy. *J Allergy Clin Immunol Pract*. 2022;10(12):3149–3155. doi:10.1016/j.jaip.2022.08.013
101. List of pregnancy exposure registries from the FDA office of women's health. Available from: https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries. Accessed October, 2024.
102. Pavord I, Chan R, Brown N, et al. Long-term safety of mepolizumab for up to ~10 years in patients with severe asthma: open-label extension study. *Ann Med*. 2024;56(1):2417184. doi:10.1080/07853890.2024.2417184
103. Day RO, Williams KM. Open-label extension studies: do they provide meaningful information on the safety of new drugs? *Drug Saf*. 2007;30(2):93–105. doi:10.2165/00002018-200730020-00001
104. Mansur AH, Gonem S, Brown T, et al. Biologic therapy practices in severe asthma; outcomes from the UK severe asthma registry and survey of specialist opinion. *Clin Exp Allergy*. 2023;53(2):173–185. doi:10.1111/cea.14222
105. d'Ancona G, Kavanagh J, Roxas C, et al. Adherence to inhaled corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. *Eur Respir J*. 2020;55(5):1902259. doi:10.1183/13993003.02259-2019
106. Jackson DJ, Heaney LG, Humbert M, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, Phase 4 study. *Lancet*. 2024;403(10423):271–281. doi:10.1016/S0140-6736(23)02284-5
107. Tanabe T, Monishi M, Mizuta T, Noma T, Honjo T. Molecular cloning and structure of the human interleukin-5 gene. *J Biol Chem*. 1987;262(34):16580–16584. doi:10.1016/S0021-9258(18)49295-2