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Targeted Anti-IL-5 Therapies and Future Therapeutics for Hypereosinophilic Syndrome and Rare Eosinophilic Conditions

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Abstract
Eosinophilic inflammation is a component of many atopic diseases such as asthma, and biologics targeting eosinophils have been shown to be effective in subsets of these patients. However, there also are conditions in which eosinophils are the key inflammatory cells responsible for driving tissue damage. In these eosinophilic diseases such as hyper-eosinophilic syndrome, eosinophilic esophagitis, and eosinophilic granulomatosis with polyangiitis (EGPA), the development of biologics inhibiting eosinophilic inflammation have offered targeted therapeutic strategies for patients that have not responded well to typical first line drugs, which often have significant adverse side effects with poor disease modification or recurrent relapse with significant morbidity. IL-5 has long been recognized as the key inflammatory cytokine involved in the priming and survival of eosinophils and their proliferation and maturation in eosinophilic disease. There are a number of trials and case series demonstrating the immunomodulatory benefits of anti-IL-5 therapies in these diseases with good clinical responses. Yet, due to the heterogeneity and rarity of these conditions, anti-IL-5 therapies have not resulted in disease remission for all patients. Clearly, further research into the use of anti-IL-5 therapies in various eosinophilic diseases is needed and ongoing investigation into other immune mechanisms underlying chronic eosinophilic diseases may provide alternative therapies for these challenging conditions.

Keywords Benralizumab · Mepolizumab · Reslizumab · Siglec-8 · Hypereosinophilic syndrome · Eosinophilic esophagitis · Eosinophilic granulomatosis with polyangiitis · Dermatitis · Eosinophilia · IL-5 · IL-4 · IL-13

Introduction

There has been recent interest in the role of biologic agents used in the treatment and management of disease phenotypes that are driven by TH2 inflammation and eosinophils. TH2-high asthmatic patients are characterized by expression of airway hyperresponsiveness, expressions of IL-5 and IL-13, and responses to inhaled corticosteroids [1, 2]. Anti-IL-5 therapies are currently approved for use in severe eosinophilic asthma but not for other diseases with eosinophilia. IL-5 is essential for the differentiation, activation, and survival of eosinophils. In an asthma model using IL-5-deficient mice, there is failure to develop characteristic eosinophilia and airway hyperreactivity [3]. Another study demonstrated that there was an increase in airway eosinophils and positive methacholine challenge when subjects inhaled recombinant IL-5 [4]. This paper will highlight a number of human studies using anti-IL-5 therapy for the treatment for hypereosinophilic syndromes and other disease with eosinophilia. Biologics provide the option of a targeted approach to therapy directed against specific cell types or inflammatory pathways, with the ability to address clinical symptoms and pathology that is resistant to conventional treatments. They also offer an alternative to non-specific anti-inflammatory medications that may have substantially negative treatment side effects or limited efficacy.

This review will address studies pertaining to the use of anti-IL-5 therapies in the treatment of hypereosinophilic syndrome (HES), eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis, and eosinophilic dermatitis due to HES.

Anti-IL-5 Drugs

Mepolizumab is a humanized IgG1κ monoclonal antibody that binds to the α chain of IL-5 and prevents binding to the α subunit of the IL-5 receptor [5]. It is currently approved for use as an add-on maintenance treatment in severe asthma with eosinophilic phenotype for ages 12 and older and has been

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released under the trade name Nucala. The recommended dose is 100 mg subcutaneous injection once every 4 weeks. Adverse effects include headache (19%), fatigue (5%), eczema (3%), pruritus (3%), upper abdominal pain (3%), neutralizing antibody immunogenicity (6%), influenza (3%), injection site reaction (8%), back pain (5%), and muscle spasm (3%). Although there is no defined frequency, delayed type hypersensitivity reactions and herpes zoster have been reported. Mepolizumab has not been approved for treatment of other eosinophilic diseases like hypereosinophilic syndromes, eosinophilic granulomatosis with polyangiitis (EGPA; formerly named Churg Strauss syndrome), or eosinophilic esophagitis.

Reslizumab is an IgG4κ humanized monoclonal antibody that binds to circulating IL-5 and prevents it from binding to its receptors on eosinophils [6]. It has been approved in the USA as an add-on maintenance treatment of severe eosinophilic asthma in adults 18 and older. The recommended dose is 3 mg kg^{-1} intravenously every 4 weeks and has been released under the trade name Cinqair. There is a black box warning indicating that 0.3% of patients were observed to have had anaphylaxis in placebo-controlled clinical studies within 20 min of completing infusions. Other adverse reactions included antibody development (5%), increased creatine phosphokinase (20% transient), myalgias (1%), and oropharyngeal pain (3%). There were reported malignancies seen within 6 months of receiving drug, but there was no specific predominance of malignancy type. It is not approved for acute asthma exacerbations or for the treatment of other eosinophilic diseases like hypereosinophilic syndromes, EGPA, or eosinophilic esophagitis.

Benralizumab is a humanized IgG1κ monoclonal antibody against the IL-5R α subunit [7]. The drug induces NK cell-mediated killing of target cells through antibody-dependent cell-mediated cytotoxicity (ADCC), due to its high affinity for FcγRIIIa [8, 9]. The enhanced ADCC activity results in reduced circulating eosinophils and basophils. Preliminary data suggest that benralizumab depletes both mature eosinophils and their precursors in the bone marrow [10]. Benralizumab has now been FDA approved, under the trade name Fasenra, for the add-on maintenance treatment of severe eosinophilic asthma in patients 12 years and older.

Hypereosinophilic Syndromes and Other Eosinophilic Disease

Hypereosinophilic Syndrome

HES is defined by the association of hypereosinophilia (absolute peripheral blood eosinophil count (AEC) > 1.5×10^9 L^{-1} on two examinations at least 1 month apart and/or pathologic confirmation of tissue HE) with eosinophil-mediated organ damage and/or dysfunction with no other cause [11]. HES can be further categorized into disease due to primary, secondary, or idiopathic cause. Primary HES is eosinophilic expansion that occurs in the setting of an underlying stem cell, myeloid, or eosinophilic neoplasm and is considered clonal. Secondary HES is eosinophilic expansion driven by overproduction of eosinophilopoietic cytokines by other cell types and is polyclonal. This can be seen in parasitic infections, certain solid tumors, T cell lymphomas, and lymphocytic variant HES. Idiopathic HES is diagnosed when no underlying cause is determined.

Eosinophilic Granulomatosis with Polyangiitis

EGPA is a multisystem small- and medium-vessel vasculitis characterized by chronic rhinosinusitis, asthma, and eosinophilia [12]. The American College of Rheumatology has established six criteria for the diagnosis of EGPA [13]. The presence of four or more criteria has a sensitivity of 85% and specificity of 99% for EGPA: asthma, > 10% eosinophils, mononeuropathy (including multiplex) or polyneuropathy, migratory or transient pulmonary opacities, paranasal sinus abnormality, and biopsy containing a blood vessel with accumulation of eosinophils (Tables 1, 2, and 3).

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic disorder often characterized by symptoms of dysphagia, food impaction, vomiting, abdominal pain, and chest discomfort. After secondary causes of esophageal eosinophilia have been excluded, diagnostic criteria for eosinophilic esophagitis (EE) outlined by the most recent guidelines include: symptoms related to esophageal dysfunction, eosinophil predominant inflammation isolated on esophageal biopsy with a peak value > 15 eosinophils per high-powered field, mucosal eosinophilia isolated to the esophagus persisting 2 months after a trial of PPI, or a response to treatment (dietary elimination, topical steroids) supports diagnosis [35].

Eosinophilic Dermatitis

Skin diseases characterized by tissue eosinophilia are a heterogeneous group of disorders sometimes grouped under the term "eosinophilic dermatoses." Eosinophil infiltration can occur in either allergic, autoimmune, infectious, or neoplastic skin diseases. While allergic skin diseases such as atopic dermatitis or allergic contact dermatitis are some of the most common causes of eosinophilic skin disease, rare entities include eosinophilic cellulitis, eosinophilic pustular folliculitis, and hypereosinophilic syndrome with eosinophilic dermatitis as a feature.

