Current and emerging biologic therapies targeting eosinophilic disorders

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ABSTRACT

Eosinophilic disorders include a wide array of conditions in which eosinophils play a primary pathophysiologic role. While historically treated with corticosteroids and immunosuppressants, knowledge of eosinophil biology has led to the development of several biologics targeting eosinophils. In this review, we discuss the current US Food and Drug Administration (FDA) approved eosinophil-specific biologics targeting IL-5 (mepolizumab and reslizumab) and IL-5R (benralizumab) along with biologics under investigation targeting siglec-8 (lirentelimab). We discuss efficacy and safety data from trials of these medications in conditions including eosinophilic asthma, hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis (EoE), and eosinophilic gastrointestinal disease (EGID). Additionally, we discuss case reports utilizing these medications in conditions including drug reaction with eosinophilia and systemic symptoms (DRESS), allergic bronchopulmonary aspergillosis (ABPA), and eosinophilic pneumonia, among others. While eosinophil targeting biologic therapy has been successful in eosinophilic asthma, HES, EGPA, and CRSwNP leading to FDA approval for these conditions, trials treating EoE and EGID have been disappointing to date. Given the increasing number of trials utilizing these biologics, it will be imperative for the allergist-immunologist to stay up to date on the latest treatment options to provide the most optimal care for eosinophilic disorders.

Keywords: Eosinophil, Biologics, Interleukin 5, Treatment, Siglec-8

INTRODUCTION

Eosinophils are bone-marrow derived, multifunctional leukocytes that initiate and propagate diverse inflammatory pathways, modulate innate and adaptive immune processes, and serve as major effector cells producing tissue injury and dysfunction through release of toxic granule proteins and lipid mediators.1 Eosinophilic disorders encompass a wide variety of conditions in which eosinophils have a primary pathophysiologic role. They may affect any body compartment and organ, including the upper and lower airways, skin, connective tissues, gastrointestinal tract, and the hematopoietic, immune, cardiovascular, and nervous systems.2 Common eosinophilic disorders include eosinophilic asthma, hypereosinophilic syndrome (HES), chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic esophagitis (EoE), and eosinophilic gastrointestinal disease (EGID), among others.2 These have been...
historically treated with corticosteroids and immunosuppressants, which are often, but not always, effective at reducing eosinophil counts and associated eosinophilic inflammation. However, these medications have long-term side effects that often limit dosing and efficacy. Capitalizing on knowledge regarding eosinophil cell biology has led to a remarkable increase in the development of eosinophil-specific therapies.

EOSINOPHIL BIOLOGY AND THERAPEUTIC STRATEGIES

Interleukin-5 (IL-5) is essential to the eosinophil life cycle, stimulating the proliferation, differentiation, and maturation of eosinophil precursors. Additionally, IL-5 plays a role in the exit of eosinophils from the bone marrow into the bloodstream, serves as a chemotactic factor, and prolongs eosinophil survival in tissue. The IL-5 receptor (IL-5R) is selectively expressed on eosinophils, basophils, and mast cells. Thus, therapies targeting IL-5 or its receptor represent a reasonably specific way to target eosinophils in eosinophilic disorders.

Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) is an inhibitory cell surface receptor expressed selectively on mature eosinophils and mast cells (and basophils to a lesser degree), which, when engaged, causes cells to undergo natural killer (NK) cell mediated, antibody dependent cellular cytotoxicity (ADCC). The restricted expression of Siglec-8 on eosinophils and subsequent cell death that occurs upon its engagement makes therapeutics targeting Siglec-8 an attractive prospect.

Based on this knowledge, several biologic medications have been developed that target IL-5, IL-5R, and Siglec-8 (Fig. 1). Key information regarding each of these medications is presented in Table 1. Mepolizumab and reslizumab are fully humanized, IgG1 and IgG4, respectively, antibodies that target IL-5 with high affinity and specificity. Benralizumab is a fully humanized, afucosylated IgG1 antibody that targets the IL-5Rα chain, which prevents the binding of IL-5. Unique to benralizumab, compared to other anti-IL-5 therapies, is its ability to induce ADCC with resultant eosinophil death and tissue depletion. Lirentelimab is a humanized, nonfucosylated IgG1 antibody that targets Siglec-8 and depletes eosinophils in the blood via NK cell mediated ADCC and in the tissue via apoptosis.
This review will address relevant trials investigating use of biologics targeting IL-5 and Siglec-8 in eosinophilic disorders. Tables 2–4 summarize details of the trials being discussed.

**ASTHMA**

Asthma is a heterogeneous condition characterized by multiple endotypes, each with its own nuances in pathophysiology and treatment. Eosinophilic asthma represents the largest endotype, accounting for 50–60% of all cases. All 3 currently available anti-IL-5 biologics are approved by the US Food and Drug Administration (FDA) for use in severe eosinophilic asthma.

