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REVIEW

Targeting eosinophils: severe asthma and beyond

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Abstract

Recent research in the field of bronchial asthma has mainly focused on eosinophilic disease phenotype. Several trials proved the efficacy and safety profile of eosinophils and interleukin (IL)-5 targeting molecules, currently approved for severe asthma and available on the market. They include mepolizumab and reslizumab, IL-5 blocking molecules, and benralizumab, targeting the IL-5 receptor and eliciting a NK cell-mediated antibody-dependent cellular cytotoxicity against eosinophils. Eosinophilic inflammation represents the common pathophysiological background of several conditions, providing the rationale for the use of the same biologics beyond asthma. Although with different evidence grade, from clinical trials to case reports, anti-IL-5 biologics have been investigated in eosinophilic granulomatosis with polyangitis, allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, nasal polyposis, hypereosinophilic syndrome, and eosinophilic esophagitis.

However, non-negligible differences between asthma and other eosinophilic diseases, particularly in eosinophils homing (blood and/or tissues), target organs and thus clinical features, probably account for the different response to the same drug in different clinical conditions and highlights the need for tailoring the therapeutic approach by modulating the drug dose and/or by combination therapy with multiple drugs.

The optimal safety and tolerability profile of anti-IL-5 drugs warrants further and larger experimental and real-life investigations, which are needed especially in the field of non-asthma eosinophilic diseases.

This review aims at summarizing the rationale for the use of biologics in eosinophilic diseases and their mechanisms of action. The current efficacy and safety evidence about eosinophils and IL-5 targeting molecules in asthma and in eosinophilic conditions beyond bronchi is also discussed.

Keywords: ABPA, benralizumab, EGPA, eosinophilic esophagitis, eosinophilic inflammation, mepolizumab, reslizumab, severe asthma.

Citation

Caminati M, Menzella F, Guidolin L, Senna G. Targeting eosinophils: severe asthma and beyond. Drugs in Context 2019; 8: 212587. DOI: 10.7573/dic.212587

Introduction

During the past 10 years, considerable advances have been achieved in understanding the inflammatory background of several immune-mediated diseases. In particular, the eosinophilic inflammation underlying respiratory and non-respiratory inflammatory diseases has been extensively investigated.[1] Bronchial asthma, mostly severe eosinophilic and allergic phenotypes, has recently represented a main focus of both basic and pharmacological research. As a consequence, several new molecules have been conceived and explored and some of them are already available on the market.[2]

The new biologic drugs for severe eosinophilic asthma are substantially enlarging the treatment options and also contributing to a better understanding of the pathophysiologic mechanisms targeted by the therapeutic molecules.[3] The increasing amount of knowledge and evidence in the field has paved the way to the potential use of biologics for treating eosinophilic inflammation beyond bronchi.

This review aims at summarizing the evidence about safety and efficacy of eosinophils and interleukin (IL)-5 targeting molecules approved for severe asthma and at exploring the published data about the use of the same biologics for eosinophilic diseases beyond asthma.

Methods

A selective search on PubMed and Medline (keywords: benralizumab, mepolizumab, reslizumab, anti-IL-5 monoclonal antibody, anti-IL-5 receptor monoclonal antibody) was carried out, including papers published up to January 2019. For severe eosinophilic asthma, we selected original articles, randomized clinical trials, and review papers relevant to the topic (drug mechanisms, drug safety, and efficacy). For eosinophilic diseases other than asthma, any type of article relevant to the topic, conducted on human subjects, was included.

Targeting Eosinophils: pharmacological insights

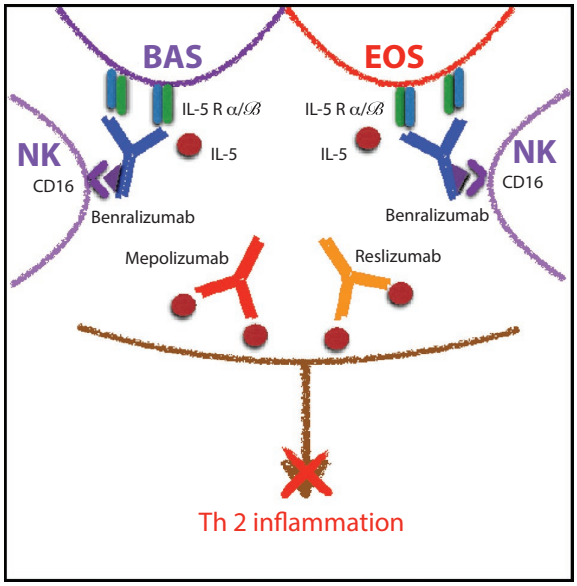
Anti-IL-5 drug mechanisms and effects

Th2 cells and tissue-resident innate lymphoid cells type 2 (ILC2s) are the main producers of Th2 cytokines (including IL-5, IL-4, and IL-13) responsible for eosinophils proliferation, activation, and tissue recruitment. Activated eosinophils induce tissue lesions through different pathways, further enhanced by other cell types, including mast cells (MCs), basophils, T-helper type 1 (Th1) and T-helper type 17 (Th17) T cells, B cells, and humoral mediators (antibodies, cytokines).[4]

IL-5 was first described in mice as a B-cell growth and differentiation factor.[5,6] Subsequently, evidence in humans showed a main effect on eosinophils and to a less lesser extent on basophils.[7] IL-5 is secreted by Th2 cells, namely CD4+ and CD8+ T cells, as well as by ILC2s, B cells, MCs, eosinophils, basophils, and epithelial cells.[3] IL-5 signalling triggers the production of factors, which are essential for eosinophil differentiation and inhibit cell apoptosis. IL-5 exerts its actions via a specific receptor α-subunit (IL-5Rα), with the induction of JAK/STAT, MAPK, and PI-3K pathways, or through an IL-13/GM-CSF shared β-subunit receptor; MAPK pathway activates NF-kB with subsequent eosinophilic/Th2 cytokines production.[8,9] From a clinical point of view, eosinophils and Th2 players are responsible for several pathophysiological mechanisms. The most relevant ones are endothelial cell damage, altered repair processes, and induction of fibrosis. In bronchial asthma, they lead to airways hyperactivity and wall remodelling, which are extremely relevant in poor asthma control and exacerbations.[3]

Mepolizumab and reslizumab are humanized monoclonal antibodies (mAb) targeting circulating IL-5 and thus preventing IL-5 binding to its receptor (Figure 1). Mepolizumab is an IgG1 kappa mAb; reslizumab is a humanized IgG4k mAb with high affinity for IL-5.[2] Benralizumab is an IgG1 kappa mAb targeting the epitope of the α-subunit of the IL-5 receptor (IL-5Rα) on the eosinophils surface and inhibiting IL-5-mediated cell proliferation.[2] Moreover, its afucosylated constant (Fc) oligosaccharides region increases the affinity to the FcγRIIIa

Figure 1. Overview of anti-IL-5 biologics.