Table 1 Anti-IL-5 studies and hypereosinophilic syndrome

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
Rothenberg et al. [14]	Mepolizumab	IV 750 mg vs. placebo (saline) every 4 weeks for 36 weeks	Double-blind, placebo-controlled, multicenter, parallel group	Hypereosinophilic syndrome, > 1500 eosinophils for ≥ 6 months and eosinophilia-related organ involvement with no other cause FIP1L1-PDGFRA negative Blood eosinophil count < 1000 μL^{-1} after 6-week run-in period with stable disease and monotherapy prednisone dose (20 to 60 mg)	18–85	85	Primary endpoint: reduction of prednisone dose to 10 mg or less day^{-1} for 8 or more consecutive weeks. Secondary endpoint: blood eosinophil count less than 600 μL^{-1} for 8 or more consecutive weeks, prednisone dose of 7.5 mg or less day^{-1}, receipt of no prednisone for 1 or more days, prednisone dose of 10 mg or less day^{-1} by week 20 and for 8 or more consecutive weeks, time to treatment failure (clinical worsening requiring other therapy, prednisone dose > 60 mg day^{-1} or withdrawal.	36 patients (84%) of 43 mepolizumab-treated patients achieved a prednisone dose of ≤ 10 mg day^{-1} for ≥ 8 weeks. That is 77% (> 30 mg day^{-1} prednisone) and 87% (≤ 30 mg day^{-1}) reached primary endpoint in mepolizumab group. Decreased steroid use, 77% of mepolizumab group vs. 38% of placebo were on a prednisone dose of ≤ 10 mg day^{-1} by week 20 for ≥ 8 weeks. Mean prednisone use of 6.2 ± 1.9 mg by week 36 compared with placebo at 21.8 ± 1.9 mg. Decrease eosinophil count to < 600 μL^{-1} for 8 weeks seen 100% of patients receiving more than 30 mg prednisone day^{-1} at baseline compared with 8% of placebo.
Roufosse et al. [15]	Mepolizumab	Stage 1, IV 750 mg every 4 week; stage 2, IV 750 mg every 4 or more weeks	Open-label multicenter	Hypereosinophilic syndrome (> 1500 eosinophils mm^{-3} for ≥ 6 months), eosinophil-related organ involvement, no identifiable cause of eosinophilia FIP1L1-PDGFRA negative Patients that had completed 9 months of treatment or withdrew after receiving at least 2 doses Baseline dose of > 10 mg prednisone daily	18–75	78	Primary endpoint: overall frequency of adverse events Secondary endpoint: proportion of subjects maintain a daily dose of ≤ 10 mg day^{-1} prednisone for ≥ 12 weeks, proportion of subjects corticosteroid free for ≥ 12 weeks, proportion of subjects in each dosing frequency group	All patients reported adverse events, only one third of these were determined to be related to mepolizumab. There rate of serious adverse events was similar between groups and was not related to mepolizumab. At time of study termination, 34 out of 54 subjects (63%) were on mepolizumab monotherapy.
Stein et al. [17]	Mepolizumab	IV 10 mg kg^{-1} mepolizumab at weeks 8, 12, and 16	Open-label phase I/II	HES, eosinophilic esophagitis or eosinophilic-associated gastrointestinal disorder	18–57	25	Assess safety of mepolizumab and to characterize the hematologic and immunologic effects of anti-IL-5 therapy in patients with eosinophilic disorders	Decrease in blood eosinophils in 23 out of 25 patients (92%) 16 of the 21 subjects (76.2%) had significantly decreased peripheral blood eosinophils for 3 months after the final mepolizumab infusion. 13-fold decrease in peripheral blood CCR3+ cells after mepolizumab therapy in all patients IL-5 levels did not correlate with responsiveness to mepolizumab therapy. There was 25 to 50% reduction in immunosuppressant use with mepolizumab.
Mehr et al. [18]	Mepolizumab	IV 10 mg kg^{-1} mepolizumab every 4 weeks for 3	Case study	9-year-old male diagnosed with FIP1L1-PDGFRA-negative		1		Decrease number of flares while on mepolizumab compared with steroid

Table 1 (continued)

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
		infusions, then every 3 months		HES (blood eosinophilia 3.4×10^9 L^{-1})				alone, IFN/prednisone, and imatinib/steroid Improvement in growth while on mepolizumab (steroid sparing effect) Decrease in peripheral blood eosinophils with mepolizumab compared with other treatments
Garrett et al. [36]	Mepolizumab	IV 10 mg kg^{-1} mepolizumab every 4 weeks for a total of 3 treatments over 28 weeks	Open label	Patients with HES, idiopathic HES, and eosinophilic esophagitis	18–65	4	Effect of treatment on safety, eosinophil levels (in blood and tissue), pulmonary function, and quality of life	Decreased peripheral eosinophil at end of 28-week period with pronounced drop after mepolizumab treatment. Decreased tissue eosinophils in esophagus with a decrease in number of eosinophils/hpf Improved quality of life and FEV1
GlaxoSmithKline [19]	Mepolizumab	Subcutaneous mepolizumab every 4 weeks compared with placebo over 32 weeks	Phase III, double-blind, parallel, multicenter, randomized controlled trial	Severe HES: at least 2 HES flares within the past 12 months, blood eosinophil count > 1000 μL^{-1} or higher	12 or older		Primary endpoint: proportion of patients who experience an HES flare Secondary endpoint: time to first flare, proportion of patients experiencing flare during weeks 20 and 32, fatigue severity	Ongoing, gsk.com, and ClinicalTrials.gov (Identifier NCT02836496)
Klion et al. [20]	SCH55700 (reslizumab)	Subcutaneous single mepolizumab 1 mg kg^{-1} dose, patients who had clinical improvement and reduction in eosinophilia could receive 5 more monthly doses	Pilot phase I/II	Refractory HES or intolerance to therapy with corticosteroids, hydroxyurea, and interferon α FIP1L1-PDGFRA negative	32–52	4	Efficacy and safety	Drug was well tolerated. 1 patient had transient long bone pain 6–12 h after first and second infusions. Fever, upper respiratory symptoms occurred within 3 days of drug infusion on 2 occasions for 1 study patient, but this was felt not due to drug. Patients 1 and 2 experienced rapid decrease in eosinophilia and improved clinical symptoms. Clinical and hematologic response last > 30 days but was accompanied with rebound in peripheral eosinophil count. That exceeded baseline level. It was also accompanied by rise in serum IL-5 levels. Patient 3 did not have decrease in eosinophil count or improvement in symptoms but had a self-limited exacerbation during weeks 1 to 4. Patient 4 had rapid drop in eosinophils but no change in symptoms; this patient also had high IL-5 levels at start of study. Only patients 1 and 2 received additional 5 doses with associated decrease in eosinophil count and improved clinical symptoms but the magnitude of improvement was less compared with

Table 1 (continued)

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
								first dose.
Kuang et al. [21]	Benralizumab	30 mg subcutaneous Benralizumab vs. placebo every 4 weeks	Phase 2a randomized, double-blind, placebo-controlled trial	FIP1L1-PDGFRA-negative HES	18–65	20	Primary endpoint: 50% reduction in peripheral blood eosinophilia on stable HES background therapy Secondary endpoint: percent reduction peripheral blood eosinophilia, frequency, and severity of adverse events, eosinophil count, and background HES therapy at 1 year	90% of benralizumab group vs. 30% of placebo group achieved primary endpoint. In open-label extension, AEC was < 200 cells mm^{-3} in 17 of 19 patients (89%) after 1st open-label dose (week 13). All 17 patients with laboratory response at week 13 had clinical improvement

Anti-IL-5 Treatments for Hypereosinophilic Syndromes

Studies Using Mepolizumab

A study by Rothenburg et al. demonstrates a steroid sparing effect and decreased eosinophil count in HES patients treated with mepolizumab [14]. This randomized, double-blind, placebo-controlled, parallel, multicenter study trial evaluating the safety and efficacy of an anti-interleukin-5 (anti-IL-5) monoclonal antibody, mepolizumab, in patients with hypereosinophilic syndromes was conducted between 2004 and 2006. The study population was 18 to 85 years old with hypereosinophilia defined as a peripheral blood eosinophil count > 1500 μL^{-1} for ≥ 6 months and eosinophilia-related organ involvement or dysfunction with no identifiable secondary cause of eosinophilia at baseline. All patients enrolled were FIP1-like1-platelet-derived growth factor receptor-α (FIP1L1-PDGFRA) negative. FIP1L1-PDGFRA is an activated fusion tyrosine kinase associated with chronic myeloproliferative disorders including HES and chronic eosinophilic leukemia. Patients entered into a 6-week run-in period after enrollment where non-corticosteroid medications for HES were discontinued and were managed on prednisone monotherapy (20 to 60 mg day^{-1} or equivalent steroid dose for at least 1 week) to achieve stable clinical status (no new or worsening clinical signs or symptoms and blood eosinophil count < 1000 μL^{-1}). Eighty-five patients underwent 1:1 randomization to receive intravenous infusion of mepolizumab 750 mg or placebo (saline) and were stratified by prednisone dose (≤ 30 mg or > 30 mg). Treatment was given at baseline and every 4 weeks during a 36-week period. Prednisone dose was tapered from week 1 until week 36 depending on clinical symptoms. There were 34 withdrawals (7 in active treatment and 27 in placebo). The authors indicate that there was lack of treatment efficacy in 21 of the placebo group compared with 5 in active treatment, leading to withdrawals. There were no differences in baseline characteristics between treatment and placebo group. Mean duration of disease in this study group was greater than 5 years with a mean eosinophil count of 0.447×10^{-9} L^{-1}. Thirty-six out of forty-three patients enrolled in the mepolizumab group (84%) met the primary endpoint of prednisone dose ≤ 10 mg day^{-1} for ≥ 8 weeks compared with 43% of placebo group. Twenty-six out of thirty patients (87%) receiving less than 30 mg day^{-1} of prednisone at baseline, and ten of thirteen (77%) patients receiving more than 30 mg day^{-1} at baseline in mepolizumab group met primary endpoint. Forty-one of forty-three patients (95%) in the mepolizumab group had an eosinophil count < 600 μL^{-1} for 8 or more weeks compared with 45% of placebo-treated patients. The steroid sparing effect of treatment was seen in 77% of mepolizumab group, being on a prednisone dose of ≤ 10 mg day^{-1} by week 20 for ≥ 8 weeks, and had a mean