**Mepolizumab**

**Efficacy**

Three trials established the efficacy of mepolizumab in asthma: DREAM, SIRIUS, and MENSA. DREAM randomized 621 patients ages 12–74 with severe eosinophilic asthma (defined as requiring 800 μg of inhaled fluticasone or its equivalent with at least 2 exacerbations in the prior year along with any of the following: sputum eosinophilia >3%, absolute eosinophil count (AEC) > 300/μl, or fraction of exhaled nitric oxide (FeNO) > 50 ppb) to receive placebo or 75, 250, or 750 mg intravenous (IV) mepolizumab monthly for 13 months. All mepolizumab groups met the primary endpoint of reduction in rate of clinically significant exacerbations (48%, 39%, and 52% reductions in the 75, 250, and 750 mg groups, respectively) with a significant increase in the time to first exacerbation. SIRIUS randomized 135 patients ages 16–74 with severe eosinophilic asthma (defined as requiring both high dose inhaled corticosteroid (ICS) and oral corticosteroid (OCS) with an AEC >300/μl in the year before screening or >150/μl during the 8 week optimization phase) to receive 100 mg subcutaneous (SC) mepolizumab monthly for 20
| Author          | Year | Study design | Study population                                                                 | Drug     | Dose                          | Primary outcome                                                                 | Secondary outcome                                                                 |
|-----------------|------|--------------|----------------------------------------------------------------------------------|----------|-------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Pavord\(^a\)\(\) (DREAM) | 2012 | Multicenter  | 621 patients age 12–74 with SEA (sputum eosinophil >3%, FeNO ≥50 ppb, or AEC >300/μl) with 2 exacerbations in last year on 800 μg inhaled fluticasone or equivalent plus additional controller medication | Mepolizumab | 75, 250, or 750 IV every 4 weeks for 52 weeks | - Exacerbation rate                                                              | - Rate of exacerbations requiring hospitalization - ER visits - Sputum eosinophil count - AEC - FEV1 - AQLQ - ACQ-5 |
| Bel\(^b\)\(\) (SIRIUS) | 2014 | Multicenter  | 135 patients age 16–74 with SEA (AEC >300/μl in 12 months prior to screening or >150/μl during optimization phase) on high dose ICS + other controller medication and 5–35 mg prednisone for at least 6 months | Mepolizumab | 100 mg SC every 4 weeks for 20 weeks | - Degree of prednisone dose reduction - Lack of asthma control during weeks 20–24 - Study withdrawal | - Proportion with >50% prednisone dose reduction - Proportion with prednisone dose ≤5 mg - Proportion with complete prednisone cessation - Exacerbation rate - ACQ-5 - SGRQ - FEV1 - Safety |
| Ortega\(^c\)\(\) (MENSA) | 2014 | Phase 3      | 576 patients age 12–82 with SEA (same definition as SIRIUS) who had ≥2 exacerbations in last year while receiving 880 μg inhaled fluticasone or equivalent plus another controller medication | Mepolizumab | 75 IV or 100 mg SC every 4 weeks for 32 weeks | - Annualized rate of exacerbation                                               | - FEV1 - ACQ-5 - SGRQ - Adverse events                                          |
| Study          | Year | Design          | Population Details                                                                                                                                                                                                 | Intervention                                                                 | Outcomes                                                                 | Additional Details                                                                 |
|---------------|------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Castro        | 2015 | Phase 3 multicenter RDBPC | 953 patients age 12–75 with uncontrolled SEA (AEC > 400/μl) with ACQ ≥ 1.5 on at least medium dose ICS with an exacerbation in past month                                                                      | Reslizumab 3 mg/kg IV every 4 weeks for 52 weeks                             | Annual exacerbation rate                                                    | Time to first exacerbation, FEV1, ACQ-7, ASUI, AQLQ at weeks 16, 32, and 52, SABA use, AEC |
| Corren        | 2016 | Phase 3 multicenter RDBPC | 492 patients age 18–65 with uncontrolled asthma (same definitions as Castro, but did not recruit only eosinophilic patients)                                                                 | Reslizumab 3 mg/kg IV every 4 weeks for 16 weeks                            | FEV1                                                                      | FVC, SABA use, ACQ-7                                                                 |
| Bjermer       | 2016 | Phase 3 multicenter RDBPC | 315 patients age 12–75 with uncontrolled SEA (same definitions as Castro) on at least medium dose ICS but no OCS                                                                                                       | Reslizumab 0.3 or 3.0 mg/kg IV every 4 weeks for 16 weeks                  | FEV1                                                                      | FVC, FEF25-75, ACQ, ASUI, AQLQ, SABA use, AEC, Safety                           |
| Bleecker      | 2016 | Phase 3 multicenter RDBPC | 1205 patients age 12–75 with asthma ≥ 2 exacerbations in last year while on high dose ICS + LABA and ACQ-6 ≥ 1.5                                                                                                       | Benralizumab 30 mg SC every 4 weeks for 48 weeks - 30 mg every 4 weeks for 12 weeks, then every 8 weeks | Annual exacerbation rate ratio                                              | FEV1 at week 48, Total asthma symptom score at week 48, Time to first exacerbation, Annual rate of exacerbations (continued) |
| Author          | Year | Study design            | Study population                                                                 | Drug       | Dose                        | Primary outcome                                                                 | Secondary outcome                                                                 |
|-----------------|------|-------------------------|----------------------------------------------------------------------------------|------------|-----------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Fitzgerald²⁹ (CALIMA) | 2016 | Phase 3 multicenter RDBPC | - 1306 patients with same criteria as SIROCCO, except patients on medium dose ICS were eligible | Benralizumab | Same as SIROCCO, except 52 weeks total | - Same as SIROCCO                                                                 | - Same as SIROCCO                                                                 |
| NAIR³⁰ (ZONDA)  | 2017 | - 220 patients age 18–75 with asthma on either medium dose ICS + LABA for 12 months OR high dose ICS + LABA for 6 months, requiring prednisone 7.5–40 mg for at least 6 months, and AEC >150/µl | Benralizumab | Same as SIROCCO/ CALIMA for 28 weeks | - % change in prednisone dose at week 28 | - Annual exacerbation rates                                                   | - FEV1                                                                         |
|                 |      |                         |                                                                                  |            |                             | - Total asthma symptom core                                                        | - Safety                                                                         |
|                 |      |                         |                                                                                  |            |                             | - % with prednisone reduction of ≥25%, ≥50%, and 100%                        | - % with prednisone dose ≤5 mg                                                    |
|                 |      |                         |                                                                                  |            |                             | - Time to first exacerbation                                                      | - % with exacerbation requiring ER visit or hospitalization                      |