BAS, basophils; EOS, eosinophils; IL-5 R, IL-5 receptor; NK, natural killer cells.

receptor on NK cells, basophils, and mast cells and is able to recruit them as part of benralizumab mechanism of action (Figure 1). Through these effector cells, benralizumab is able to induce antibody-dependent cellular cytotoxicity (ADCC) against both eosinophils and basophils, executed by NK cells and/or macrophages.[10] As a consequence, a complete depletion of eosinophils in the bone marrow and blood within 24 hours after the first administration, and an almost complete depletion in sputum and tissues (90% and 96%, respectively)[11] can be observed. In eosinophil-driven diseases such as severe asthma, CD34+ and IL-5Rα positive eosinophil progenitors have been also recognized in tissue and peripheral blood, suggesting the occurrence of extramedullary eosinophilopoiesis.[12]

In the bone marrow, mepolizumab (750 mg IV) significantly reduced mature and late immature eosinophils compared to placebo, whilst the amount of early eosinophil progenitors did not decrease in blood or bone marrow.[12,13] This finding could be explained by the hypothesis that IL-5 mainly contributes to eosinophil proliferation and maturation of relatively late progenitors and does not affect the differentiation of early progenitors.

A low dose of mepolizumab (100 mg SC) seemed insufficient to decrease blood and sputum eosinophil progenitors and sputum mature eosinophils,[14] whilst a weight-adjusted relatively high dose of IV reslizumab attenuated the number of early progenitors in a comparable cohort of patients with prednisone-dependent severe asthma.[15]

So far, only one small cohort of four asthmatic patients treated with a single dose of benralizumab (1 mg/kg IV) documented complete depletion of bone marrow eosinophils and their early progenitors. In addition, blood and sputum eosinophils dramatically decreased under benralizumab treatment.[16] It is possible that the ADCC-related action of benralizumab may account for the different impacts of mepolizumab and benralizumab on the amount of bone marrow eosinophils and late progenitors.[10] However, more evidence is needed to understand the true clinical relevance of the different mechanisms of action.

Safety concerns

Currently, the role of eosinophils is not yet fully understood and their depletion has not been related to any pathology, as a consequence of a primary immunodeficiency or IgG-mediated eosinophil precursor destruction.[17] The absence of characteristic syndromes in eosinophil-deficient mice supports that the potential onset of infections, tumours, autoimmune diseases, or neoplasms is unlikely. Available scientific data suggest that, in healthy subjects, eosinophils do not play a critical homeostatic role. Although long-term studies are needed, the published evidence supports a convincing anti-eosinophils and anti-IL-5 compounds safety profile.

Anti-IL-5 and anti-eosinophils monoclonal antibodies for severe asthma

A significant oral corticosteroids (OCS) sparing effect and clinical improvement under mepolizumab treatment was first described in hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (EGPA).[18] When initially tested on asthmatic patients, the drug was not able to achieve the expected clinical outcomes, in terms of respiratory function parameters (specifically peak expiratory flow [PEF], forced expiratory rate in one second [FEV_1], and bronchial hyper-responsiveness) and exacerbation rate.[19,20] An important bias in the selection of patients accounted for those negative results, namely an improper stratification and recruitment according to blood eosinophil levels and asthma severity. Later on, DREAM, MENSA, and SIRIUS randomized clinical trials (RCTs) demonstrated a significant clinical effect of mepolizumab in asthma control and steroid-sparing effect in subjects with blood eosinophils >300 cells/μL and refractory asthma.[21–23] The MUSCA study also demonstrated an important and significant improvement of the health-related QoL and in the pre-bronchodilator FEV_1 values, which was maintained up to the end of the study time frame (24 weeks).[24]

A *post hoc* analysis of DREAM and MENSA studies confirmed the relevance of baseline blood eosinophil count as a predictive biomarker of clinical efficacy.[25] However, a clinically significant decrease in exacerbation rate has been highlighted also in patients with 150 cells/μL or more at baseline. Those findings should be taken into account when selecting potential candidates to the treatment. An optimal safety and tolerability profile with a stable and long-lasting effect up to 4.5 years was demonstrated by COSMOS extension study and even more by COLUMBA study.[26,27] Interestingly, during the last, a decrease in lung function was noted, possibly due to a natural progression of asthma or to the reduction of OCS dose.

A recent indirect treatment comparison (ITC) based on literature data and Cochrane review showed that in patients with similar levels of blood eosinophilia, mepolizumab was more effective in reducing clinically significant exacerbations and asthma control in comparison with reslizumab and benralizumab.[28] The indirect comparison design itself entails methodological limitations, so it will be important to carry out head-to-head studies to define the real superiority of one of the competitors over the others.

Mepolizumab subcutaneous injection with a dose of 100 mg every 4 weeks is registered as a treatment for severe eosinophilic asthma.[29]

Patients with uncontrolled eosinophilic asthma and blood eosinophil level >400 cells/μL are eligible to reslizumab, which showed a significant improvement of FEV_1 and QoL, reduction of sputum eosinophil count, and reduction of exacerbation rate in RCTs.[30,31]

Data from a *post hoc* analysis of two pivotal RCTs showed higher benefits of reslizumab as add-on therapy in patients with severe asthma, higher blood eosinophilia values and chronic sinusitis with nasal polyposis (CRSwNP). The subjects treated with reslizumab had a reduction of 83% of the annual rate of exacerbations, whilst the overall reduction was 54%.[32]

An open-label extension trial enrolled 1.051 patients treated with intravenous (IV) 3.0 mg/kg reslizumab up to 2 years. This mAb confirmed a good safety profile with a long-term clinical efficacy and improvement of lung function.[33] However, the IV-approved administration could represent a limitation in a real-life setting, due to the need of a venous access and an IV perfusion over 20–50 minutes. In overweight or obese subjects, the weight-adjusted dosage could overcome the practical limitation mentioned previously, as shown in a recent study that compared the response to reslizumab in 10 patients with OCS-dependent asthma previously treated with mepolizumab.[15] Reslizumab showed best outcomes compared to mepolizumab in airway eosinophilia reduction and asthma control. Currently, two phase III RCTs evaluating the efficacy of reslizumab SC (ClinicalTrials.gov identifier: NCT02452190 and NCT02501629) and a phase II–III study on patients with steroid-dependent refractory eosinophilic asthma previously treated with mepolizumab and subsequently treated with IV reslizumab for 4 months (ClinicalTrials.gov identifier: NCT02559791) are ongoing. The efficacy of reslizumab was also confirmed in a 24-week switch study on patients with severe eosinophilic asthma previously treated with omalizumab

without clinical benefits.[34] At the end of the study (week 24), 60% of patients showed a significant improvement of asthma control test (ACT) score and experienced no more exacerbations. Reslizumab had also shown a steroid-sparing effect, with a meaningful decrease of daily dose of OCS, from 72.4% to 52.0% (p=0.019).