Table 2 Anti-IL-5 studies and eosinophilic esophagitis

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
Stein et al. [22]	Mepolizumab	IV 10 mg kg^{-1} (max 750 mg) mepolizumab every 4 weeks for 3 consecutive doses over 28 weeks	Open-label, phase I/II trial	Participants with eosinophilic esophagitis > 24 eosinophils hpf^{-1} and no other pathology in gastrointestinal segments	18–41	4	Safety and efficacy of mepolizumab for eosinophilic esophagitis	All enrolled patients had eosinophilic esophagitis for 9 or more years. 2 out of the 4 patients had associated atopic disease. 1 out of the 4 patients was not on any therapy at baseline. All 4 patients had skin prick sensitivity to foods. All 4 patients responded to anti-IL-5 therapy with better clinical outcomes in improved dysphagia, vomiting, swallowing, food impaction. There was also an improvement in endoscopic findings after treatment for 3 of the patients. There was overall improved quality of life scores after treatment. Anti-IL-5 treatment reduced peripheral eosinophilia from 444 ± 112 to 69.5 ± 12.8 ($p = 0.005$) and the percentage of CCR3+ cells in the blood decreased from 6.5 ± 2.1 to 0.83 ± 0.4. There was a 14.6-fold decrease in esophageal eosinophils.
Stein et al. [17]	Mepolizumab						See this study in HES section	
Straumann et al. [23]	Mepolizumab	IV 750 mg mepolizumab with 2 infusions 1 week apart followed by further 2 infusions 4 weeks apart of 1500 mg if not in remission	Randomized, placebo--controlled, double-blind trial	Active eosinophilic esophagitis with at least 1 episode of dysphagia $wee-k^{-1}$ in the past 4 weeks, > 20 eosinophils hpf^{-1}	18 or older	11	Primary endpoint: proportion of responders with < 5 eosinophils hpf^{-1} on histology	There were 80% males in the mepolizumab group compared with 50% in the placebo group. No patients met the primary endpoint of < 5 eosinophils hpf^{-1} There was a marked reduction in eosinophil count on histology at weeks 4 and 13 in the mepolizumab group. There was decrease in peripheral blood eosinophils in the mepolizumab group compared with placebo. There was more than 20% improvement in clinical symptoms between weeks 9–13 for mepolizumab group.
Conus et al. [24]	Mepolizumab	IV 750 mg mepolizumab or placebo, dose given at 0 and 7 days. Those not in remission received 2 or more doses 4 weeks apart of 1500 mg mepolizumab	Randomized, double-blind, placebo-controlled trial	Active eosinophilic esophagitis	18 or older	11	Eosinophil per hpf in duodenal biopsy	There was no difference in mean number of eosinophils and mean IL-5Rα expression levels in duodenal tissue. The number of mast cells and T cells did not change with treatment compared with placebo. The proportion of CD25 and IL-13-positive duodenal eosinophils did not change with treatment.
Assa'ad et al. [25]	Mepolizumab	IV 0.55, 2.5, or 10 mg kg^{-1} mepolizumab every 4 weeks for 3 infusions for 34 weeks	Multicenter, double-blind, randomized, stratified, parallel group	Eosinophilic esophagitis with peak > 20 eosinophils hpf^{-1} from biopsy of distal and mid esophagus	2–17	59	Primary endpoint: proportion of patients with peak esophageal intraepithelial eosinophil count of 5 hpf^{-1}, safety and tolerability, and pharmacokinetics Secondary endpoint: changes in peak and mean intraepithelial eosinophil counts, endoscopic	Baseline peak eosinophils were 122.5 and 8.75, and the mean was 39.1 3.63 hpf^{-1}. After the third infusion, peak eosinophil counts were < 5 hpf^{-1} in 5 of 57 children (8.8%). There was no difference between different treatment groups. The mean eosinophil count was decreased to < 20 in 89.5% of children.

Table 2 (continued)

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
							findings, blood eosinophil counts, frequency of EoE symptoms	Peak and mean esophageal counts decreased significantly from 40.2 to 9.3
Otani et al. [26]	Mepolizumab	IV 0.55, 2.5, or 10 mg kg^{-1} mepolizumab every 4 weeks for 3 infusions for 34 weeks	Multicenter, double-blind, randomized, stratified, parallel group	Eosinophilic esophagitis with peak > 20 eosinophils hpf^{-1} from biopsy of distal and mid esophagus	2–17	43	Reduction in esophageal mast cell accumulation in biopsy	Peak eosinophil numbers in the esophagus decreased in 86% of subjects 40% of subjects responded to anti-IL-5 treatment with < 15 eosinophils hpf^{-1} and 77% of subjects had decreased numbers of mast cells after treatment with anti-IL-5. In those responding to treatment, epithelial mast cell numbers decreased from 62 to 19 hpf^{-1} which was significant. Mast cells and eosinophils were in couplets prior to treatment and this number declined significantly after treatment with anti-IL-5. There was a decrease in the number of IL-9 cells after treatment.
Spergel et al. [27]	Reslizumab	IV 1, 2, or 3 mg kg^{-1} reslizumab or placebo Every 28 days for 4 doses	Multicenter, double-blind, randomized, placebo-controlled trial	Active eosinophilic esophagitis with at least 1 active symptom of moderate severity or worse within the week before randomization, and EGD with biopsy documenting active eosinophilic esophagitis (> 24 eosinophils hpf^{-1}), treatment with a proton pump inhibitor	5–18	227	Primary endpoint: percent change from baseline to end of therapy in peak esophageal eosinophil count and the change from baseline to the end of therapy in the physicians' eosinophilic esophagitis global assessment score Secondary endpoint: symptom assessment (CHQ), adverse events	Median reduction in peak esophageal eosinophil counts were 59, 67, 64, and 24% in the 1, 2, and 3 mg kg^{-1} treatment group and placebo, respectively. All treatment groups including placebo showed improvement in physician's global assessment scores, no statistical significance. Most common adverse events were headache, upper respiratory tract infection, cough, and nasal congestion. There were 4 serious adverse events (2 in reslizumab and 2 in placebo) but none were thought to be due to study drug.

Table 3 Anti-IL-5 studies and eosinophilic granulomatosis with polyangiitis/EGPA

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
Kahn et al. [28]	Mepolizumab	IV 750 mg mepolizumab every month	Case study	Female with EGPA	28	1		Normal eosinophil count 1 month after first mepolizumab infusion, disappearance of parenchymal lung findings on CT lung, and reduction in corticosteroid after 6 months Attempt to change frequency of infusions to once every 2 months resulted in relapse with lung infiltrates, increased eosinophils. This resolved after resumption of once a month dosing of mepolizumab
Kim S et al. [29]	Mepolizumab	IV 750 mg mepolizumab 12-week active treatment followed by washout period and 19 weeks off mepolizumab	Open-label pilot	Subjects meeting criteria for EGPA Syndrome as per American College of Rheumatology On stable dose of at least 10 mg prednisone daily or other stable dose of immunosuppressant	28–62	7	Primary endpoint: assess whether mepolizumab safely decreased EGPA syndrome disease activity and permitted scheduled tapering of systemic corticosteroids. The lowest prednisone dose achieved at the end of the treatment phase. Assessment of treatment-related adverse effects	There was a decrease in the mean steroid dose from 12.9 to 4.6 mg day^{-1} after 12 weeks from treatment compared with baseline. There was a decrease in eosinophilia during treatment which returned to baseline after treatment withdrawn. Active treatment phase with mepolizumab had the least amount of exacerbations compared with withdrawal of treatment
Moosig et al. [30]	Mepolizumab	IV 750 mg mepolizumab, 9 infusions every 4 weeks	Phase 2, single-center, uncontrolled trial	Subjects meeting criteria for refractory or relapsing EGPA (defined by Birmingham vasculitis activity score BVAS of greater than 2) Steroid dose of 12.5 mg day^{-1} or higher	43–78	10	Primary endpoint: remission at 32 weeks defined as BVAS of 0 and glucocorticoid dosage of less than 7.5 mg day^{-1} Secondary endpoint: BVAS, Vasculitis Damage Index, Disease Extent Index, glucocorticoid dose, eosinophil counts, adverse events	8 out of 10 patients achieved primary endpoint with remission being reached after 2 or 3 treatments. 1 patient had a BAVS of 0 but was on a dose of glucocorticoid greater than 7.5 mg day^{-1} There were no cases of relapse during treatment with mepolizumab. The daily glucocorticoid dose was decreased from a median dose of 19 mg day^{-1} at baseline to 4 mg at week 32. Eosinophil counts rapidly dropped and stayed near 0 through active treatment. There was relapse of disease in 7 patients after switching treatment to methotrexate.
Herrmann et al. [31]	Mepolizumab	IV 750 mg mepolizumab given previously, none given during this follow-up period 22 months median	Phase 2, single-center, uncontrolled group	Subjects meeting criteria for refractory or relapsing EGPA (defined by Birmingham vasculitis activity score of greater than 2) Steroid dose of 12.5 mg day^{-1} or higher	43–78	9	Primary endpoint: Association between Birmingham Vascular Activity (BVAS) and ECP levels (eosinophilic cationic protein)	3 of 9 patients were in remission at the end of the previous study There were an additional 2 major and 2 minor relapses that occurred. The mean eosinophil count rose after stopping anti-IL-5 medication 6 out of 9 patients had an increase in glucocorticoid dose above 7.5 mg day^{-1} There was a strong correlation between BVAS and ECP ($p < 0.0001$; $r = 0.31$) There was a correlation between eosinophil count and ECP ($r = 0.36$; $p < 0.0001$) and between BVAS and eosinophil count ($r = 0.28$; $p < 0.0001$)
Weschler et al. [32]	Mepolizumab	300 mg subcutaneous mepolizumab or placebo every 4 weeks for 52 weeks	Multicenter double-blind, parallel, placebo-controlled, phase 3 trial	Subjects with relapsing or refractory eosinophilic granulomatosis with polyangiitis at least	18 or older	136; 68 in each group	Primary endpoint: (1) Total accrued weeks of remission defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and	A total of 14 participants stopped mepolizumab (5) or placebo (9), and a total of10 participants withdrew (3 in mepolizumab and 7 in placebo)