Table 2. Relevant clinical trials in asthma. Abbreviations: RDBPC, randomized double-blind placebo-controlled; SABA, short acting beta agonist; AHR, airway hyperresponsiveness; AEC, absolute eosinophil count; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; BAL, bronchoalveolar lavage; MBP, major basic protein; AQLQ, Asthma Quality of Life Questionnaire; SEA, severe eosinophilic asthma; ICS, inhaled corticosteroid; ACQ, Asthma Control Questionnaire; OCS, oral corticosteroid; FeNO, Fraction of exhaled nitric oxide; ppb, parts per billion; SC, subcutaneous; SGRQ, St. George respiratory questionnaire; ASUI, asthma symptom utility index; FEF25-75, forced expiratory flow at 25–75% of forced vital capacity; FVC, forced vital capacity; RDB, randomized double-blind; LABA, long acting beta agonist; AQLQ(S)+12, Asthma quality of life questionnaire, standardized, age 12+; ER, emergency room; IV, intravenous. *Two separate trials published as one paper
weeks or placebo.\textsuperscript{17} Primary outcomes included the degree of daily OCS dose reduction, lack of asthma control during weeks 20-24, and study withdrawal.\textsuperscript{17} There was a 50% median reduction in OCS dose in the mepolizumab group compared to 0% in the placebo group and a significantly lower number in the mepolizumab group who had no dose reduction, lack of asthma control, or withdrew from the study.\textsuperscript{17} Annualized exacerbation rate, a secondary endpoint, was reduced 32% in the mepolizumab group relative to the placebo group.\textsuperscript{17} MENSA randomized 576 patients ages 12-82 with severe eosinophilic asthma to receive 75 mg IV or 100 mg SC mepolizumab or placebo monthly for 32 weeks.\textsuperscript{18} The primary outcome (annualized exacerbation rate) was significantly reduced by 47% in the IV and 53% in the SC groups compared to placebo.\textsuperscript{18} Additionally, both groups showed statistically significant improvement in St. George Respiratory Questionnaire (SGRQ) and Asthma Control Questionnaire (ACQ-5) scores.\textsuperscript{18} None of these trials demonstrated statistically significant improvement in measures of airflow obstruction.\textsuperscript{17-19} A subsequent combined post hoc analysis of MENSA and DREAM published in 2016 showed that the magnitude of exacerbation rate reduction was associated with the degree of peripheral eosinophilia, with a 52% reduction in patients with an AEC >150/\mu\text{L} compared to a 70% reduction in patients with an AEC >500/\mu\text{L}.\textsuperscript{20} Importantly, there was decreased efficacy of mepolizumab in patients with an AEC <150/\mu\text{L}.\textsuperscript{20} Open-label extensions of MENSA and SIRIUS (COSMOS and COSMEX) showed that clinical response was durable with patients maintaining their exacerbation rate and OCS dose reductions throughout the extension.\textsuperscript{21,22}

An additional non-randomized trial investigated SC mepolizumab use in 36 children ages 6-11 with severe eosinophilic asthma at a dose of either 40 mg (if weight <40 kg) or 100 mg.\textsuperscript{23} Both groups showed trends toward exacerbation rate reduction and improvement in symptom scores.\textsuperscript{23}

Safety

There was no significant difference in adverse events between placebo or treatment groups in MENSA, SIRIUS, or DREAM.\textsuperscript{17-19} Long-term safety of mepolizumab was established by COSMOS and COSMEX.\textsuperscript{21,22} Nasopharyngitis was the most commonly reported adverse effect, occurring in 30-42% of patients.\textsuperscript{21,22} Serious adverse effects occurred in 14-28% of patients with worsening or exacerbation of asthma being most common (6-10%).\textsuperscript{21,22} Systemic and local injection site reactions occurred in 2% and 4% of patients, respectively, but there were no reports of anaphylaxis or fatal adverse events.\textsuperscript{21,22} Similarly, the aforementioned pediatric trial and a subsequent open label extension showed no treatment related severe or fatal adverse effects, with minor adverse effects of headache and nasopharyngitis being among the most common.\textsuperscript{23,24}

Clinical indications and dosing

These trials led to the 2015 FDA approval of mepolizumab for add-on therapy in patients age 12 or older with severe asthma at a dose of 100 mg SC monthly. In 2019, mepolizumab received FDA approval for the same indication in patients age 6-11 at a dose of 40 mg SC monthly.