Reslizumab intravenous injection with a weight-adjusted concentration of 3 mg/kg is approved for severe eosinophilic asthma.[35]

Phase I and II RCTs including patients with severe eosinophilic asthma and blood eosinophils >300 cells/μL, demonstrated that benralizumab is able to significantly reduce blood eosinophil count, inflammatory biomarkers such as derived neurotoxin (EDN) and eosinophil cationic protein (ECP), and the exacerbation rate.[36–38] A proteomic analysis on benralizumab impact showed a significant decrease in the expression of genes associated with eosinophils and basophils proliferation, such as CLC, IL-5Rα, and PRSS33; immune-signalling complex genes (FCER1A); G-protein-coupled receptor genes (HRH4, ADORA3, P2RY14); and further immune-related genes (ALOX15 and OLIG2). This modulatory effect of gene expression was higher for patients with greater blood eosinophilia levels.[39]

Of note, benralizumab is insensitive to circulating IL-5 levels, which can increase during asthma exacerbations (this sensitivity limits the effectiveness of the two other anti-IL-5 agents).[40] Through the intense depletion of eosinophils, benralizumab is also insensitive to the effect of IL-3 and GM-CSF, making the response to this drug even more impactful.[41] All these peculiarities allowed for interesting results in improvement of exacerbation rate and steroid-sparing effect. A potential advantage of benralizumab treatment in clinical practice is represented by its schedule – it is administered in a prefilled syringe every 4 weeks for the first three doses and subsequently every 8 weeks, which is a longer interval than the monthly schedule of competitors.[28]

The ZONDA trial substudy highlighted a greater tissue depletion of eosinophils due to benralizumab compared to mepolizumab and reslizumab.[42] Furthermore, the ADCC mechanism could overcome the possibility of immune complex formation between IL-5 and mepolizumab or reslizumab, which may provide a type of IL-5 reservoir leading to an incomplete response to treatments, as reported by some studies.[43] Benralizumab demonstrated a sustained higher improvement in FEV_1, as showed by the SIROCCO and CALIMA RCTs *post hoc* analysis, even in overweight or obese patients with fixed airflow obstruction (FAO).[44] In two very recent case reports, benralizumab was effective in patients previously treated with omalizumab and mepolizumab without clinical response.[45,46]

A 56-week extension study was recently published on patients initially enrolled in the SIROCCO or CALIMA studies. It mainly focused on the potential consequences of eosinophils depletion. No adverse events, including opportunistic infections, were recorded confirming the safety of the drug.[47] Table 1 summarizes the main features of anti-IL-5 drugs for severe asthma.

In a recent systematic review, Bourdin and colleagues performed a matching-adjusted indirect comparison (MAIC) between benralizumab, mepolizumab, and reslizumab.[48] Benralizumab and mepolizumab reduced the overall exacerbation rate by 52% and 49%, respectively, in comparison

Table 1. Anti-IL-5 at-a-glance comparison.

Compound		Administration route	Dosage	Ideal patients	Main strengths
Benralizumab	**IgG1k mAb against IL-5Rα subunit**	Subcutaneous	Every 4 weeks for the first three doses, then every 8 weeks	Eosinophilic asthma ≥300 cells/μL, CSwNP, late-onset asthma	High affinity for IL-5 receptor and ADCC activity, eosinophils sustained tissue depletion, improvement of pulmonary function even in patients with FAO
Mepolizumab	**IgG1k mAb anti-IL-5**	Subcutaneous	100 mg every 4 weeks	Eosinophilic asthma ≥300 cells/μL, CSwNP, late-onset asthma	Excellent safety profile, demonstrated clinical efficacy and steroid sparing effect
Reslizumab	**IgG4k mAb anti-IL-5**	Intravenous	3 mg kg^{-1} every 4 weeks	Eosinophilic asthma ≥400 cells/μL, CSwNP	Personalized dosage, clinical efficacy, improvement of pulmonary function

ADCC, antibody-dependent cell cytotoxicity; CSwNP, chronic sinusitis with nasal polyposis; FAO, fixed airway obstruction; IL-5Rα, interleukin-5 receptor α-subunit.

with placebo (rate ratio [RR] 0.94, 95% CI: 0.78–1.13, n=1524) and decreased the percentage of clinically significant and severe exacerbations both of 52% (RR 1.00, 95% CI: 0.57–1.75; n=1524). In addition, the pre-bronchodilator FEV_1 improvement was similar. A comparison between benralizumab and reslizumab has not been carried out because the patient characteristics were too different to obtain a reliable estimate. However, a similar effectiveness of benralizumab and reslizumab through the indirect analysis was detected. As previously mentioned, the study design itself weakens the reported results, to be verified by direct comparison studies. The subcutaneous administration of Benralizumab is approved for the treatment of patients with severe eosinophilic asthma and aged 12 years or older.

The biologic drugs revolution: the steroid-sparing effect

Since the advent of biological therapies, researchers and clinicians have tried to define to what extent these drugs reduce the need for OCS in patients with severe refractory asthma.

In a recent study by Bleecker and colleagues,[49] the OCS dose was the most important predictive marker of benralizumab efficacy in reduction of exacerbations and FEV_1 improvement, especially for the blood eosinophil threshold of >300 cells/μL. Other predictors of positive response to benralizumab are represented by frequent asthma exacerbations, nasal polyposis and forced vital capacity (FVC) <65% predicted.

Of note, the OCS-sparing effect was not similar for all the anti-IL-5 drugs. In the ZONDA study,[42] benralizumab significantly reduced the median OCS dose from baseline by 75%. In particular, patients with blood eosinophils >150 cells/μL were on prednisone maintenance treatment for at least 6 months; then, they started a period of OCS optimization for up to 6 weeks including an induction phase, a dose-reduction phase and a dose-maintenance phase. The primary endpoint was the overall OCS dose reduction from randomization to maintenance period (weeks 24–28), and the 100% reduction of OCS in patients with optimized OCS dose of 12.5 mg prednisone or equivalents was included amongst the secondary endpoints. In the SIRIUS study (mepolizumab),[14] eligible patients had at least a 6-month history of prednisone treatment and eosinophils counts of >150 cells/μL before enrolment (or 300 cells/μL in the previous 12 months). Subsequently, patients followed a period of OCS optimization treatment. After the start of mepolizumab therapy, the reduction phase took place. The primary endpoint of the study was the overall reduction of OCS from randomization to maintenance period (weeks 20–24). A comparison between benralizumab and mepolizumab showed that the benefit in OCS reduction seems to be similar (about 50%), whilst the number of patients able to discontinue OCS therapy was higher for benralizumab compared to mepolizumab (52% and 14%, respectively; the number needed to treat (NNT) was 3 for benralizumab and 17 for mepolizumab).

The greater OCS-sparing effect of benralizumab represents a real advantage in the treatment of eosinophilic severe refractory asthma, as highlighted by the indirect comparison between prednisone-reduction studies (ZONDA-SIRIUS).[42,23] Although head-to-head studies are needed to confirm the described trend, the mentioned result could help the clinician in identifying the more proper treatment amongst the different available options in this field.

Targeting eosinophils besides severe asthma: the current evidence

Table 2 summarizes the available evidence about the use of anti-IL-5 and anti-eosinophil monoclonal antibodies as a treatment option for hypereosinophilic conditions other than asthma.

Eosinophilic granulomatosis with polyangitis

Eosinophilic granulomatosis with polyangiitis is a primary small vessel vasculitis characterized by asthma, eosinophilia, multiorgan involvement (lung, peripheral nerves, heart, gastrointestinal tract, skin), and the possible presence (<30% of patients) of anti-neutrophil cytoplasmic antibodies (ANCAs).[1] Corticosteroids alone represent the traditional therapeutic option in the absence of negative prognostic factors, whilst cyclophosphamide is recommended for severe or corticosteroid-resistant cases. The conventional immunosuppressant options also include methotrexate, azathioprine, and mycophenolate. Intravenous immunoglobulins, IFN-α, infliximab, and rituximab have been also used, mainly to target ANCA-associated pathophysiologic background, and to a less extent blood and tissue eosinophilia. Few data are available concerning omalizumab.[50]

The supposed key role of eosinophils, and the elevated IL-5 levels in the inflammatory EGPA background supported the rationale for including anti-IL-5 agents amongst the treatment options. Kahn and colleagues reported the first case documenting the successful use of mepolizumab (750 mg IV) in a patient with refractory EGPA,[51] and experiencing improvement in peak flow, decrease blood eosinophils count, withdrawal of inhaled treatments during anti-IL-5 treatment. Before the second infusion, complete regression of parenchymal findings was documented at chest-computed tomography, which persisted after 6 months. Other small open-label pilot studies investigated the effect of mepolizumab in EGPA patients.[52–54] In particular, Moosig and colleagues conducted a phase II open-label study, involving 10 patients with relapsing/refractory EGPA, who received 9 monthly

Table 2. Summary of published evidence about anti IL-5 drugs for eosinophilic diseases other than asthma.