Table 3 (continued)

Study	Drug	Dose	Study design	Study population	Age (years)	Number of enrolled patients (*N*)	Outcome measure	Findings
				6 months previously and had been taking a stable dose of prednisolone or prednisone (7.5 to 50 mg day^{-1} with or without additional immunosuppressive therapy) for at least 4 weeks before baseline.			prednisone dose of 4.0 mg or less day^{-1} over the 52-week period. (2) The proportion of participants who had remission at both weeks 36 and 48. Secondary endpoint: proportion of participants who had remission within the first 24 weeks and continued to have remission until 52 weeks. The time to first relapse, the proportion of participants with an average prednisone dose of 0, 0–4, and 4–7.5 mg day^{-1} during weeks 48–52.	Baseline characteristic similar The trial met both primary endpoints. 28% of the mepolizumab group vs. 3% of the placebo group were in remission for at least 24 weeks (OR, 5.91; 95% CI, 2.68 to 13.03; $p < 0.001$) A total of 47% of the participants in the mepolizumab group compared with 81% of the placebo group did not reach remission. At both 36 and 48 weeks, 32% of the mepolizumab group vs. 3% of the placebo group were in remission (OR, 16.74; 95% CI, 3.61–77.56; $p < 0.001$) For participants with AEC of 150 cells or more mm^{-3} at baseline, 33% of the mepolizumab group vs. 0% of the placebo were in remission after 24 weeks (OR, 26.10; 95% CI, 7.02–97.02) The time to first relapse over the 52-week period was longer in the mepolizumab group (56%) vs. placebo (82%)
National Jewish Health and TEVA [33]	Reslizumab	IV 3 mg kg^{-1} reslizumab every 4 weeks for 28 weeks, 7 treatments	Phase 2, open label	Eosinophilic granulomatosis with polyangiitis for past 6 months based on diagnosis of asthma and eosinophilia of > 10% or > 1×10^9 L^{-1} with 2 other additional features Patient must be on stable dose of corticosteroid and another immunosuppressant agent	18 or older		Primary endpoint: safety of reslizumab therapy in EGPA, all adverse events Secondary endpoint: demonstrate steroid sparing effect of reslizumab therapy by titrating steroid dosage	Ongoing, clinicaltrials.gov (Identifier NCT02947945)
National Jewish Health and AstraZeneca [34]	Benralizumab	Subcutaneous 30 mg benralizumab every 4 weeks for 8 weeks, then every 8 weeks for 24 weeks	Phase 2, open level	Eosinophilic granulomatosis polyangiitis for past 6 months based on diagnosis of asthma and eosinophilia of > 10% or > 1×10^9 L^{-1} with 2 other additional features Patient must be on stable dose of corticosteroid and another immunosuppressant agent	18 or older		Primary endpoint: all adverse events Secondary endpoint: Change in corticosteroid dosage, change in rate of EGPA exacerbations during study period	Ongoing, clinicaltrials.gov (Identifier NCT03020436)

prednisone use of 6.2 ± 1.9 mg by week 36 compared with placebo at 21.8 ± 1.9 mg. Adverse events were similar between both treatment arms. There were 14 serious adverse events in the mepolizumab group compared with 7 events in the placebo group, none of which were felt to be related to treatment.

Roufosse et al. described a subanalysis of the above study by Rothenburg et al. [14], examining the effect of mepolizumab in those patients with lymphocytic-variant HES [15]. Thirteen enrolled patients between the ages of 18–75 with FIP1L1-PDGRA-negative HES met criteria for L-HES, of which seven received mepolizumab and six received placebo. Patients with L-HES receiving mepolizumab maintained an average daily prednisone dose of 4.64 mg for at least 24 weeks compared with L-HES patients receiving placebo required a mean daily prednisone dose of 28.23 mg. Four of the seven patients in the mepolizumab arm were corticosteroid free at the end of the trial vs. none in the placebo group ($p = 0.07$). Patients also receiving mepolizumab in the L-HES group were more likely to achieve a blood eosinophil count below 600 μL^{-1} for 8 weeks but were less likely to achieve a sustained eosinophil count below 600 μL^{-1} compared with the L-HES-negative group treated with mepolizumab. There were two patients in the mepolizumab group (one with L-HES and one without) that were not able to achieve the primary endpoint and failed to reduce their prednisone dose.

A study by Roufosse et al. evaluated the efficacy and safety of mepolizumab for HES as a corticosteroid sparing agent [16]. This was a multicenter open-label extension to the study published by Rothenberg et al. [14]. Out of 78 eligible patients, 37 patients with > 10 mg day^{-1} baseline prednisone use were enrolled in stage 1 with monthly infusions of 750 mg mepolizumab IV. The other 41 patients were those with a stable dose of HES medication, AEC < 600 mm^{-3} and no worsening HES symptoms; these patients were placed into stage 2 of the study, where mepolizumab dosing was guided by HES symptoms and AEC > 600 mm^3, with a minimum dosing interval of at least 4 weeks apart. Baseline characteristics between both groups were similar except for 7 out of 37 patients (19%) in the stage 1 group had received mepolizumab previously compared with 33 out of 41 (80%) in stage 2. Also, prednisone use was different, with 2 out of 37 (5%) in stage 1 being prednisone free at entry with a median prednisone use of 20 mg, compared with 22 out of 41 (54%) in stage 2 being prednisone free at entry with a median prednisone use of 0 mg. Ninety-seven percent of subjects reported at least 1 adverse event during the trial, most common being cough (33%), fatigue (31%), headache (29%), upper respiratory tract infection (29%), and sinusitis (28%). Those patients that had a median prednisone use of 20 mg at baseline saw a decrease to 0 mg by 24 weeks of treatment with mepolizumab and remained stable. Forty-eight of seventy-eight subjects (62%) received mepolizumab monotherapy for HES for ≥ 12 weeks. For those patients participating in the study for more than 1 year, 41 out of 67 subjects (61%) received mepolizumab as monotherapy. For those who participated for 3 or more years, 24 out of 60 patients (40%) received mepolizumab as monotherapy. Only three patients required other immunosuppressive treatment for HES during the study (azathioprine, methotrexate, and cyclosporine). Mean AEC remained below 500 mm^{-3} during stage 2 except for one patient. The median dosing interval in stage 2 was 12.8 weeks for all subjects. Six patients withdrew from the study due to lack of efficacy, five of whom had persistent HES-related symptoms involving the skin, respiratory system, and digestive tract. Forty-one subjects reported at least one severe adverse event including severe arthralgia, pneumonia, severe nausea, abdominal pain, dyspnea, pruritus, and pyrexia. Out of the reported adverse events, 20 subjects (26%) were thought to be related to mepolizumab including fatigue and nausea. There were a total of four fatal serious adverse events.

Stein et al. enrolled 25 subjects in an open-label phase I/II trial to assess the safety of mepolizumab in patients with eosinophilic disorders such as HES, eosinophilic esophagitis, or eosinophilic-associated gastrointestinal disorder and to characterize the hematologic and immunologic effects of anti-IL-5 [17]. None of the subjects had ever received mepolizumab previously except for 7 of the 25 enrolled subjects (4 with EE and 3 with HES) were concurrently enrolled in other mepolizumab clinical trials. These concurrent studies did not assess tissue and eosinophil response to mepolizumab. All 25 subjects received IV mepolizumab at 10 mg kg^{-1} dose (max dose 750 mg) at weeks 8, 12, and 16 and then were monitored for another 12 weeks. From weeks 0 to 8, subjects with an eosinophil count less than 750 cells mm^{-3} had their steroid dose decreased until their AEC was increased to 2-fold greater than their baseline count or greater than 750 cells mm^{-3}. Subjects were split into three cohorts with Cohort A ($n = 14$) having no modification of immunosuppressant medication, Cohort B ($n = 6$) having a 50% reduction, and Cohort C ($n = 5$) having a 25% reduction in concurrent prescribed immunosuppressant medication. Two out of the twenty-five enrolled subjects withdrew due to concern about potential risk of treatment or lack of therapy efficacy. Baseline eosinophils ranged from 1183 ± 2073 to 1400 ± 2179 cells mm^{-3}. After mepolizumab therapy, there was a sustained decrease in blood eosinophils in 23 out of 25 patients (92%) with a significant decrease to 64 ± 54 cells mm^{-3}, a 21.8-fold decrease. Sixteen of the twenty-one subjects (76.2%) had significantly decreased peripheral blood eosinophils for 3 months after the final mepolizumab infusion. There was a 13-fold decrease in peripheral blood $CCR3^+$ cells after mepolizumab therapy in all patients. IL-5 levels did not correlate with responsiveness to mepolizumab therapy. Mepolizumab did allow for patients to tolerate a reduction in immunosuppressive therapy by either 25 or 50%. Only 1 of the 25 enrolled patients had no response in eosinophil count to mepolizumab; this patient had HES

with a negative FIP1L1-PDGFRA fusion gene. This study, despite demonstrating an immunologic response to anti-IL-5 therapy, enrolled subjects with varying eosinophilic disorders making the results hard to extrapolate, especially given the smaller size of the study.