Reslizumab

Efficacy

Four trials established the efficacy of reslizumab in the treatment of asthma. Castro and colleagues performed 2 separate trials randomizing a total of 953 patients ages 12-75 with uncontrolled eosinophilic asthma (defined as use of medium dose ICS with an OCS requiring exacerbation in the last month, an ACQ-7 of \(>1.5\), and an AEC \(>400/\mu\text{L}\) to receive 3 mg/kg IV reslizumab or placebo monthly for 1 year.\textsuperscript{25} The primary outcome of annual exacerbation rate was significantly reduced in both studies with rate ratios of 0.5 and 0.41.\textsuperscript{25} The probability of not having an exacerbation was significantly higher in the reslizumab groups (61%, 73%) compared to placebo (44%, 52%).\textsuperscript{25} Additionally, the time to first exacerbation was significantly increased in both studies, and there were significant improvements in FEV1 and a variety of symptom scores that were seen as soon as week 16 and sustained through week 52.\textsuperscript{25} A third trial randomized 492 patients ages 18-65 with uncontrolled asthma to receive 3 mg/kg IV reslizumab monthly for 4 months, but a key difference was their enrollment of patients regardless of AEC.\textsuperscript{26} The primary endpoint was change in FEV1 with secondary endpoints
| Author          | Year | Study design | Condition | Study population                                                                 | Drug          | Dose                                      | Primary outcome                                                                                      | Secondary outcome                                                                                       |
|-----------------|------|--------------|-----------|----------------------------------------------------------------------------------|---------------|------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Rothenberg      | 2008 | Multicenter RDBPC | HES      | 85 patients with PDGFR negative HES (defined as AEC >1500/μl for ≥6 months with organ involvement and no secondary cause requiring 20-60 mg prednisone) | Mepolizumab | 750 IV every 4 weeks for 32 weeks        | Reduction of prednisone dose to ≤10 mg for ≥8 consecutive weeks                                       | AEC <600/μL ≥8 consecutive weeks; Time to treatment failure; Prednisone dose <7.5 mg; No prednisone use for 1+ days; Mean prednisone dose at week 36; Prednisone dose ≤10 mg by week 20 AND for ≥8 consecutive weeks |
| Roufosse        | 2020 | Phase 3 multicenter RDBPC | HES      | 108 patients age 12+ with PDGFR negative HES with ≥2 flares in previous year with AEC >1000/μl | Mepolizumab | 300 mg SC every 4 weeks for 32 weeks | Proportion who had flare; Flare definition: 1) HES related clinical manifestation with increase in prednisone by ≥ 10 mg for 5 days or any increase/addition of additional HES therapy 2) Receipt of ≥2 blinded steroid courses given if AEC increased above pre-defined level | Time to first flare; Proportion with flare during weeks 20-32; Annualized rate of flares; Change in fatigue severity (BFI score) at week 32 |
| Study | Year | Design | Eosinophilic Condition | Treatments | Outcomes |
|-------|------|--------|------------------------|------------|----------|
| Kuang 42 | 2019 | Phase 2 single center trial | HES | Benralizumab | - 20 patients with symptomatic PDGFRA negative HES and AEC >1000-μl | - % of patients with 50% reduction in AEC at week 12 |
| | | | | | - 30 mg SC every 4 weeks for 12 weeks |
| | | | | | - At week 12 all patients received 30 mg SC every 4 weeks |
| | | | | | - At week 24 patients with clinical or laboratory response could continue benralizumab |
| | | | | | - Reduction in AEC at 12 weeks |
| | | | | | - Adverse events |
| | | | | | - Changes in bone marrow and tissue eosinophilia |
| | | | | | - Reductions in concomitant therapy at week 48 |
| Wechsler 45 | 2017 | Phase 3 multicenter RDBPC | EGPA | Mepolizumab | - 136 patients age 18+ with relapsing or refractory EGPA on 7.5–50 mg prednisone at stable dose | - Accrued weeks of remission (BVAS 0 plus ≤4 mg prednisone) over 52 weeks |
| | | | | | - Proportion of patients in remission at weeks 36 and 48 |
| | | | | | - Time to first relapse |
| | | | | | - Average prednisone dose during weeks 48–52 |
| | | | | | - Proportion of patients with remission within first 24 weeks |
| Han 49 (SYNAPSE) | 2021 | Phase 3 multicenter RDBPC | CRSwNP | Mepolizumab | - 407 patients with severe bilateral nasal polyposis | - 100 mg SC every 4 weeks for 52 weeks |
| | | | | | - All patients treated with intranasal mometasone |
| | | | | | - Total endoscopic nasal polyp score at week 52 |
| | | | | | - Nasal obstruction VAS score during weeks 49–52 |
| | | | | | - % requiring surgery |
| | | | | | - Overall VAS score during weeks 49–52 |
| | | | | | - SNOT-22 at week 52 |
| | | | | | - % needing systemic steroids |
| | | | | | - Anosmia at weeks 49–52 |
| | | | | | - Composite VAS score at weeks 49–52 |
| | | | | | - Reduction in AEC at 12 weeks |
| | | | | | - Adverse events |
| | | | | | - Changes in bone marrow and tissue eosinophilia |
| | | | | | - Reductions in concomitant therapy at week 48 |
| Author     | Year | Study design          | Condition | Study population                                           | Drug            | Dose                          | Primary outcome                                           | Secondary outcome                                      |
|------------|------|-----------------------|-----------|------------------------------------------------------------|-----------------|-------------------------------|-----------------------------------------------------------|----------------------------------------------------------|
| Bachert    | 2021 | Phase 3 multicenter   | CRSwNP    | 413 patients with severe bilateral nasal polyposis        | Benralizumab    | 30 mg SC every 4 weeks for 12 weeks then every 8 weeks for 48 weeks total | Total endoscopic nasal polyp score at week 40             | SNOT-22 at weeks 40 and 56 |
| (OSTRO)    |      | RDBPC                 |           |                                                            |                 |                               | Nasal obstruction VAS score at week 40                    | Time to first surgery                                   |

**Table 3. (Continued)** Relevant clinical trials in HES, EGPA, and CRSwNP. Abbreviations: HES, hypereosinophilic syndrome; PDGFRA, platelet derived growth factor A; AEC, absolute eosinophil count; FEV1, forced expiratory volume in 1 s; RDBPC, randomized double-blind placebo controlled; CUP, compassionate use protocol; SC, subcutaneous; BFI, Big Five Inventory; EGPA, eosinophilic granulomatosis with polyangiitis; CBC, complete blood count; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; FeNO, fraction of exhaled nitric oxide; ACQ, Asthma Control Questionnaire; BVAS, Birmingham Vasculitis Activity; CRSwNP, chronic rhinosinusitis with nasal polyposis; PIF, peak inspiratory flow; AEC, absolute eosinophil count; VAS, visual analog scale; SNOT-22, Sino-Nasal Outcome Test 22; PFT, pulmonary function test; SC, subcutaneous; DSS, Difficulty with Sense of Smell; IV, intravenous Score; AQLQ, Asthma Quality of Life Questionnaire; SNOT-22, Sino-Nasal Outcome Test 22.
| Author   | Year | Study design | Condition | Study population                                                                 | Drug            | Dose                                                                 | Primary outcome                                                                 | Secondary outcome                                                                 |
|----------|------|--------------|-----------|-----------------------------------------------------------------------------------|-----------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Assa’ad  | 2011 | Multicenter  | EoE       | 59 children age 2-17 with EoE refractory to medical therapy                        | Mepolizumab     | - 0.55 mg/kg every 4 weeks - 2.5 mg/kg every 4 weeks - 10 mg/kg every 4 weeks | - Proportion of patients with esophageal eosinophil count <5/hpf at week 12 - Safety, tolerability, pharmacokinetics | - Changes in peak and mean intraepithelial eosinophil counts - Improvement in histopathological and endoscopic findings - AEC - Frequency and severity of symptoms |
| Spergel  | 2012 | Multicenter  | EoE       | 227 patients age 5-18 with moderate EoE                                           | Reslizumab      | - 1-3 mg/kg every 4 weeks for 16 weeks                               | - % change in peak esophageal eosinophil count - Change in physician’s EoE global assessment score | - Patient’s EoE predominant symptoms - CHQ |
| Dellon   | 2020 | Phase 2      | EGID      | 65 patients age 18-80 with eosinophilic gastritis/duodenitis inadequately controlled with medication or dietary modification | Lirentelimab    | - High dose: 0.3, 1, 3, 3 mg/kg - Low dose: 0.3, 1, 1, 1 mg/kg - 4 IV doses given every 4 weeks | - % change in mean peak gastric/duodenal eosinophil count | - Treatment response (>30% reduction in total symptom score AND >75% reduction in gastrointestinal eosinophilia count) - % change in total symptom score |