Disease	Drug	Reference	Drug schedule	Study design	Population (no. of subjects)	Study duration	Outcomes overview
EGPA	Mepolizumab	Wechsler (55)	300 mg SC Q4W	DBPC parallel group phase III trial	136	52 weeks	Weeks of remission; time to first relapse; steroid sparing effect
		Moosig (53)	750 mg IV Q4W	Phase II trial	10	9 months	Weeks of remission; time to first relapse; steroid sparing effect
		Kahn (51)	750 mg IV Q4W	Case report	1	28 months	Asthma control; blood eosinophilia; radiological assessment
		Kim (54)	750 mg IV Q4W	Open-label study	7	40 weeks	Steroid sparing effect
Nasal Polyposis	Mepolizumab	Gevaert (70)	750 mg IV or placebo Q4W	RCT	20 active; 10 placebo	48 weeks	Clinical and CT score
		Bachert (72)	750 mg IV or placebo Q4W	DBPCT	54 active;51 placebo	25 weeks	Need for surgery, endoscopic score, VAS symptoms score, patient-reported outcomes
	Reslizumab	Weinstein SF (32)	3 mg/kg IV	***Post hoc* analysis**	953	52 weeks	No significant effect
		Gevaert (71)	n=8 at 3 mg/kg; n=8 at 1 mg/kg	RCT	24	36 weeks	Clinical and CT score
HES	Mepolizumab	Garrett (75)	10 mg/kg or 750 mg IV Q4W	Open-label study	4	28 weeks	Symptoms; patient reported outcomes; lung function; blood eosinophils
		Rothenberg (76)	750 mg IV Q4W	DBPC parallel group Trial	85	36 weeks	Steroid sparing effect
EoE	Mepolizumab	Stein (80)	750 mg IV Q4W	Open-label phase I/ II safety and efficacy study	4	3 months	Esophageal eosinophilia; patient-reported outcomes
		Straumann (81)	750 mg IV 2 doses, 1 week apart. Non responders --> after 8 weeks 2 further doses 4 weeks apart	DBPCT	11	9 weeks	Esophageal eosinophilia; molecular biomarkers; limited clinical improvement
		Assa'ad (82)	0.55, 2.5, or 10 mg/kg mepolizumab IV Q4W	DBPCT	59	3 months	Esophageal eosinophilia; limited clinical improvement

	Reslizumab	Markowitz JE (84)	1 or 2 or 3 mg/kg IV Q4W	RCT+open-label extension+ compassionate use	226; 8; 4	3–9 years	Patient-reported outcomes; endoscopic assessment; esophageal eosinophilia
		Spergel (83)	1 or 2 or 3 mg/kg IV Q4W	RCT+open-label extension	226	4 weeks	Esophageal eosinophilia; limited clinical improvement
ABPA	Mepolizumab after Omalizumab (switch)	Hirota S (58)	100 SC mg Q4W	Case report	1	56 weeks	Asthma control; blood eosinophils; radiological assessment; no improvement of lung function
	Mepolizumab+ Omalizumab	Altman (59)	Omalizumab 375 mg SC Q2W+Mepolizumab 100 mg SC Q4W	Case report	1	7 months	Symptoms; no improvement of lung function
	Mepolizumab	Terashima (61)	100 mg SC Q4W	Case report	1	4 weeks	Symptoms, lung function, radiological assessment
		Oda (60)	100 mg SC Q4W	Case report	1	9 months	Symptoms, lung function, radiological assessment
		Soeda S (62)	100 mg SC Q4W	Case series	2	24; 21 months	Blood eosinophili, symptoms, lung function, radiological assessment
	Benralizumab	Soeda S (63)	30 mg SC Q4Wx3 --> Q8W	Case report	1	2 months	Radiological assessment, eosinophilia, IgE levels, symptoms (cough, sputum)
CEP	Mepolizumab	To M (65)	100 mg SC Q4W	Case report	1	3 months	Symptoms, blood eosinophilia, radiological assessment

ABPA, allergic bronchopulmonary aspergillosis; CEP, chronic eosinophilic pneumonia; DBPC, double-blind, placebo-controlled; DBPCT, double-blind, placebo-controlled trial; EGPA, eosinophilic granulomatosis with polyangitis; EoE, eosinophilic esophagitis; HES, hypereosinophilic syndrome; IgE, immunoglobulin E; RCT, randomised control trial; VAS, visual analogue scale.

infusions of mepolizumab (750 mg IV), after stopping previous immunosuppressant therapy, and were subsequently switched to methotrexate maintenance therapy (0.3 mg/kg/week SC) and a tapered dosage of glucocorticoids. This study showed disease remission and glucocorticoid daily dose reduction to the lowest dose over the course of the disease in almost all patients, with no relapses during the active 9-month treatment phase. These findings suggested a steroid-sparing effect and the potential for induction and maintenance of remission in the absence of further conventional immunosuppressive treatments.

Recently, the first large-scale multinational RCT on relapsing/refractory EGPA[55] proved the efficacy of anti-IL-5 mAb and paved the way to the approval of mepolizumab for this condition by the United States Food and Drug Administration. Mepolizumab was administered subcutaneously (300 mg) every 4 weeks or placebo (68/group) for 1 year, in addition to the standard of care treatment. Over a 52 weeks period, 28% of patients in the treated group *versus* 3% in the placebo group experienced at least 42 weeks of remission (OR 5.91, 95% CI: 2.68–13.03; $p<0.001$), and the percentage of participants in remission both at week 36 and week 48 were significantly higher in the active group (32 *versus* 3%; OR 16.74; 95% CI: 3.61–77.56). Remission was less likely for patients with baseline eosinophil counts <150 cells/mm^3. Moreover, as a secondary endpoint, mepolizumab was able to provide a longer time to first relapse within 52 weeks, the reduction of daily glucocorticoid dose, a lower circulating eosinophil counts, an improved Asthma Control Questionnaire and rhinosinusitis 22-item Sino nasal Outcome Test score. Conversely, lung function did not increase – differently from previous studies on severe eosinophilic asthma.[2] The most common adverse events (AEs) were headache, nasopharyngitis, arthralgia, sinusitis, and upper respiratory tract infection. These AEs and their frequency were similar in the placebo group. Overall, mepolizumab was effective in nearly the 50% of the participants. The reason why mepolizumab was ineffective in almost 50% of the patients remains unexplained, and further characterization of specific EGPA phenotypes, e.g. ANCA-negative *versus* ANCA-positive patients needs to be investigated.[50] In fact, a recent genome-wide association study has confirmed that different genes may underlie the complex and diverse potential expressions of EGPA in symptoms and clinical subsets.[56] With this perspective, the investigation of the genetic background may increase in accuracy the treatment selection process.