Mehr et al. describe the case of a 9-year-old boy with FIP1L1-PDGFRA-negative HES treated with mepolizumab [18]. This patient had asthma, erythematous rash, and pericardial effusion with eosinophilia that initially responded to steroids but flared up after dose reduction. The patient developed adrenal suppression, cataract, and poor growth for which IFNα was initiated for steroid sparing. However, after 3 months, the patient developed paresthesia above the right knee and the patient was switched to imatinib with daily prednisolone. Despite this treatment, the patient continued to have frequent flares and increased blood eosinophils. At the age of 12, the patient stopped imatinib for 1 week and started mepolizumab for three monthly infusions at 10 mg kg^{-1}. His mean daily prednisolone requirement decreased from 0.25 to 0.07 mg kg^{-1} day^{-1}. The patient remained symptom free for 3 months after the third infusion when he again experienced a flare with an increase in eosinophil count to 1.2×10^9 L^{-1}. The decision was made to place the child on every 3-month mepolizumab treatment. Overall, the patient experienced fewer flares with mepolizumab (only one) due to tapering of steroids compared with three flares on steroid alone, two flares with IFNα/steroid, and five flares with imatinib/steroid. The patient's height velocity improved with mepolizumab, and there was a lower blood eosinophil level (0.2×10^9 L^{-1}).

Garrett et al. present a study on the steroid sparing effect of mepolizumab for HES with lowered eosinophil levels [36]. This was an open-label trial of mepolizumab given IV at 10 mg kg^{-1} (max 750 mg) every 4 weeks for three treatments (weeks 8, 12, and 14) over a 28-week period in four patients between the ages of 18 and 65 years. This study included patients diagnosed with HES, idiopathic HES, and eosinophilic esophagitis. There was an 8-week run-in period where patients with idiopathic HES had their steroid therapy decreased so that the eosinophil level was 2-fold greater than baseline eosinophil level or > 750 cells μL^{-1}. All four patients experienced a decrease in peripheral blood eosinophils by week 28, with a pronounced drop after treatment with mepolizumab. All patients reported improvement in specific symptoms during the study duration along with improvement in QOL and FEV1. One of the patients with eosinophilic esophagitis had a statistically significant 10-fold decrease in mean number of tissue eosinophils per high-powered field. The only reported adverse events were fatigue after the first two infusions and infusion-related headaches in another patient.

There is a phase III clinical trial currently open and recruiting patients with severe hypereosinophilic syndrome to receive mepolizumab every 4 weeks for 32 weeks in a randomized double-blind, placebo-controlled study [19]. This study is eligible for adolescents and adults and is sponsored by GlaxoSmithKline. The primary endpoint of the study is the proportion of patients who experience a HES flare (worsening of symptoms requiring escalation in therapy) during the 32-week treatment period. Secondary endpoints aim to demonstrate supportive evidence for the benefit of mepolizumab compared with placebo and include times to first HES flare, proportion of patients who experience a HES flare during weeks 20 through 32 and fatigue severity.

Studies Using Reslizumab

Klion et al. describe the use of reslizumab, a humanized monoclonal antihuman IL-5 antibody, as useful in treating a subset of HES patients [20]. Four subjects with refractory HES or intolerant to treatment with corticosteroids, hydroxyurea, and interferon α were enrolled in a pilot phase I/II study of a single dose of SCH55700, a humanized anti-human IL-5 antibody, at 1 mg kg^{-1} IV. Patients with a clonal hematopoietic process were excluded; however, patients with the FIP1L1-PDGFRA fusion gene were included. Patients were admitted to the hospital and monitored for 72 h after the first dose of SCH55700 and had labs drawn daily for 3 days, then weekly for 4 weeks, then monthly for 2 months. Patients showing a decrease in eosinophilia were eligible for five additional doses of the study drug. The ages of the patients ranged from 32 to 52 years with various organ involvements. The study drug was well tolerated; however, one patient complained of long bone pain occurring 6–12 h after the first and second infusions. In another patient, low-grade fever and upper respiratory symptoms occurred within 3 days of infusion on two separate occasions, but family members of the patient had similar symptoms. Two out of the four patients had a rapid decline in eosinophils after infusion accompanied by improvement in symptoms such as resolution of skin rash, mucosal ulceration, angioedema, fatigue, myalgia, and arthralgia. A decrease in eosinophil count lasted about 30 days before rebounding along with eosinophil counts higher than the baseline count, severe exacerbation of symptoms, and a rise in serum IL-5. One out of the four patients did not respond to treatment with neither a decrease in eosinophil count or improvement in symptoms. Another patient had an initial rapid decrease in eosinophil count after baseline; however, the patient never had appreciable symptom control and eosinophil levels rebounded despite further treatment. The baseline IL-5 level of this patient was highest among all participants and was still detectable after treatment. Drug levels remained consistently elevated in blood after infusions, indicating there was no neutralizing antibody production. Bone marrow biopsy was completed 1 month

following treatment with no indication of change in bone marrow cellularity or eosinophilia.

Studies Using Benralizumab

The results of a phase 2a randomized double-blind, placebo-controlled study of benralizumab in hypereosinophilic syndrome was recently reported by Kuang et al. [21]. This study randomized 20 patients to receive either 30 mg benralizumab every 4 weeks or placebo. The primary endpoint of 50% reduction in peripheral blood eosinophilia was achieved by 90% of the benralizumab group and 30% of the placebo group ($p = 0.02$). Six patients in the benralizumab group had transient, mild lymphopenia after the first dose vs. one patient with persistent lymphopenia in the placebo group ($p = 0.06$). Eight patients had systemic symptoms including fever, chills, headache, nausea, and fatigue after the first dose of benralizumab, but these symptoms self-resolved and did not recur with subsequent doses. Serum lactate dehydrogenase levels increased in 16 of 19 patients after the first dose of benralizumab but normalized.

Anti-IL-5 Treatments for Eosinophilic Granulomatous Polyangiitis

Studies Using Mepolizumab

Kahn et al. present a case of refractory EGPA treated with mepolizumab [28]. A 28-year-old Caucasian female with a history of asthma presented with hypereosinophilia (26.7×10^9 L^{-1}), interstitial pneumonia (60% eosinophils in BAL), and myocarditis. Serum IgE was 1000 kIU L^{-1}, ANCA negative, and was treated with a course of steroids despite many relapses. She was subsequently treated with methotrexate, IFNα, cyclophosphamide, intravenous immunoglobulin, and azathioprine but continued to relapse, with eosinophilia as high as 18×10^9 L^{-1}, worsening asthma, interstitial pneumonia, and mononeuritis multiplex. Mepolizumab 750 mg every 4 weeks IV was started with rapid improvement and resolution of asthma. Attempts at spacing infusions to every 8 weeks resulted in relapse. Reintroduction of monthly infusion resulted in disease control, lowered eosinophil count, normalization of chest CT findings, lower steroid dose, and a subsequent rise in IL-5 after 8 months of treatment.

Kim et al. describe the steroid sparing effect of mepolizumab in the treatment of EGPA [29]. This is an open-label pilot study of seven adult patients with EGPA as classified by the American College of Rheumatology by at least four of the following: eosinophil count > 10% of peripheral blood leukocytes on more than one occasion off prednisone, asthma, neuropathy (poly or mono), pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. The patient had to be maintained on a stable dose of at least 10 mg of prednisone daily or a stable dose of another immunosuppressant like cyclophosphamide, azathioprine, or methotrexate. The patient received a total of four monthly infusions of 750 mg IV mepolizumab. Two weeks after the first infusion, the corticosteroid dose was tapered throughout the 12-week treatment phase. There was a subsequent 7-week washout phase where the steroid and mepolizumab dose was decreased. The final steroid dose was determined 4 weeks after the last infusion. During the last 19 weeks, there was a safety monitoring phase to assess patient stability on a stable tapered dose. Baseline mean FEV1 was 76% of predicted, mean eosinophil count of 3.4%, mean prednisone dose of 12.9 mg at baseline. There were no reported severe adverse events, but three patients noted mild transient headaches within 48 h of infusion that resolved on their own or with over-the-counter analgesic. All other symptoms experienced during the study were thought not due to infusions administration but what were thought to be due to corticosteroid tapering or clinical disease activity. The mean dose of corticosteroid after 12 weeks of therapy was 4.6 mg, a 64% reduction ($p = 0.0001$) after four doses of mepolizumab. After 24 weeks in the study, mean corticosteroid was 5 mg or a 61% decrease in dose ($p = 0.02$). After 40 weeks at the completion of the study, the mean prednisone dose was 15.7 mg. On cessation of mepolizumab treatment, EGPA manifestations recurred, necessitating steroid bursts with a more gradual resurgence of percentage eosinophils. The rate of exacerbations during the treatment period was 0.14 vs. 0.69 during the non-treatment phase.