Table 4. Relevant clinical trials in EoE and EGID. Abbreviations: EoE, Eosinophilic esophagitis; EGID, eosinophilic gastrointestinal disease AEC, Absolute eosinophil count; RDBPC, randomized, double-blind, placebo-controlled; HPF, high-power field; RDB, Randomized, double-blind; CHQ, children’s health questionnaire; CUP, compassionate use protocol.
including change in FVC, SABA use, and ACQ-7.\textsuperscript{26} In the total population, none of these were significantly changed between groups, but when stratified by those with an AEC >400/μl, there was a statistically significant increase in FEV1 (mean increase 270 ml) in the reslizumab group with non-significant improvements in FVC, ACQ-7, and SABA use.\textsuperscript{26} A fourth trial randomized 315 patients with poorly controlled eosinophilic asthma (same criteria as the Castro trials with the additional requirement of documented airway reversibility) to receive either 0.3 mg/kg or 3 mg/kg IV reslizumab or placebo monthly for 4 months.\textsuperscript{27} The primary endpoint of change in pre-bronchodilator FEV1 was met in both groups, with an increase of 115 ml and 160 ml in the low and high dose groups, respectively.\textsuperscript{27} Key secondary outcomes included changes in FVC, FEF25-75, multiple patient reported surveys, and SABA use.\textsuperscript{27} The high dose reslizumab group showed a significant increase in FVC (130 ml) and a non-significant increase in FEF25-75 (233 ml).\textsuperscript{27} Additionally, ACQ, ASUI, and SABA use were significantly improved in both groups.\textsuperscript{27}

Safety
In these trials, there were 3 episodes of anaphylaxis deemed related to reslizumab.\textsuperscript{25–27} Otherwise, there was no significant difference in severe adverse events between the placebo and treatment groups.\textsuperscript{25–27} The most common adverse events included asthma worsening, headache, nasopharyngitis, and upper respiratory tract infections, which occurred in 8–22% of patients in the treatment groups.\textsuperscript{25–27}

Clinical indications and dosing
These trials led to the 2016 FDA approval of reslizumab for add-on therapy in patients age 18 or older with severe asthma at a dose of 3 mg/kg IV monthly.

Benralizumab

Efficacy
Three trials established the efficacy of benralizumab in asthma: SIROCCO, CALIMA, and ZONDA. SIROCCO randomized 1205 patients ages 12–75 with asthma who had ≥2 exacerbations in the past year while on high dose ICS plus LABA to receive placebo or 30 mg SC benralizumab at intervals of either every 4 weeks for 48 weeks or every 4 weeks for the first 3 doses then every 8 weeks through week 48.\textsuperscript{28} The primary endpoint was annual exacerbation rate ratio with key secondary endpoints including time to first exacerbation and pre-bronchodilator FEV1 and total asthma symptom scores at week 48 with results stratified by an AEC >300/μl.\textsuperscript{28} In those with an AEC >300/μl, both dosing groups had significant reductions in exacerbation rate, improvements in FEV1, and increased time to first exacerbation.\textsuperscript{28} Additionally, the 8 week dosing group had a significant decrease in total asthma symptom score.\textsuperscript{28} In those with an AEC <300/μl, the 4 week dosing group had a significantly decreased exacerbation rate and the 8 week group had significant improvement in asthma symptom scores, but no other endpoints achieved statistical significance.\textsuperscript{28} CALIMA utilized the exact dosing scheme, outcomes, and patient population characteristics (with the exception of allowing patients on medium dose ICS) as SIROCCO.\textsuperscript{29} In patients with an AEC >300/μl, there was a significant reduction in exacerbation rate (36% and 28% in every 4 week and every 8 week group, respectively), increased time to first exacerbation, increase in FEV1, and decreased total symptom score.\textsuperscript{29} A significant reduction in exacerbation rate was also seen in those with an AEC <300/μl, but no secondary outcomes achieved statistical significance.\textsuperscript{29} ZONDA randomized 220 patients with asthma requiring medium to high dose ICS plus LABA, OCS for at least the past 6 months, and an AEC >150/μl to benralizumab or placebo at the same dosing scheme as SIROCCO and CALIMA, but for a duration of 28 weeks.\textsuperscript{30} The primary outcome was the percent change in OCS dose at 28 weeks with key secondary outcomes including annual exacerbation rates, time to first exacerbation, percentage of patients with an OCS dose ≤5 mg, pre-bronchodilator FEV1, and total symptom scores.\textsuperscript{30} Both groups experienced a 75% reduction in OCS dose compared to 25% in the placebo group, and 61% and 59% of patients in the 4 week and 8 week dosing group, respectively, achieved a final OCS dose of ≤5 mg compared to 33% in the placebo group.\textsuperscript{30} There was a 55% decrease in exacerbation rate in the 4 week group and a 70% decrease in the 8 week group.\textsuperscript{30} No significant changes were seen in
FEV1 in any group. Two open label extensions of these trials, BORA and MELTEMI, showed durable reductions in rates of exacerbation in those with an AEC >300/µl and sustained improvements in FEV1. Additionally, in a recent single arm study (PONENTE) 490 of 598 OCS dependent severe asthmatics (81.9%) were able to achieve an OCS dose of ≤5 mg following benralizumab treatment irrespective of baseline eosinophil counts or baseline OCS dosage, with 75% of patients doing so without experiencing asthma exacerbations during the OCS taper.

Safety
In SIRROCO, CALIMA, and ZONDA, there were no significant differences in severe adverse effects between treatment and placebo groups. Nasopharyngitis was the most common adverse effect occurring in 12–21% of patients. Worsening asthma was the most common serious adverse effect occurring in 5–13% of patients. Drug-related hypersensitivity reactions were uncommon, occurring in 0–2% of patients in the treatment groups. Long-term safety was confirmed by BORA and MELTEMI, which showed similar findings to the original trials in terms of safety and tolerability with patients on treatment for up to 5 years.

Clinical indications and dose
These trials led to the 2017 FDA approval of benralizumab for add-on therapy in patients age 12 or older with severe asthma at a dose of 30 mg SC every 4 weeks for 3 doses with subsequent increase in dosing interval to every 8 weeks.

Summary
While these 3 anti-IL-5 biologics are FDA approved and are effective in reducing exacerbation rates, no trial has directly compared any of them. An indirect treatment comparison assessed the relative efficacy of each through analysis of several pre-existing trials. Outcomes included exacerbation rate, ACQ score, and change in pre-bronchodilator FEV1. Comparisons were stratified by AEC cutoffs that had been established in the prior clinical trials (>150/µl, >300/µl, >400/µl for mepolizumab, benralizumab, and reslizumab, respectively). Mepolizumab significantly reduced the rate of exacerbations and improved ACQ scores compared to both benralizumab and reslizumab in patients with an AEC >400/µl and compared to benralizumab in patients with an AEC >150/µl and >300/µl. Benralizumab was associated with a significantly greater improvement in FEV1 compared to reslizumab in patients with an AEC >400/µl, but there was otherwise no significant difference at any AEC threshold between mepolizumab and benralizumab or reslizumab.