Phase II trials including reslizumab (NCT02947945) and benralizumab (NCT03010436) for EGPA are currently ongoing.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is the result of a complex hypersensitivity reaction to *Aspergillus fumigatus* (*A. fumigatus*), characterized by asthmatic symptoms, systemic and airway eosinophilia, elevated serum immunoglobulin E (IgE) levels, lung infiltration, bronchiectasis, bronchial mucoid impaction, and lung fibrosis. The current treatment includes the long-term use of oral corticosteroids, in addition to antifungal agents, which is potentially associated with serious side effects.[57] Some evidence supports the potential efficacy of omalizumab due to its IgE-blocking activity.[58] Although the pathophysiology of this condition is not fully understood, a pivotal role is played by an impaired innate and adaptive immune response, which is not able to clear inhaled fungal spores from their respiratory epithelium and sustains an intense Th2 inflammation. Innate immunity response to *A. fumigatus* in the lung recruits and activates Th2 cells, leading to IL-4 and IL-5 production, and driving the differentiation of IgE-secreting plasma cells, as well as recruitment and activation of eosinophils. These mechanisms suggest that both IgE and IL5 may represent potential treatment targets in patients affected by ABPA. As clinical trials on mepolizumab excluded ABPA patients, the efficacy of mepolizumab in ABPA remains basically unknown. To the best of our knowledge, four case reports of ABPA treated with mepolizumab have been reported in the literature. In 2018,[59] a case report was published of a patient with ABPA previously treated with omalizumab (600 mg Q2W) with poor response (no improvements on radiological findings and eosinophilic sinusitis/otitis media). The patient was switched to mepolizumab (100 mg SC Q4W) with subsequent resolution of asthmatic symptoms, normalization of blood eosinophils and serum IgE value, improvement of radiological findings. No improvement of FEV_1 was observed.

Another case report described the synergistic and steroid sparing effect of omalizumab plus mepolizumab combination therapy in a patient showing poor disease control when treated with omalizumab only.[60]

In two further cases,[61,62] mepolizumab use in addition to standard therapy, resulted in symptoms and FEV_1 improvement, and in the reduction of ABPA-associated mucoid impaction and lung infiltration. The role of IL-5-induced inflammation in the pathogenesis and maintenance of symptoms in patients with ABPA seems predominant in most cases, independently of IgE levels, especially in patients with corticosteroid-dependent severe asthma, with suppressed serum IgE levels.[58]

Recently, Soeda and colleagues[63] reported a case series including two patients with uncontrolled severe asthma and ABPA on long-term treatment with mepolizumab (100 mg SC). Blood eosinophilia reduction, symptoms (cough and sputum) improvement, FEV_1 increase, and radiological findings resolution were observed. ACT score significantly increased in one case only. The same author in 2018 reported the case of a patient affected by ABPA-serologic (ABPA-s), without bronchiectasis and/or fibrosis, treated with benralizumab.[64] The drug was well tolerated and rapidly (over 2 months) provided symptoms improvement and radiological remission.

Chronic eosinophilic pneumonia

Chronic eosinophilic pneumonia (CEP) is an inflammatory disease of unknown aetiology characterized by eosinophilic

infiltration in the lung. The typical symptoms include cough and increasing dyspnea.[65] For the treatment of CEP, systemic corticosteroid therapy is recommended, and the clinical response to corticosteroids is usually very good. However, approximately 50% of patients with CEP relapse after cessation of steroids treatment or during tapering.[65] Only one case of CEP successfully treated with mepolizumab has been reported.[66]

Chronic rhinosinusitis with nasal polyposis

Chronic rhinosinusitis (CRS) is a clinical syndrome with multiple phenotypes. The presence of polyps is usually associated with local Th2 inflammation, increased eosinophils levels, and elevated IL-5 and IgE.[67] Non-eosinophilic inflammation sustained by Th1 and Th17 pathways may also be observed in CRSwNP.[68] CRSwNP is often part of a late-onset eosinophilic asthma, representing a most relevant comorbidity.

Current treatment options for patients with NP, based on the 2016 International Consensus Statement on Allergy and Rhinology, include nasal saline irrigations and intranasal corticosteroid sprays for maintenance therapy and systemic corticosteroids with antibiotics for acute exacerbations. For refractory cases, endoscopic sinus surgery should be considered.[69,70] The underlying eosinophilic inflammation provided the rationale for investigating the effect of new therapeutic approaches aimed at blocking IL-5 in CRSwNP.

Gevaert and colleagues conducted two randomized, double-blind, placebo-controlled trial studies[71,72] on the safety and efficacy of mepolizumab and reslizumab in patients with CRSwNP refractory to endoscopic surgery. A statistically significant improvement in nasal symptoms and nasal polyp score (NPS) was recorded in both studies, whilst only mepolizumab treatment positively impacted on CT score. In the mepolizumab study, when divided into allergic (n=7) and non-allergic (n=8) responders, CT score significantly decreased in the allergic group, but the validated Asthma Quality of Life Questionnaire (AQLQ) decreased significantly in the non-allergic group. As expected, individuals with high serum IL-5 levels had more benefit from blocking IL-5.

The effects of two different reslizumab regimens, 1 mg/kg and 3 mg/kg, were also investigated.[71] Amongst the eight patients receiving a 1 mg/kg infusion, five subjects experienced a significant improvement in Total Nasal Polyp Score (TPS) for up to 12 weeks. Half of the patients who received a 3 mg/kg infusion maintained a reduction in TPS for 4 weeks. Elevated local nasal IL-5 levels at baseline *versus* systemic levels were predictive of a positive response to reslizumab.

Mepolizumab efficacy in NP refractory to surgery was more recently explored in a larger randomized clinical trial.[73] This involved 105 patients of whom 54 were treated with mepolizumab (monthly infusion 750 mg IV) and 51 were randomly assigned to the placebo group for a total of six doses in addition to daily topical corticosteroids. Nasal symptoms and NPS significantly improved, and a reduced need for surgery was reported at the end of the 25 weeks period. Of note, there was no reactive eosinophilia, which has been observed with reslizumab.

Oda and colleagues[74] reported the case of a patient with ABPA and CRSwNP treated with mepolizumab at the dose of 100 mg Q4W without significant benefit on the nasal component, despite reductions in eosinophilia. This finding suggests that the high-dose approach used by Gevaert and colleagues is needed to properly target the amount of eosinophils underlying the nasal polyps inflammation.

A phase II (ClinicalTrials.gov Identifier: NCT03450083) and a phase III (ClinicalTrials.gov Identifier: NCT03627286) randomized, placebo-controlled trials are currently ongoing to evaluate the efficacy of benralizumab on eosinophilic rhinosinusitis.

Hypereosinophilic syndrome

Hypereosinophilic syndrome (HES) includes different disorders characterized by a large amount of eosinophils in the blood and/or tissues. Idiopathic hypereosinophilic syndrome (IHES) is characterized by elevated levels of blood eosinophils (>1500 eosinophils/μL) and by the involvement of multiple organs as well as tissue-specific disorders such as eosinophilic esophagitis (EoE).[75]

So far, two preliminary studies investigated the effect of mepolizumab in patients affected by both IHES and EoE. The former[76] evaluated three monthly infusions of mepolizumab (10 mg/kg or 750 mg IV) in four patients with HES and reported a significant improvement in symptoms and QoL in all patients. A FEV_1 increase and blood eosinophil count decrease were also observed at the 8 weeks follow-up assessment.