Moosig et al. present results of study where anti-IL-5 therapy for severe EGPA was beneficial in inducing remission and steroid reduction [30]. This was a phase 2, single-center, uncontrolled investigator initiated trial. Ten patients with active refractory and relapsing EGPA (as defined by Birmingham vasculitis activity score (BVAS) > 3) were given nine infusions of IV 750 mg mepolizumab every 4 weeks after stopping immunosuppressant therapy. After the nine infusions were completed, patients were then placed on methotrexate 0.3 mg kg^{-1} weekly and a tapered dose of glucocorticoid as tolerated. Eight out of the ten patients reached the primary endpoint of remission by week 32, a BVAS of 0, and a glucocorticoid dose of 7.5 mg day^{-1} or less. Remission occurred after two or three treatments. One patient did not see a reduction of glucocorticoid below 7.5 mg daily but had a BVAS score of 0. There was no relapse of active disease while on treatment with mepolizumab. There was a decrease in the median dose of glucocorticoid from 19 mg day^{-1} at baseline to 4 mg day^{-1} at week 32 ($p = 0.006$). Eosinophil counts rapidly decreased after the first mepolizumab infusion and remained near 0 until end of active treatment. A total of seven relapses occurred after switching to methotrexate and glucocorticoid for maintenance. There were two severe adverse events that were thought to not be due to mepolizumab.

There were 11 adverse events that were thought to be related to mepolizumab.

Hermann et al. present a follow-up of patients enrolled in the study described by Moosig et al., highlighting not only the potential of mepolizumab to induce and maintain remission but also as an agent that should be used regularly to prevent further disease relapse and dependence on steroid [31]. In the original study, ten patients with refractory or relapsing EGPA were given nine treatments with IV 750 mg mepolizumab and then switched to methotrexate 0.3 mg kg^{-1} for maintenance in an uncontrolled, single-center, phase 2 trial [30]. Patients were followed up for a median of 22 months, and the study aimed to find correlations between eosinophil cationic protein (ECP) and BVAS. There were an additional two major relapses and two minor relapses that occurred during this follow-up period. The mean eosinophil count rose after stopping anti-IL-5 medication and six of the nine patients had an increase in glucocorticoid steroid use above 7.5 mg day^{-1}. There was correlation between BVAS and ECP that was significant along with correlations between ECP and eosinophil count and between BVAS and eosinophil count.

Another study discussing the potential of mepolizumab to decrease steroid dependence, prevent relapse, and induce sustained remission during treatment is by Weschler et al. [32]. This is a multicenter randomized, placebo-controlled, double-blind, parallel group, phase 3 trial of 136 patients with relapsing or refractory EGPA randomized to receive 300 mg subcutaneous mepolizumab or placebo every 4 weeks for 52 weeks. A total of 136 patients were enrolled with 68 patients in each group. The corticosteroid dose had to be stable between baseline and week 4 and could then be reduced thereafter as per investigators discretion. Participants on immunosuppressive therapy had to be on a stable dose prior to baseline. EGPA was defined as a history of asthma, blood eosinophil level of 10% or an AEC of more than 1000 cells mm^{-3}, and the presence of two or more criteria that are typical of EGPA. The baseline characteristics of the study population were similar. The trial met both of its primary endpoints. Time in remission was greater in the mepolizumab group (28%) compared with placebo (3%). A total of 46% of participants in the mepolizumab group compared with 81% of the placebo group did not reach remission. There was a significantly higher percentage of those in the mepolizumab group (32%) compared with placebo (3%) that attained remission between week 36 and week 48. There was clinical efficacy among the mepolizumab group (33%) compared with placebo (0%) for those patients with an AEC of 150 cells or greater mm^{-3} at baseline. Of those in the mepolizumab group 56% had relapse during the 52 weeks of the study compared with 82% in the placebo group. The annual relapse rate was 50% lower in the mepolizumab group compared with the placebo. Patients in the mepolizumab group had a significantly lower prednisone dose than placebo. A total of 12 participants (18%) in the mepolizumab group were able to discontinue prednisone use compared with 2 (3%) in the placebo group, and 30 participants (44%) in the mepolizumab group were able to taper glucocorticoid dose to 4.0 mg or less day^{-1} compared with 5 (7%) in the placebo group. Although the percentage of adverse events was similar between the two groups, there were 12 serious adverse events in the mepolizumab group compared with 18 in the placebo group, which was thought to be due to disease activity. The most commonly reported adverse events were headache, nasopharyngitis, arthralgia, and upper respiratory infection. Systemic reactions were infrequent but were seen in the mepolizumab group.

Future Studies of Anti-IL-5 Treatment and EGPA

At this time, there is an open-label study of reslizumab looking at efficacy and safety as well as steroid sparing effect in adults [33]. In this study, participants will be given a reslizumab dose of 3 mg kg^{-1} IV every 4 weeks for 28 weeks (seven treatments). The primary outcome of this study is documentation of safety and adverse events. The secondary outcome is to demonstrate steroid sparing effect by titrating corticosteroid dose. An open label study of benralizumab in EGPA looking at safety, steroid sparing effect in adults, as well as EGPA exacerbations has also been listed on clinicaltrials.gov [34]. Benralizumab has recently been granted orphan drug status by the FDA for use in EGPA.

Anti-IL-5 Treatments for Eosinophilic Esophagitis

Studies Using Mepolizumab

Stein et al. present a study of mepolizumab in the treatment of eosinophilic esophagitis demonstrating improvement in clinical symptoms, quality of life and endoscopic findings [22]. This was an open-label phase I/II trial of four patients with eosinophilic esophagitis receiving IV 10 mg kg^{-1} (maximum dose 750 mg) mepolizumab every 4 weeks for three consecutive treatments over a 28-week period. All patients enrolled in the study responded to anti-IL-5 therapy with a decrease in absolute eosinophil count ($p < 0.05$), decrease in CCR3+ cells ($p < 0.05$), and clinical improvement in symptoms such as dysphagia, food impaction, vomiting, abdominal pain, constipation, and inability to swallow. After treatment with anti-IL-5, patients reported improvement of overall quality of life, which was significant. There were also improved endoscopic findings for three out of the four patients with improvement in narrowing, strictures, rings, and furrows. There was a 14.6-fold decrease in the mean esophageal eosinophils on biopsy with resolution of micro-abscess seen in two out of four patients. There was no correlation between eotaxin-3 and IL-5 levels with response to treatment. The most common side effects were headache and upper respiratory tract infection.

One patient did have hypotension within 30 min of her third infusion.

Straumann et al. describe a randomized, double-blind, placebo-controlled study of 11 adult patients with eosinophilic esophagitis receiving 750 mg IV mepolizumab vs. placebo for two doses 1 week apart, followed by 1500 mg IV mepolizumab if not in remission [23]. Baseline characteristics for the groups were similar except that there were 80% males in the mepolizumab group compared with 50% in the placebo group. The primary endpoint of the study of < 5 eosinophils hpf^{-1} was not achieved. There was improvement in clinical symptoms for > 20% of the mepolizumab group. There were improvements in both peripheral blood eosinophil count and number of eosinophils per hpf in the mepolizumab group. Eosinophil derived neurotoxin was significantly less in the mepolizumab group as was TNFα and eotaxin-3 expression. There were only two adverse events in both groups, none were serious. Most common complaints were mild fatigue and upper respiratory tract infection. None the adverse events were attributed to the study drug.

In the study by Conus et al., 11 adults with active eosinophilic esophagitis (> 20 peak eosinophils hpf^{-1} and dysphagia) were randomized to receive IV 750 mg mepolizumab or placebo in this randomized, double-blind, placebo-controlled study [24]. Infusions were given at days 0 and 7, and if the patient did not achieve remission by 4 weeks, they received two more doses of mepolizumab IV 1500 mg. There was a higher proportion of men in the mepolizumab group (80%) compared with placebo (50%) at baseline. There was no difference in the mean IL-5Rα and mean number of eosinophils of duodenal tissue between mepolizumab and placebo. The number of IL-5Rα-positive cells was smaller compared with the number of eosinophilic cationic protein positive cells in both groups. The mean number of infiltrating mast cells and T cells did not change as a result of treatment group.

Assa'ad et al. present a study of 59 children with EE between the ages of 2 and 17 years were randomized in this multicenter, placebo-controlled double-blind study to receive either 0.55, 2.5, or 10 mg kg^{-1} IV mepolizumab every 4 weeks for three infusions and then followed up [25]. EE was defined as a baseline peak count of esophageal intraepithelial eosinophils of ≥ 20 in at least 1 hpf. The baseline peak and mean esophageal intraepithelial eosinophil counts were 122.5 ± 8.78 and 39.1 ± 3.63 hpf^{-1}. Four weeks after completing all three infusions, the peak eosinophil counts were < 5 hpf^{-1} in 5 of 57 children (8.8%). There was reduced peak and mean eosinophils counts < 20 hpf^{-1} in 18 of 57 (31.6%) and 51 of 57 (89.5%) of children. Peak and mean esophageal intraepithelial eosinophil counts were decreased significantly to 40.2 ± 5.17 and 9.3 ± 1.25 hpf^{-1}. At least 86.4% of patients reported ≥ 1 adverse event, the most frequent being gastrointestinal (vomiting, diarrhea, and abdominal pain). There were no dose-related adverse events. Three serious adverse events occurred, one which may have been due to the study drug. This was the first published anti-IL-5 trial in pediatric participants for eosinophilic esophagitis.