HYPEREOSINOPHILIC SYNDROME
HES comprises a rare group of systemic disorders characterized by peripheral and/or tissue eosinophilia, the clinical evaluation and treatment of which has been extensively reviewed elsewhere.

Mepolizumab
Efficacy
The first large trial demonstrating efficacy of mepolizumab in HES randomized 85 patients with PDGFRA negative HES (defined as an AEC >1500/µl for at least 6 months with organ involvement and no identifiable secondary cause) to receive 750 mg IV mepolizumab or placebo monthly for 8 months after a run-in period where controller medications were adjusted to where clinical stability was achieved using prednisone monotherapy at 20–60 mg. In the mepolizumab group, 84% of patients achieved the primary end point of prednisone dose reduction to ≤10 mg for at least 8 consecutive weeks. Key secondary end points included achievement of an AEC <600/µl for at least 8 consecutive weeks, time to treatment failure, mean prednisone dose at week 36, achievement of a prednisone dose ≤7.5 mg, achievement of a prednisone dose ≤10 mg by week 20 for at least 8 weeks, and receipt of no prednisone for at least 1 day, all of which favored the mepolizumab group. An open label extension demonstrated durability of mepolizumab’s corticosteroid sparing effect with 83% of patients able to maintain a prednisone dose ≤10 mg for ≥12 weeks during the extension.

After years of compassionate use, questions arose surrounding optimal dosing of mepolizumab for HES. This led to a trial randomizing 108 patients age 12+ with PDGFRA negative HES with an AEC ≥1000/µl and 2+ flares in the preceding 12 months to receive either 300 mg SC mepolizumab
monthly or placebo for 32 weeks, in addition to pre-existing HES therapy. The primary outcome, the proportion of patients who experienced a disease flare in 32 weeks, was met with 28% of patients in the mepolizumab group experiencing a flare compared to 56% in the placebo group. Secondary outcomes included the time to first flare, proportion of patients with a flare during weeks 20–32, annualized flare rate, and change in fatigue severity. There was a significantly decreased proportion of patients in the mepolizumab group with a flare during weeks 20–32, decreased annualized rate of flare (0.50 vs. 1.46), and improvement in fatigue scores.

Safety

Long-term safety of mepolizumab in HES was established in the open label extension where 78 patients received a mean of 25 mepolizumab doses over 251 weeks with 20 patients experiencing adverse events attributed to mepolizumab, the most common of which were fatigue (n = 6) and nausea (n = 3). One fatal (angioimmunoblastic T cell lymphoma) and 3 non-fatal (motor neuron disease, transverse myelitis, increased T lymphocyte count) serious adverse events were attributed to mepolizumab.

In the post compassionate use trial, there was a similar percentage of adverse events in the placebo and mepolizumab groups with no reported severe adverse events attributed to mepolizumab. Additionally, there were no reports of malignancy or anaphylaxis in the mepolizumab group. The most common adverse events included bronchitis (15%), upper respiratory tract infection (15%), headache (13%), and nasopharyngitis (13%).

Clinical indications and dosing

These trials led to the 2020 FDA approval of mepolizumab for patients age 12 or older with HES with no identifiable secondary cause at a dose of 300 mg SC monthly.

Benralizumab

Efficacy

A phase 2 trial investigated the efficacy of benralizumab at a dose of 30 mg SC in 20 patients with symptomatic PDGFRα negative HES with an AEC ≥1000/µl. The study was randomized, double-blind, and placebo-controlled for the initial 12 weeks, open-label for the next 12 weeks, and transitioned to an open label extension for the next 24 weeks for those who had a clinical or laboratory response in the initial 24 weeks. The primary endpoint, the percentage of patients with a 50% reduction in AEC at 12 weeks was met in 9/10 patients in the benralizumab group compared to 3/10 in the placebo group. Key secondary endpoints included the frequency and severity of adverse events and the proportion of patients with reductions in concomitant therapy at 48 weeks. At week 48, 9 of 14 patients still receiving benralizumab were able to taper other HES therapy, and 7 of those 9 were on benralizumab alone. A phase 3 trial investigating benralizumab efficacy in HES is ongoing (NATRON, NCT04191304).

Safety

There was a similar number of adverse events reported in the benralizumab and treatment groups with lymphocytopenia (n = 6) and headache (n = 5) being most common. There were no serious adverse events reported in the benralizumab group.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic disorder characterized by peripheral eosinophilia, severe eosinophilic asthma, sinus disease, and small vessel vasculitis with demonstrated increases in airway levels of IL-5.

Mepolizumab

Efficacy

The efficacy of mepolizumab in EGPA was established in a trial that randomized 136 patients age 18+ with relapsing or refractory EGPA requiring a stable prednisone dose of 7.5–50 mg to receive 300 mg SC mepolizumab or placebo every 4 weeks for 52 weeks. The 2 primary endpoints were the accrued weeks of remission (defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and prednisone dose ≤4 mg) over 52 weeks and the proportion of patients in remission at weeks 36 and 48. Secondary endpoints included the time to first relapse,
average OCS dose during weeks 48–52, and the proportion of patients with remission within the first 24 weeks. There was a significantly greater accrued time in remission with 28% of participants in the mepolizumab group experiencing 24+ weeks of remission compared to 3% in the placebo group with an increased time to first exacerbation in the mepolizumab group. Additionally, there were significantly more patients in the mepolizumab group in remission at weeks 36 and 48 compared to placebo (32% vs. 3%). Prednisone doses were significantly lower in the mepolizumab group with 44% achieving a dose ≤4 mg and 18% discontinuing prednisone compared to 7% and 3%, respectively, in the placebo group.

Safety

The overall rate of adverse effects was similar in the mepolizumab and treatment groups. Similar to trials in asthma and HES, the most common adverse effects reported in the mepolizumab group were headache (32%), upper respiratory infection (21%), nasopharyngitis (18%), and local injection site reaction (15%). There were only 3 serious adverse events considered to be related to mepolizumab, and there were no reports of anaphylaxis.