The latter study was a multicentre, randomized, double-blind, placebo-controlled trial carried out on 85 patients treated monthly with 750 mg IV of mepolizumab for up to 36 weeks.[77] It described a reduction of prednisone dose to ≤10 mg without clinical flare-up in 84% of active group *versus* 43% placebo ($p<0.0001$), showing a potential glucocorticoid-sparing effect of this biologic treatment.

Eosinophilic esophagitis

A predominant infiltration of eosinophils in the oesophageal tract underlies EoE, a chronic immune-mediated disease presenting with peculiar endoscopic and histologic abnormalities. Several eosinophil-derived products cause barrier dysfunction, which leads to nonspecific gastrointestinal symptoms.[78]

The 2017 European guidelines indicate as first-line treatment proton pump inhibitors (PPIs). Other options include topical corticosteroids, elimination or restriction diet, and oesophageal

dilation, the last related to long-term safety concerns and potential complications.[79,80]

An open-label phase I/II study involving four adult patients over 28 weeks[81] firstly investigated mepolizumab for EoE at the dose of 750 mg intravenously monthly. The main observations were a significant decrease in mean and maximal oesophageal eosinophilia ($p<0.001$, $p<0.05$, respectively), better clinical control and improved quality of life ($p=0.03$) with respect to the baseline values. Of note, responsiveness to anti-IL-5 therapy did not correlate with plasma IL-5 levels.

More recently, the efficacy of a different mepolizumab schedule (750 mg IV, 2 doses 1 week apart, repeated after 8 weeks with 4 weeks interval between each dose if complete remission was not achieved – <5 peak eosinophil number/hpf) was explored in a randomized, double-blind, placebo-controlled trial including 11 patients.[82] A significant reduction of tissue eosinophilia and of the expression of molecules associated with oesophageal remodelling (TGF-β) was observed 4 weeks after the first mepolizumab administration, without further improvement compared with the placebo group. Nevertheless, a minimal clinical improvement was achieved. No safety issues were recorded.

A larger multicentre, randomized, placebo-controlled trial[83] carried out on 59 children (2–17 years old) investigated the impact of three monthly infusions of mepolizumab (0.55, 2.5, or 10 mg/kg) or placebo, and reported negligible improvement in symptoms, remission (only less than 10% of subjects), and reduction of tissue eosinophil count <20 hpf (only 31.6% of subjects) compared with the placebo group.

Reslizumab has also been evaluated as a treatment option for EoE. Spergel and colleagues[84] conducted a multicentre RCT including 226 subjects randomly assigned to 1, 2, or 3 mg/kg of reslizumab. No significant differences in physician s' global assessment scores were recorded between the active and placebo groups, independently of the treatment dose and oesophageal eosinophil counts. A recent open-label 9-year-long study was conducted by Markowitz and colleagues[85] as an extended-access program of RCT mentioned previously. It explored treatment at the dose of 2 mg/kg in 12 children and adolescents. The authors reported a significant decrease in reduction in peak oesophageal eosinophilic count in treated patients compared to control groups (67 *versus* 24% had a reduction in peak oesophageal eosinophilic counts to <5 hpf). Nevertheless, no difference in symptoms between reslizumab and control groups was seen. However, the positive impact on tissue eosinophilia and on relapse or disease progression documented by endoscopy under therapy, as well as an optimal safety profile, paves the way to larger longitudinal studies.

Conclusions

Recent basic and pharmacological research has specifically addressed the Th2 high inflammation phenotype, leading to the development of new biologic drugs, especially in the field of severe eosinophilic asthma. Eosinophilic inflammation represents the common pathophysiological background of several conditions, providing the rationale for the use of the same therapeutic molecules beyond asthma. However, non-negligible differences between asthma and other eosinophilic diseases occur, particularly regarding eosinophils homing (blood and/or tissues), target organs and thus clinical expression. Furthermore, despite the increasing knowledge and evidence in the field, some issues are still under debate.

The correlation between tissue and blood eosinophilia, as well as their specific clinical relevance, is not completely clear. In addition, the observed discrepancy between known Th2 biomarkers and clinical response under biologic treatment suggests that the underlying inflammatory pathways may be much more complex than expected and targeting one mechanism may not be enough. This variability probably accounts for the different response to the same drug in different clinical conditions and highlights the need for tailoring the therapeutic approach by modulating the drug dose and/or a multiple-treatments association.

Few data are currently available about the long-term management of anti-IL-5 drugs in treatment duration, tapering, or withdrawal. In fact, whether biologics exert a disease-modifying effect or their action is limited to the ongoing treatment is still controversial.[2,3]

The clinical relevance of anti-IL-5 tapering has been investigated in a small study comparing the effect of the fixed dose of mepolizumab and the weight-adjusted dose of reslizumab.[86] The reported results suggest the superiority of the latter particularly in the prednisone-dependent asthma phenotype with elevated sputum eosinophilia. The available evidence is not sufficient to support practical recommendations; however, dose adjustment may represent a strategy for management of poor responders. Of note, the approved mepolizumab dose for patients with eosinophilic granulomatosis is 300 mg every 4 weeks.[55] It supports the hypothesis that an adjusted mepolizumab dose could be considered in difficult-to-treat patients with a more severe eosinophilic asthma phenotype or with specific comorbidities.

Conversely, especially in the field of severe asthma, the need for biologic therapy continuation should be carefully evaluated in light of the overall adherence to anti-asthmatic treatments, which is known to be suboptimal.[87,88] Biologic drugs are currently intended as add-on options; thus, once disease control has been achieved and oral corticosteroids are no longer needed, if poor adherence to inhaled medications occurs the biologic drug should be withdrawn for clinical and sustainability reasons.

However, the optimal safety and tolerability profile of anti-IL-5 drugs needs to be established in further and larger experimental and real-life investigations, which are needed especially in the field of non-asthma eosinophilic diseases.

Contributions: MC and GS conceived the manuscript outline, contributed to all the sections and revised the whole manuscript. FM drafted the paragraphs concerning severe asthma. LG drafted the paragraphs concerning eosinophilic diseases. All the authors read and approved the final version. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2019/07/dic.212587-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/targeting-eosinophils:-severe-asthma-and-beyond

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Provenance: invited; externally peer reviewed.