In the study by Otani et al., 43 biopsy specimens from EE subjects obtained from a previous double-blind placebo-controlled multicenter trial treating children between the ages of 2 and 17 with 0.55, 2.5, or 10 mg kg^{-1} mepolizumab monthly for 12 weeks was used to determine the number of mast cells, eosinophils and IL-9+ cells post-treatment [26]. Forty percent of subjects responded to anti-IL-5 (< 15 eosinophils hpf^{-1}), and 77% of all subjects had decreased numbers of mast cells after anti-IL-5 treatment. In biopsies of responders, mast cells decreased from 62 to 19 hpf^{-1} ($p < 0.001$). There was a decrease in the number of mast cell and eosinophil couplets after treatment with anti-IL-5 ($p < 0.001$). IL-9+ cell numbers decreased from 102 to 71 hpf^{-1} after anti-IL-5 treatment ($p < 0.001$).

Studies Using Reslizumab

In the study by Spergel et al., 227 pediatric patients between the ages of 5 and 17 years were randomized in a multicenter, placebo-controlled, double-blind study to receive reslizumab 1, 2, or 3 mg kg^{-1} compared with placebo for the treatment of EE [27]. The majority of enrolled patients was male and had a history of atopic disease. All patients had 24 or more esophageal eosinophils per hpf at baseline. The median number of eosinophils at baseline was 80 eosinophils hpf^{-1}. Dysphagia was the predominant symptom (43.4%) of patients, followed by abdominal/chest pain and vomiting/regurgitation at baseline. Over 83% of patient had some previous dietary restriction or food elimination diet. Peak esophageal eosinophil counts were reduced in the reslizumab group compared with baseline. The percent improvement in peak esophageal eosinophil count was greater in all three reslizumab groups compared with placebo. There was no significant difference in physician's eosinophilic esophagitis global assessment score when comparing treatment groups. More than 80% in 1 mg kg^{-1} group, 80.7% in 2 mg kg^{-1} group, 84.2% in 3 mg kg^{-1} group, and 75.4% in the placebo group maintained the same diet they had at the start of the study. Reslizumab was generally well tolerated with the most common adverse events being cough and headache. There were no differences between treatment and placebo for adverse events. There were some mild infusion site reactions. Five patients had one or more serious adverse events, but none were considered to be related to the study drug.

Anti-IL-5 Therapies in Eosinophilic Dermatitis

In a case series by Plotz et al., anti-IL-5 (mepolizumab) was used for the treatment of hypereosinophilic syndrome with eosinophilic dermatitis [37]. In case 1, a 60-year-old woman

with eosinophilic dermatitis for 5 years that initially manifested as erythematous centrally ulcerated nodules, angioedema, eczematous lesions, evolved into a diffuse erythroderma with severe pruritus, swelling, and tenseness. She also had mononeuropathy and thickening of the mitral valve leaflets. Her peripheral blood eosinophil count ranged from 15 to 41%, and bone marrow manifested numerous eosinophils. She had a serum IgE of 655 UI mL^{-1} and skin biopsy revealed dense eosinophilic infiltration of the dermis and subdermis. There was no evidence of clonal T or B cells or gene fusion of FIP1L1-PDGFRA. She did not respond to immunosuppressive treatment and was initiated on 750 mg of mepolizumab IV with a significant drop in percent of eosinophils after 1 day. After receiving a second infusion, her skin cleared and she no longer required treatment as she was symptom free for 17 months.

Case 2 is that of a 62-year-old woman with eosinophilic dermatitis associated with night sweats, dyspnea, low-grade fever, fatigue, and weight loss. Her IgE was 244 UI mL^{-1}, and skin and bone marrow biopsy contained many eosinophils. This patient also did not have any T or B cell clonality or gene fusion of FIP1L1-PDGFRA. Within 24 h of receiving mepolizumab, she had a dramatic decrease in the number of eosinophils, and after a second infusion of mepolizumab, her skin cleared. The patient remained symptom free on monthly infusions of mepolizumab.

Case 3 is an 82-year-old female with severe pruritus and eczematous skin lesions for 1 year with no other organ involvement. Her serum IgE was 710 UI mL^{-1} with skin and bone marrow biopsy demonstrating dense eosinophilic infiltration. This patient had an abnormal T cell population indicating possible clonal T cell disease. The patient was treated with 750 mg mepolizumab IV with dramatic improvement in eosinophil count and improved pruritus and eventual clearing of skin with further treatment.

Conclusion

This presentation of heterogeneous trials and clinical cases highlights some of the potential benefits of using anti-IL-5 therapies in eosinophilic diseases. Many of these studies demonstrated improving clinical symptoms, varying degrees of eosinophilia reduction in blood or tissue samples, remission of disease, and some degree of steroid dose reduction or elimination for a variety of eosinophilic diseases. The low risk and moderate benefit of anti-IL-5 therapies for eosinophilic diseases suggest that they will be an important therapeutic option for these disorders which cause significant end-organ damage, and for which non-biologic immunomodulatory therapies are associated with significant toxicities and side effects.

Eosinophilic diseases impact many organ systems and drastically affect morbidity, mortality, and quality of life of patients. Currently approved treatments used for eosinophilic diseases are not always effective in attaining or maintaining clinical remission or have wide ranging side effects which can be debilitating for patients and cause poor compliance. The first-line treatment of EGPA, HES, and eosinophilic esophagitis is corticosteroids. Chronic corticosteroid use is associated with osteoporosis, fractures, Cushing's syndrome, diabetes, hyperglycemia, psychosis, cataracts, glaucoma, infections, gastrointestinal bleeds, and poor wound healing [38]. Second-line agents for HES management include tyrosine kinase inhibitors, hydroxyurea, interferon α, and methotrexate. Other first-line agents in the treatment of EGPA include use of cyclophosphamide to induce remission and azathioprine and other agents like methotrexate, rituximab, mycophenolate mofetil, immunoglobulin G replacement, hydroxyurea, interferon α, and anti-IgE to maintain remission. Cyclophosphamide has been associated with hemorrhagic cystitis, alopecia, immunosuppression, and cardiotoxicity [39]. Addition of azathioprine to corticosteroids for the treatment of EGPA, microscopic polyangiitis, or polyarteritis nodosa did not improve remission rates or decrease treatment adverse effects compared with therapy with corticosteroids alone [40]. Currently, azathioprine has been associated with significant gastrointestinal symptoms including nausea and vomiting and hematologic toxicity such as leukopenia, thrombocytopenia, and anemia, along with an increased risk of malignancies. Hydroxyurea, which is a common second line agent in the treatment of HES, is associated with anemia, thrombocytopenia, neutropenia, GI disturbances, and fevers [41]. Remission is rarely achieved with hydroxyurea alone despite favorable cost and oral administration of drug. Interferon is costly, and due to its side-effect profile, is often discontinued by patients as a result of flulike symptoms, gastrointestinal complaints, myalgias, cytopenias, depression, and rare complications of autoimmune thyroiditis and retinopathy [41].

Drugs targeting other biologic pathways including those directed at IL-4, IL-13, Siglec-8, and dexpramipexole are being investigated for future therapeutic options in hypereosinophilic conditions. An anti-IL-13 drug, dupilumab or rpc4046, was studied in 99 adults with steroid refractory EE in a post hoc analysis of a previous trial [42]. Subjects were enrolled in a phase 2 randomized double-blind, placebo-controlled trial with subjects allocated to receive IV subcutaneous 180 mg dupilumab ($n = 14$), 360 mg dupilumab ($n = 17$), and placebo ($n = 16$) over a 16-week period with measurement of esophageal eosinophil count as primary endpoint. The secondary endpoint included a mean change from baseline to week 16 in EoE Endoscopic Reference Score (EREFS), improvements in dysphagia determined by the Daily Symptom Diary (DSD), Eosinophilic Esophagitis Activity Index (EEsAI) score, and EoE histology scoring system (EoEHSS) based on grade and stage. There was clinical significance in the treatment group with reduction in esophageal

eosinophil counts with 180 and 360 mg dupilumab compared with placebo. There was also clinical significance with histology scoring in treatment group when compared with placebo.

Another anti-IL-13 drug, dectrekumab or QAX576, was studied in EE. This was a 12-week randomized placebo-controlled trial of monthly infusions with a primary endpoint of percent of subjects with a greater than 75% decrease in endoscopic biopsy eosinophil count, which was not met. There was, however, a 60% decrease in eosinophil count when compared with placebo which produced a 23% decrease. There also were improvements in tissue eosinophil counts, mast cell counts, and markers of barrier function up to 6 months from administration of drug [43].

Dexpramipexole, a dopamine agonist used in the treatment of Parkinson's disease and restless leg syndrome, had been noted to cause sustained eosinopenia [44]. As an oral agent, there is interest in how this may contribute to treatment of hypereosinophilic diseases; therefore, there are ongoing clinical trials with this drug. The exact mechanism of how eosinophils are impacted is unknown, but it is believed to affect the bone marrow. In a nonrandomized study of ten patients with HES, patients were treated with 150 mg twice daily of dexpramipexole [45]. The primary endpoints were the proportion of patients whose minimum effective glucocorticoid dose needed to maintain an absolute eosinophil count of less than 1000 mL^{-1} and control symptoms was reduced by greater than 50% after 12 weeks of treatment. Four out of the ten subjects achieved the primary endpoint, with a 66% median minimum effective glucocorticoid dose usage from baseline. There were no adverse events and biopsy of tissue in two subjects showed normalization of pathology and depletion of eosinophils. Bone marrow biopsy in responders showed absence of mature eosinophils.

Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) is an inhibitory receptor that is expressed on mature eosinophils, mast cells, and basophils. In murine models, antibody to Siglec-F reduces blood and tissue eosinophils. Anti-Siglec-8 antibody induces apoptosis of human eosinophils. Costimulation of eosinophils with IL-5 and IL-33 demonstrated enhanced Siglec-8-induced apoptosis of eosinophils [46]. There is currently an ongoing placebo-controlled, phase 2 trial to investigate the efficacy of anti-Siglec-8 in eosinophilic gastritis and eosinophilic gastroenteritis, with change in number of eosinophils per hpf in gastric and/or duodenal biopsies as the primary endpoint, and change in patient-reported symptom score as the secondary endpoint [47].

Understanding the underlying immune mechanism(s) for eosinophilic inflammation in different eosinophilic diseases will drive innovation for novel therapies and insight into disease etiology. Eosinophilic diseases are heterogeneous and a focus on single therapeutic agents may not be the answer we need to provide effective treatments. Future trials of multiple biologic therapies given independently and concomitantly to treat eosinophilic disorders with or without comorbid atopic conditions may determine if multiple biologic therapy can achieve efficacy in those patients where monotherapy fails.

Compliance with Ethical Standards

Conflict of Interest Author Aasha Harish, MD, MPH declares that she does not have any conflict of interest. Author Stanley Schwartz, MD, PhD received a speaker honorarium from Takeda Pharmaceutical Co and CSL Behring and owns stock in Pfizer Pharmaceutical Co and Merck Pharmaceutical Co.

Research with animals and human subjects: This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. Woodruff PG, Modrek B et al (2009) T-helper type 2 driven inflammation defines major subphenotypes of asthma. Am J Crit Care Med 180:388–395
2. De Ferrari I, Chiappori A et al (2016) Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma? Expert Rev Respir Med 10:9–38
3. Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, Young IG (1996) Interleukin 5 deficiency abolishes eosinophilia, airways hyperactivity, and lung damage in a mouse asthma model. J Exp Med 183(1): 195–201
4. Shi HZ, Xiao CQ, Zhong D, Qin SM, Liu Y, Liang GR, Xu H, Chen YQ, Long XM, Xie ZF (1998) Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. Am J Respir Crit Care Med 157(1):204–209
5. Abonia JP, Putnam PE (2001) Mepolizumab in eosinophilic disorders. Expert Rev Clin Immunol 74(4):411–417
6. Bagnasco D, Ferrando M, Varrichi G et al (2017) Anti-interleukin 5 (IL-5) and IL-5Ra biological drugs: efficacy, safety, future perspectives in severe eosinophilic asthma. Frontiers in Medicine 4:1–10
7. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R et al (2013) Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 132(5):1086–96.e5
8. Kolbeck R, Kozhich A, Koike M, Peng L et al (2010) MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 125:1344–1353
9. Ghazi A, Trikha A, Calhoun WJ (2011) Benralizumab—a humanized mAb to IL-5Rα with enhanced antibody-dependent cell-mediated cytotoxicity—a novel approach for the treatment of asthma. Expert Opin Biol Ther 12(1):113–118
10. Legrand F, Klion A (2015) Biologic therapies targeting eosinophils: current status and future prospects. J Allergy Clin Immunol: In Practice 3(2):167–174
11. Velent P, Klion AD et al (2012) Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol 130(3):607
12. Mouthon L, Donogue B et al (2014) Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named as Churg Strauss syndrome). J Autoimmun 48-49:99–103
13. Masi AT, Hunder GG et al (1990) The American College of Rheumatology 1990 criteria for the classification of Churg-

Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 33(8):1094
14. Rothenburg ME et al (2008) Treatment of patients with hypereosinophilic syndrome with mepolizumab. N Engl J Med 358(12):1215–1228
15. Roufosse F, de Lavareille A, Schandené L, Cogan E, Georgelas A, Wagner L, Xi L, Raffeld M, Goldman M, Gleich GJ, Klion A (2010) Mepolizumab as a corticosteroid sparing agent in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol 126(4):828–835
16. Roufosse FE et al (2013) Long-term safety mepolizumab for treatment of hypereosinophilic syndrome. J Allergy Clin Immunol 131(2):461–467
17. Stein ML, Villanueva JM, Buckmeier BK et al (2008) Anti-IL-5 (mepolizumab) therapy reduces eosinophil activation ex vivo and increases IL-5 and IL-5 receptor levels. J Allergy Clin Immunol 121(6):1473–1483
18. Mehr S, Rego S, Kakakios A, Kilham H, Kemp A (2009) Treatment of a case of pediatric hypereosinophilic syndrome with anti-IL-5. J Pediatr 155(2):289–291
19. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). July 19, 2016. Identifier NCT02836496. Study 200622: a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome
20. Klion AD, Law MA, Noel P, Kim YJ, Haverty TP, Nutman TB (2004) Safety and efficacy of monoclonal IL-5 ab SCH55700 in treatment of patients with hypereosinophilic syndrome. Blood 103(8):2939–2941
21. Kuang et al (2019) Benralizumab for PDGFRA-negative hypereosinophilic syndrome. N Engl J Med 380:1336–1346
22. Stein M, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, Filipovich AH, Assa'ad AH, Rothenberg ME (2006) Anti IL-5 (mepolizumab) therapy for eosinophilic esophagitis. J Allergy Clin Immunol 118(6):1312–1319
23. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU (2010) Anti-interleukin 5 antibody treatment (mepolizumab) in active eosinophilic esophagitis: a randomized placebo-controlled double blind trial. Gut 59(1):21–30
24. Conus S, Straumann A, Bettler E, Simon HU (2010) Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis. J Allergy Clin Immunol 126(1):175–177
25. Assa'ad AH et al (2011) An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 141(5):1593–15604
26. Otani M et al (2013) Anti-IL-5 therapy rescues mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol 131(6):1576–1582
27. Spergel JM et al (2012) Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double blind randomized placebo-controlled trial. J Allergy Clin Immunol 129(2):4
28. Kahn JE, Grandpeix-Guyodo C, Marroun I, Catherinot E, Mellot F, Roufosse F, Blétry O (2010) Sustained response to mepolizumab in refractory Churg Strauss syndrome. J Allergy Clin Immunol 125(1):267–270
29. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME (2010) Mepolizumab as steroid sparing treatment option in patient with Churg Strauss syndrome. J Allergy Clin Immunol 125(6):1336–1343
30. Moosig F, Gross WL, Herrmann K, Bremer JP, Hellmich B (2011) Targeting interleukin 5 in refractory and relapsing Churg Strauss syndrome. Ann Intern Med 155(5):341–343
31. Hermann K et al (2012) Extended follow-up after stopping mepolizumab in relapsing/refractory Churg Strauss syndrome. Clin Exp Rheumatol 20(1 supp 70):s62–s65
32. Weschler ME et al (2017) Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 376(20):1921–1932
33. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 October 28. Identifier NCT02947945. Reslizumab in the treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) Study
34. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 January 5. Identifier NCT03020436. Benralizumab in the treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) Study
35. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, American College of Gastroenterology (2013) ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 108(5):679–92; quiz 693
36. Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, Beck LA, Boyce JA, Filipovich AH, Villanueva JM, Sutton SA, Assa'ad AH, Rothenberg ME (2004) Anti-interleukin 5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 113(1):115–119
37. Plotz SG et al (2003) Use of anti-IL-5 ab in Hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med 349(24):2334–2339
38. Volmer T et al (2018) Consequences of long term oral corticosteroid therapy and its side-effect in severe asthma in adults: a focused review of the impact data in the literature. Eur Respir J 52(4):1800703
39. Fraiser LH, Kanekal S, Kehrer JP (1991) Cyclophosphamide toxicity. Drugs 42(5):781–795
40. Puéchal X et al (2017) Adding azathioprine to remission-induction glucocorticoids for eosinophilic granulomatosis with polyangiitis (Churg-Strauss), microscopic polyangiitis, or polyarteritis nodosa without poor prognosis factors: a randomized. Control Trial Arthritis Rheumatolol 69(11):2175–2186
41. Klion AD (2007) Approach to the therapy of Hypereosinophilic syndrome. Immunol Allergy Clin N Am 27(3):551–560
42. Dellon ES et al (2018) Efficacy and Safety of Rpc4046, an anti-interleukin 13 monoclonal antibody, in patients with active eosinophilic esophagitis: analysis of the steroid refractory subgroup from the heroes study. Gastroenterology 154(6):S244
43. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, Nadeau K, Kaiser S, Peters T, Perez A, Jones I, Arm JP, Strieter RM, Sabo R, Gunawardena KA (2015) Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 135(2):500–507
44. Gleich GJ (2018) Dexpramipexole: a new antieosinophil drug? Blood 132(5):461–462
45. Panch SR, Bozik ME, Brown T, Makiya M, Prussin C, Archibald DG, Hebrank GT, Sullivan M, Sun X, Wetzler L, Ware J, Fay MP, Dunbar CE, Dworetzky SI, Khoury P, Maric I, Klion AD (2018) Dexpramipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. Blood 132(5):501–509
46. Legrand F, Klion A (2015) Biologic therapies targeting Eosinophils: current status and future prospects. J Allergy Clin Immunol: In Practice 3(2):167–174
47. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 April 12. Identifier NCT03496571. A phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacodynamic effect of AK002 in patients with eosinophilic gastritis and/or eosinophilic gastroenteritis