Clinical indications and dosing

This trial led to the 2017 FDA approval of mepolizumab for add-on therapy in patients age 18 or older with EGPA at a dose of 300 mg SC monthly.

Benralizumab

A phase 2 trial evaluating the efficacy of benralizumab is ongoing (BITE, NCT03010436). Additionally, a randomized trial directly comparing the efficacy of benralizumab compared to mepolizumab is ongoing (MANDARA, NCT04157348), which would be the first randomized trial to perform a head to head comparison of 2 anti-IL-5 biologics in any eosinophilic disease.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

It is known that nasal polyps in patients with CRSwNP have increased levels of IL-5 and that eosinophilic inflammation is associated with polyp recurrence after surgical therapy, hence the role of anti-IL-5 therapy in this condition.

Mepolizumab

Efficacy

A phase 3 trial, SYNAPSE, established the efficacy of mepolizumab in CRSwNP. SYNAPSE randomized 407 adult patients from 11 countries with severe bilateral nasal polyposis (defined as a nasal obstruction visual analog scale (VAS) score of >5) with a history of at least 1 nasal surgery in the past 10 years who were currently eligible for repeat surgery to receive 100 mg SC mepolizumab or placebo monthly for 52 weeks following a 4 week run in period where all patients were treated with intranasal mometasone. Both primary outcomes were achieved, which were significant decreases in the endoscopic nasal polyp score (adjusted median decrease of 0.73) and nasal obstruction VAS score (adjusted median decrease of 3.14) in the mepolizumab group. Secondary end points included time to first nasal surgery, proportion of patients requiring systemic steroids, and changes from baseline in mean overall VAS score, Sinonasal Outcome Test 22 scores (SNOT-22), mean composite VAS score, and mean VAS score for loss of smell, all of which showed statistically significant changes favoring mepolizumab. A second phase 3 trial (MERIT, NCT04607005) is ongoing.

Safety

In SYNAPSE, adverse events occurred in 15% of patients in the mepolizumab group compared to 9% in the placebo group with nasopharyngitis (25%) and headache (18%) being most common. There were no serious adverse events that were attributed to mepolizumab and no cases of anaphylaxis.

Clinical indications and dosing

This trial led to the 2021 FDA approval of mepolizumab for patients age 18 or older with CRSwNP at a dose of 100 mg SC monthly.

Benralizumab

Efficacy

A phase 3 trial, OSTRO, established the efficacy of benralizumab in CRSwNP. OSTRO randomized
413 adult patients with bilateral nasal polyposis with a total nasal polyp score ≥5 and a history of either systemic steroid use or prior nasal surgery to receive 30 mg SC benralizumab (every 4 weeks for the first 3 doses and every 8 weeks thereafter) or placebo for 56 weeks. Key exclusion criteria included a history of nasal or sinus surgery in the 3 months prior to enrollment or an asthma exacerbation in the 4 weeks prior to enrollment. Both co-primary endpoints were achieved, which were significant improvements in total mean endoscopic nasal polyp score (mean reduction of 0.57) and biweekly nasal obstruction score (mean reduction of 0.27), both measured at week 40. There was no statistically significant improvement in key secondary efficacy endpoints including SNOT-22 at week 40, time to first nasal polyp surgery or systemic steroid use, or Lund-Mackay score at end of treatment. An additional phase 3 trial (ORCHID, NCT 04157335) is ongoing.

Safety
The most common adverse events were nasopharyngitis (17.4%) and asthma (9.2%). Serious adverse events occurred at rates of 8.4% in the placebo group and 11.1% in the benralizumab group, although none of these were deemed related to benralizumab. Only 2 serious adverse events occurred in more than 1 patient (pericarditis and gastritis each occurred in 2 patients in the benralizumab group). There were no reports of anaphylaxis, and local injection site reactions occurred at similar rates (1.9% benralizumab, 2.0% placebo).

Reslizumab
There are no large published trials of reslizumab use in CRSwNP, but a phase 3 trial investigating its use is ongoing (NCT02799446).

EOSINOPHILIC ESOPHAGITIS
EoE has traditionally been treated with a mixture of elimination diets, proton pump inhibitors, and corticosteroids (systemic and swallowed topical) with a goal of reducing both symptoms and eliminating esophageal eosinophilia. While biologics targeting eosinophils are a plausible method of treating EoE, clinical trials to date have been disappointing.

Mepolizumab
Efficacy
The largest trial investigating the efficacy of mepolizumab in EoE randomized 59 children ages 2-17 with EoE with a peak esophageal eosinophil count >20/hpf refractory to medical therapy to receive 0.55, 2.5, or 10 mg/kg IV mepolizumab monthly for 3 months. The primary endpoint, the proportion of patients with an esophageal eosinophil count of <5/hpf was met in only 8.8% of patients. Secondary outcomes included changes in peak and mean esophageal eosinophil counts, improvement in histopathologic and endoscopic findings, and the frequency and severity of symptoms. Peak and mean esophageal eosinophil counts <20/hpf were observed in 31.6% and 89.5% of patients, respectively. While there were decreases in reports of pain, regurgitation, and vomiting, these findings were limited by wide confidence intervals. An additional phase 3 trial is ongoing (NCT03656380).

Safety
Only one serious adverse event related to mepolizumab was reported (chest pain), and there were no hypersensitivity reactions.