Submitted: 18 March 2019; **Peer review comments to author:** 17 May 2019; **Revised manuscript received:** 30 May 2019; **Accepted:** 3 June 2019; **Publication date:** 23 July 2019.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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References

1. Ramirez GA, Yacoub MR, Ripa M, et al. Eosinophils from physiology to disease: a comprehensive review. *Biomed Res Int.* 2018;28:9095275. http://dx.doi.org/10.1155/2018/9095275
2. Menzella F, Bertolini F, Biava M, Galeone C, Scelfo C, Caminati M. Severe refractory asthma: current treatment options and ongoing research. *Drugs Context.* 2018;7:212561. http://dx.doi.org/10.7573/dic.212561
3. Caminati M, Pham DL, Bagnasco D, Canonica GW. Type 2 immunity in asthma. *World Allergy Organ J.* 2018;11:13. http://dx.doi.org/10.1186/s40413-018-0192-5
4. Morita H, Moro K, Koyasu S. Innate lymphoid cells in allergic and nonallergic inflammation. *J Allergy Clin Immunol.* 2016;138(5):1253–1264. http://dx.doi.org/10.1016/j.jaci.2016.09.011
5. McKenzie DT, Filutowicz HI, Swain SL, Dutton RW. Purification and partial sequence analysis of murine B cell growth factor II (interleukin 5). *J Immunol.* 1987;139(8):2661–2668.
6. Baumann MA, Paul CC. Interleukin-5 and human B lymphocytes. *Methods.* 1997;11(1):88–97. http://dx.doi.org/10.1006/meth.1996.0392
7. Denburg JA, Silver JE, Abrams JS. Interleukin-5 is a human basophilopoietin: induction of histamine content and basophilic differentiation of HL-60 cells and of peripheral blood basophil-eosinophil progenitors. *Blood.* 1991;77(7):1462–1468.
8. Milburn MV, Hassell AM, Lambert MH, et al. A novel dimer configuration revealed by the crystal structure at 2.4 A resolution of human interleukin-5. *Nature.* 1993;363(6425):172–176. http://dx.doi.org/10.1038/363172a0
9. Rossjohn J, McKinstry WJ, Woodcock JM, et al. Structure of the activation domain of the GM-CSF/IL-3/IL-5 receptor common beta-chain bound to an antagonist. *Blood.* 2000;95(8):2491–2498.
10. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol.* 2010;125(6):1344–1353.e2. http://dx.doi.org/10.1016/j.jaci.2010.04.004
11. Ghazi A, Trikha A, Calhoun WJ. Benralizumab--a humanized mAb to IL-5Ralpha with enhanced antibody-dependent cell-mediated cytotoxicity--a novel approach for the treatment of asthma. *Expert Opin Biol Ther.* 2012;12(1):113–118. http://dx.doi.org/10.1517/14712598.2012.642359
12. Gauvreau GM, Denburg JA. Hemopoietic progenitors: the role of eosinophil/basophil progenitors in allergic airway inflammation. *Expert Rev Clin Immunol.* 2005;1(1):87–101. http://dx.doi.org/10.1586/1744666X.1.1.87

13. Menzies-Gow A, Flood-Page P, Sehmi R, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol.* 2003;111(4):714–719.
14. Sehmi R, Smith SG, Kjarsgaard M, et al. Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. *Clin Exp Allergy.* 2016;46(6):793–802. http://dx.doi.org/10.1111/cea.12695
15. Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous Mepolizumab. *Am J Respir Crit Care Med.* 2018;197(1):38–46. http://dx.doi.org/10.1164/rccm.201707-1323OC
16. Sehmi R, Lim HF, Mukherjee M, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. *J Allergy Clin Immunol.* 2018;141(4):1529–1532.e8. http://dx.doi.org/10.1016/j.jaci.2018.01.008
17. Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. *Allergy.* 2013;68(7):829–835. http://dx.doi.org/10.1111/all.12169
18. Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. *J Allergy Clin Immunol Pract.* 2015;3(2):167–174. http://dx.doi.org/10.1016/j.jaip.2015.01.013
19. 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.
20. 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. http://dx.doi.org/10.1172/JCI17974
21. 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. http://dx.doi.org/10.1056/NEJMoa1403290
22. 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. http://dx.doi.org/10.1016/S0140-6736(12)60988-X
23. 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. http://dx.doi.org/10.1056/NEJMoa1403291
24. 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. http://dx.doi.org/10.1016/S2213-2600(17)30125-X
25. 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. http://dx.doi.org/10.1016/S2213-2600(16)30031-5
26. Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther.* 2016;38(9):2058–2070.e1. http://dx.doi.org/10.1016/j.clinthera.2016.07.010
27. 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.e7. http://dx.doi.org/10.1016/j.jaci.2018.09.033
28. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison. *J Allergy Clin Immunol.* 2019;143(1):190–200.e20. http://dx.doi.org/10.1016/j.jaci.2018.08.031
29. European Medicines Agency - European Public Assessment Report (EPAR) for Nucala (mepolizumab). https://www.ema.europa.eu/en/medicines/human/EPAR/nucala. Accessed March, 2019.
30. 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. http://dx.doi.org/10.1164/rccm.201103-0396OC
31. Castro M, Zangrilli J, Wechsler ME, et al. 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. http://dx.doi.org/10.1016/S2213-2600(15)00042-9
32. Weinstein SF, Katial RK, Bardin P, et al. Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps. *J Allergy Clin Immunol Pract.* 2019;7(2):589-596. http://dx.doi.org/10.1016/j.jaip.2018.08.021
33. 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.e3. http://dx.doi.org/10.1016/j.jaip.2017.08.024
34. Perez de Llano LA, Cosio BG, Domingo C, et al. Efficacy and safety of reslizumab in patients with severe asthma with inadequate response to omalizumab: a multicenter, open-label pilot study. *J Allergy Clin Immunol Pract.* 2019; pii: S2213-2198(19)30069-8. http://dx.doi.org/10.1016/j.jaip.2019.01.017

35. European Medicines Agency - European Public Assessment Report (EPAR) for Nucala (mepolizumab). https://www.ema.europa.eu/en/medicines/human/EPAR/nucala. Accessed March, 2019.
36. 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. http://dx.doi.org/10.1016/S2213-2600(14)70201-2
37. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha 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. http://dx.doi.org/10.1016/S0140-6736(16)31322-8
38. 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 beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115–2127. http://dx.doi.org/10.1016/S0140-6736(16)31324-1
39. Sridhar S, Liu H, Pham TH, Damera G, Newbold P. Modulation of blood inflammatory markers by benralizumab in patients with eosinophilic airway diseases. *Respir Res.* 2019;20(1):14. http://dx.doi.org/10.1186/s12931-018-0968-8
40. Tai PC, Sun L, Spry CJ. Effects of IL-5, granulocyte/macrophage colony-stimulating factor (GM-CSF) and IL-3 on the survival of human blood eosinophils in vitro. *Clin Exp Immunol.* 1991;85(2):312–316.
41. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol.* 2013;132(5):1086–1096.e5. http://dx.doi.org/10.1016/j.jaci.2013.05.020
42. 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. http://dx.doi.org/10.1056/NEJMoa1703501
43. Egan RW, Athwal D, Bodmer MW, et al. Effect of Sch 55700, a humanized monoclonal antibody to human interleukin-5, on eosinophilic responses and bronchial hyperreactivity. *Arzneimittelforschung.* 1999;49(9):779–790. http://dx.doi.org/10.1055/s-0031-1300502
44. Chipps BE, Hirsch I, Trudo F, et al. Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction. *Am J Respir Crit Care Med.* 2018;197:A2489.
45. Kurosawa M, Sutoh E. Severe uncontrolled eosinophilic asthma, which responded to benralizumab after failure to respond to mepolizumab. *Ann Allergy Asthma Immunol.* 2019;122(4):431–433. http://dx.doi.org/10.1016/j.anai.2018.12.014
46. Minami D, Kayatani H, Sato K, Fujiwara K, Shibayama T. Effectiveness of benralizumab for allergic and eosinophilic predominant asthma following negative initial results with omalizumab. *Respirol Case Rep.* 2018;7(1):e00388. http://dx.doi.org/10.1002/rcr2.388
47. 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. http://dx.doi.org/10.1016/S2213-2600(18)30406-5
48. Bourdin A, Husereau D, Molinari N, et al. Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. *Eur Respir J.* 2018;52(5):1801393. http://dx.doi.org/10.1183/13993003.01393-2018
49. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J.* 2018;52(4):1800936. http://dx.doi.org/10.1183/13993003.00936-2018
50. Raffray L, Guillevin L. Treatment of eosinophilic granulomatosis with polyangiitis: a review. *Drugs.* 2018;78(8):809–821. http://dx.doi.org/10.1007/s40265-018-0920-8
51. Kahn JE, Grandpeix-Guyodo C, Marroun I, et al. Sustained response to mepolizumab in refractory Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010;125(1):267-70. http://dx.doi.org/10.1016/j.jaci.2009.10.014
52. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome. *Clin Exp Rheumatol.* 2012;30(1 Suppl 70):S62–S65.
53. Moosig F, Gross WL, Herrmann K, Bremer JP, Hellmich B. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. *Ann Intern Med.* 2011;155(5):341–343. http://dx.doi.org/10.7326/0003-4819-155-5-201109060-00026
54. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010;125(6):1336–1343. http://dx.doi.org/10.1016/j.jaci.2010.03.028
55. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med.* 2017;376(20):1921–1932. http://dx.doi.org/10.1056/NEJMoa1702079
56. Lyons PA, Peters JE, Federico A, et al. Genetically distinct clinical subsets, and associations with asthma and eosinophil abundance, within Eosinophilic Granulomatosis with Polyangiitis. *bioRxiv.* 2018;8:1–41. http://dx.doi.org/10.1101/491837
57. Alastruey-Izquierdo A, Cadranel J, Flick H, et al. Treatment of chronic pulmonary aspergillosis: current standards and future perspectives. *Respiration.* 2018;96(2):159–170. http://dx.doi.org/10.1159/000489474
58. Li JX, Fan LC, Li MH, Cao WJ, Xu JF. Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: a synthesis review of published literature. *Respir Med.* 2017;122:33–42. http://dx.doi.org/10.1016/j.rmed.2016.11.019