Reslizumab
Efficacy
A multi-center trial assessing the effect of reslizumab in EoE randomized 227 patients ages 5-18 with moderately severe EoE with a peak esophageal eosinophil count >24/hpf to receive 1, 2, or 3 mg/kg IV reslizumab or placebo monthly for 4 months. Primary outcomes included the percent change in peak esophageal eosinophil count and change in the physician’s EoE global assessment score. Secondary outcomes included changes in the patient’s predominant symptoms and the children’s health questionnaire (CHQ). While there was a significant reduction in the peak esophageal eosinophil count in all the reslizumab groups (40-50% reduction compared to 5% increase in the placebo group), no group was able to achieve a peak esophageal eosinophil count of <5/hpf, and there was no significant improvement in the physician’s EoE global assessment, patient’s predominant symptoms, or CHQ scores.
Safety

A 9-year open label extension demonstrated long-term safety of reslizumab with no serious adverse events reported.\(^{56}\)

Benralizumab and lirentelimab

There are ongoing phase 3 trials investigating the efficacy of SC benralizumab (MESSINA, NCT04543409), and IV lirentelimab (KRYPTOS, NCT04322708). Preliminary results from KRYPTOS showed histologic improvement in the treatment group, but did not show significant symptom improvement.\(^{57}\)

EOSINOPHILIC GASTROINTESTINAL DISEASE

Eosinophilic gastrointestinal disease distal to the esophagus (gastritis, duodenitis, colitis) can present with a wide range of symptoms and is treated similarly to EoE but has had less targeted therapeutic investigation.\(^{58-60}\)

Lirentelimab

Efficacy

A phase 2 trial investigating the efficacy of lirentelimab in EGID randomized 65 patients ages 18–80 with eosinophilic gastritis or duodenitis not adequately controlled with pharmacologic therapy or dietary modification to receive 4 monthly infusions of IV lirentelimab at high dose (0.3, 1, 3, 3 mg/kg) or low dose (0.3, 1, 1, 1 mg/kg) or placebo.\(^{61}\) The primary outcome was the percent change in mean peak gastric or duodenal eosinophil count with secondary outcomes including treatment response (defined as those with >30% reduction in total symptom score AND >75% reduction in gastrointestinal eosinophil count) and the percent change in total symptom score.\(^{61}\) The primary outcome was achieved with 79% and 86% reductions in mean peak gastrointestinal eosinophil count in the low and high dose groups, respectively, compared to a 9% increase in the placebo group.\(^{61}\) Treatment response was seen at a significantly higher rate in both dosing groups (59%, 67%, and 5% in the low dose, high dose, and placebo groups, respectively).\(^{61}\) Total symptom scores were reduced in both dosing groups compared to placebo (55%, 42%, and 22% in the high dose, low dose, and placebo groups, respectively).\(^{61}\)

ENIGMA 2 (NCT04322604) is an ongoing phase 3 trial investigating the efficacy of lirentelimab in EGID. Preliminary results showed histologic improvement in the treatment group, but (similarly to KRYPTOS for EoE) did not result in significant symptom improvement.\(^{57}\)

Safety

Infusion related reactions were common, occurring in 60% of patients who received lirentelimab.\(^{61}\) The majority of these reactions were mild to moderate, consisting of flushing, warmth, headache, nausea, or dizziness.\(^{61}\) Otherwise, the rates of other adverse events were similar between the lirentelimab and placebo groups.\(^{61}\) Serious adverse events occurred in 4 patients in the lirentelimab group (hypoxia, abdominal pain, dehydration, and a grade 4 infusion reaction) and 3 patients in the placebo group (dehydration, anemia, and altered mental status).\(^{61}\)

Benralizumab

A randomized trial investigating efficacy of benralizumab in EGID is ongoing (BEGS, NCT03473977).

OTHER

There have been case reports of successful anti-IL-5 therapy in a variety of other conditions. Positive effects have been reported in chronic spontaneous urticaria, and there are ongoing trials investigating the efficacy of mepolizumab (NCT03494881), benralizumab (ARROYO, NCT04612725) and lirentelimab (NCT03436797) in this condition.\(^{62-64}\) Drug reaction with eosinophilia and systemic symptoms (DRESS) has been treated successfully with mepolizumab and benralizumab.\(^{65,66}\) Mepolizumab has been successfully used in allergic bronchopulmonary aspergillosis,\(^{67}\) chronic eosinophilic pneumonia,\(^{68}\) eosinophilic bronchitis,\(^{59}\) and in one patient with concomitant severe eosinophilic asthma, EGID, and AERD.\(^{70}\) There are ongoing trials investigating the use of mepolizumab in eosinophilic fasciitis (NCT04305678), COPD with...
frequent exacerbations and eosinophilia (MATINEE, NCT04133909), and episodic angioedema with eosinophilia (Gleich syndrome, NCT04128371) as well as trials investigating the use of benralizumab in atopic dermatitis (NCT04605094, NCT03563066) and bullous pemphigoid (FJORD, NCT04612790).

**SUMMARY**

There are 20 years of experience in the use of anti-IL-5 therapy for eosinophilic diseases and a nascent but growing level of experience in the use of anti-Siglec-8 therapy. There is already FDA approval of anti-IL-5 biologics for severe eosinophilic asthma and mepolizumab for EGPA, idiopathic HES, and CRSwNP. Despite initial positive results, the FDA has not yet granted approval for benralizumab in CRSwNP, and preliminary unpublished results from phase 3 trials of lirilintelimab in EoE and EGID are disappointing. Despite this, there are still several ongoing trials which will potentially result in additional FDA approved indications for eosinophil targeting biologic therapy in the coming years, which will provide new therapeutic options for these often debilitating diseases. This review provides one of the most comprehensive summaries of eosinophil directed biologic therapy, and it will be important for the practicing allergist-immunologist to stay up to date with the accelerating release of new trials.

**Abbreviations**

HES, hypereosinophilic syndrome; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; EOE, eosinophilic esophagitis; EGID, eosinophilic gastrointestinal disease; IL-5, interleukin-5; IL-5R, interleukin 5 receptor; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; NK, natural killer; ADCCC, antibody dependent cellular cytotoxicity, AEC, absolute eosinophil count; IV, intravenous; ICS, inhaled corticosteroid; SC, subcutaneous, SGRQ, St. George respiratory questionnaire, ACQ, asthma control questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; SABA, short acting beta agonist; FEF25-75, forced expiratory flow at 25-75% of forced vital capacity; ASU, asthma symptom utility index; FDA, Food and Drug Administration; LABA, long acting beta agonist; PDGFRA, platelet derived growth factor receptor A; BVAS, Birmingham vasculitis activity score; VAS, visual analog scale; SNOT-22, sinonasal outcome test-22; CHQ, children’s health questionnaire; AERD, aspirin exacerbated respiratory disease.

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**Availability of data and materials**

All abstracted data is available to the readers in the tables of the manuscript and references.

**Ethics**

The authors report no ethical concerns in this literature review.

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The authors declare this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

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The authors report no conflicts of interest, financial or otherwise.

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