59. Hirota S, Kobayashi Y, Ishiguro T, et al. Allergic bronchopulmonary aspergillosis successfully treated with mepolizumab: case report and review of the literature. *Respir Med Case Rep.* 2018;26:59–62. http://dx.doi.org/10.1016/j.rmcr.2018.11.013
60. Altman MC, Lenington J, Bronson S, Ayars AG. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract.* 2017;5(4):1137–1139. http://dx.doi.org/10.1016/j.jaip.2017.01.013
61. Oda N, Miyahara N, Senoo S, et al. Severe asthma concomitant with allergic bronchopulmonary aspergillosis successfully treated with mepolizumab. *Allergol Int.* 2018;67(4):521–523. http://dx.doi.org/10.1016/j.alit.2018.03.004
62. Terashima T, Shinozaki T, Iwami E, Nakajima T, Matsuzaki T. A case of allergic bronchopulmonary aspergillosis successfully treated with mepolizumab. *BMC Pulm Med.* 2018;18(1):53. http://dx.doi.org/10.1186/s12890-018-0617-5
63. Soeda S, To M, Kono Y, et al. Case series of allergic bronchopulmonary aspergillosis treated successfully and safely with long-term mepolizumab. *Allergol Int.* 2019. http://dx.doi.org/10.1016/j.alit.2018.12.008
64. Soeda S, Kono Y, Tsuzuki R, et al. Allergic bronchopulmonary aspergillosis successfully treated with benralizumab. *J Allergy Clin Immunol Pract.* 2019;7(5):1633–1635. http://dx.doi.org/10.1016/j.jaip.2018.11.024
65. Cottin V. Eosinophilic lung diseases. *Clin Chest Med.* 2016;37(3):535–556. http://dx.doi.org/10.1016/j.ccm.2016.04.015
66. To M, Kono Y, Yamawaki S, et al. A case of chronic eosinophilic pneumonia successfully treated with mepolizumab. *J Allergy Clin Immunol Pract.* 2018;6(5):1746–1748.e1. http://dx.doi.org/10.1016/j.jaip.2018.06.017
67. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol.* 2017;118(2):220–225. http://dx.doi.org/10.1016/j.anai.2016.10.028
68. Cao PP, Li HB, Wang BF, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol.* 2009;124(3):478–484.e1–2. http://dx.doi.org/10.1016/j.jaci.2009.05.017
69. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;23:3 p preceding table of contents, 1–298.
70. Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic agents for the treatment of chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy.* 2018;27:1945892418814768. http://dx.doi.org/10.1177/1945892418814768
71. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol.* 2006;118(5):1133-1141. http://dx.doi.org/10.1016/j.jaci.2006.05.031
72. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J *Allergy Clin Immunol.* 2011;128(5):989–995.e1–8. http://dx.doi.org/10.1016/j.jaci.2011.07.056
73. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol.* 2017;140(4):1024–1031.e14. http://dx.doi.org/10.1016/j.jaci.2017.05.044
74. Oda N, Miyahara N, Senoo S, et al. Severe asthma concomitant with allergic bronchopulmonary aspergillosis successfully treated with mepolizumab. *Allergol Int.* 2018;67(4):521–523. http://dx.doi.org/10.1016/j.alit.2018.03.004
75. Curtis C, Ogbogu P. Hypereosinophilic syndrome. *Clin Rev Allergy Immunol.* 2016;50(2):240–251. http://dx.doi.org/10.1007/s12016-015-8506-7
76. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol.* 2004;113(1):115–119. http://dx.doi.org/10.1016/j.jaci.2003.10.049
77. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med.* 2008;358(12):1215–1228. http://dx.doi.org/10.1056/NEJMoa070812
78. O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology.* 2018;154(2):333–345. http://dx.doi.org/10.1053/j.gastro.2017.06.065
79. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128(1):3–20.e6; quiz 21–22. http://dx.doi.org/10.1016/j.jaci.2011.02.040
80. Pesek RD, Gupta SK. Emerging drugs for eosinophilic esophagitis. *Expert Opin Emerg Drugs.* 2018;23(2):173–183. http://dx.doi.org/10.1080/14728214.2018.1483335
81. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol.* 2006;118(6):1312–1319. http://dx.doi.org/10.1016/j.jaci.2006.09.007
82. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut.* 2010;59(1):21–30. http://dx.doi.org/10.1136/gut.2009.178558
83. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology.* 2011;141(5):1593–1604. http://dx.doi.org/10.1053/j.gastro.2011.07.044
84. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2012;129(2):456–463.e1-3. http://dx.doi.org/10.1016/j.jaci.2011.11.044

85. Markowitz JE, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. *J Pediatr Gastroenterol Nutr.* 2018;66(6):893–897. http://dx.doi.org/10.1097/MPG.0000000000001840
86. Mukherjee M, Paramo FA, Kjarsgaard M, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med.* 2018;197:38–46. https://doi.org/10.1164/rccm.201707-1323OC
87. Vianello A, Caminati M, Andretta M, et al. Prevalence of severe asthma according to the drug regulatory agency perspective: an Italian experience. *WAO J.* 2019;12(4):100032. https://doi.org/10.1016/j.waojou.2019.100032
88. Corren J, Panettieri RA Jr. How important is adherence to inhaled medications before starting a biologic therapy for asthma? *J Allergy Clin Immunol Pract.* 2018;6(5):1578–1579. https://doi.org/10.1016/j.jaip.2018.07.007