Drugs (2024) 84:661–684
https://doi.org/10.1007/s40265-024-02037-0

REVIEW ARTICLE

Anti-IL-5 Pathway Agents in Eosinophilic-Associated Disorders Across the Lifespan

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Accepted: 24 April 2024 / Published online: 8 June 2024

Abstract

Monoclonal antibodies targeting interleukin (IL)-5 pathways have revolutionized the treatment expectations for eosinophilic-associated conditions, particularly in patients with respiratory involvement. Mepolizumab (IL-5 antagonist monoclonal antibody), benralizumab (IL-5 receptor blocker monoclonal antibody), and reslizumab (IL-5 antagonist monoclonal antibody) have collectively contributed to the overall improvement of the disease burden in various conditions. Eosinophilic asthma currently boasts the most robust evidence across all age groups: all three biologics are approved for adults (aged ≥18 years); mepolizumab is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) also in children (aged ≥ 6 years), while bernalizumab was recently approved by the FDA for patients aged ≥6 years in the USA. In chronic rhinosinusitis with nasal polyps, subcutaneous mepolizumab is the only anti-IL-5 therapy approved so far and can be used in adult patients (aged ≥18 years). For eosinophilic esophagitis, conflicting evidence surrounds both mepolizumab, reslizumab, and benralizumab, leading to non-approval of these agents by the FDA/EMA. Recently, mepolizumab was approved for eosinophilic granulomatosis with polyangiitis patients aged ≥6 years or older and for hypereosinophilic syndrome adult patients. A phase III trial proving noninferiority of benralizumab versus mepolizumab in eosinophilic granulomatosis with polyangiitis has been recently published, while evidence on reslizumab is scant. Overall, current evidence on anti-IL-5 biologics for eosinophilic-associated disorders is mostly focused on adults, whereas data for individuals aged under 18 years and over 65 years are scarce, resulting in a lack of evidence, particularly regarding efficacy, for the use of anti-IL-5 agents in these specific patient populations. This review addresses high-quality evidence from randomized controlled trials and real-world post-marketing studies regarding the use of anti-IL-5 therapies for eosinophilic-associated disorders across all age groups, spanning childhood, adulthood, and older age.

1 Introduction

In recent years, a close association emerged between peripheral blood eosinophils and several chronic idiopathic diseases characterized by eosinophilic inflammation, leading to organ dysfunction and damage (i.e., eosinophilic-associated disorders) [1]. From a clinical perspective, those conditions characterized by single-organ involvement, such as chronic rhinosinusitis with nasal polyps (CRwNP) or eosinophilic asthma, are often associated with lower levels of blood eosinophils, whereas systemic diseases, such as eosinophilic granulomatosis with polyangiitis (EGPA) and

Key Points

Mepolizumab, benralizumab, and reslizumab have collectively contributed to the control and improvement of the main recognized eosinophil-associated disorders.

Trial data on adult patients showed efficacy and safety for most of these agents in eosinophilic asthma, chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome, but not in eosinophilic esophagitis.

Data for children and subjects aged <65 years are however scarce, resulting in a lack of evidence for the use of anti-interleukin-5 agents in these specific patient populations.

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hypereosinophilic syndrome (HES), are usually associated with higher levels (Fig. 1). In between this spectrum, a variety of combinations of single-organ disorders (e.g., eosinophilic asthma complicated with CRwNP or with eosinophilic esophagitis [EoE]) are associated with intermediate levels of blood eosinophilia [1]. Notably, these diseases may have different triggers, and be sustained by disparate pathogenic mechanisms other than just eosinophil-mediated inflammation; and, therefore, the role of eosinophils may not be central in the disease development for all of them.

Eosinophils are multi-functional leukocytes that can release various biologically active substances once activated, including cytotoxic proteins (eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase), lipid mediators (leukotrienes and prostaglandins), reactive oxygen species, growth factors, chemokines and cytokines (and among these, interleukin [IL]-5)) [1, 2]. Notably, the levels and functions of eosinophils change with age and other demographic features, being significantly higher in children (aged <18 years), in male individuals as compared to female individuals, and increasing with the increasing of the age and body mass index [1, 2]. Similarly, the effector functions of peripheral blood eosinophils (i.e. degranulation in response to IL-5 stimulation) are known to be decreased in the older subjects as compared with young healthy subjects [1, 2].

The close relationship between IL-5 and eosinophils has been demonstrated through experimental and clinical studies [1, 2]. Because of the crucial role that it plays for eosinophils (from eosinophilopoiesis to their activation), IL-5 has been identified a therapeutic target for eosinophilic disorders, and its pathway can be antagonized by several biological agents (mepolizumab, benralizumab, and reslizumab, already licensed, and depemokimab, under investigations) (Fig. 2) [3]. Mepolizumab, a humanized IgG1-κ monoclonal antibody, binds to IL-5, preventing its interaction with the IL-5 receptor, hence inhibiting its cascade [4]. Similarly, reslizumab, a humanized IgG4-κ monoclonal antibody, and depemokimab, a humanized IgG1-κ monoclonal antibody with remarkably higher binding affinity for IL-5 as compared with mepolizumab, sequestrate this molecule from extracellular space, as done by mepolizumab [1, 5]. In contrast, benralizumab, an IgG1-κ humanized afucosylated monoclonal antibody, antagonizes the IL-5 receptor α (IL-5-Rα), blocking downstream the action of IL-5. Benralizumab, by targeting IL-5Rα-bearing cells, prevents receptor stimulation and activates natural killer-mediated eosinophil cytotoxicity, resulting in a higher eosinophil depletion within the tissues [6].

Overall, the efficacy of these drugs changes according to the clinical conditions treated, whereas their safety and tolerability are considered overall good. Meta-analyses and post-marketing US Food and Drug Administration (FDA) analyses did not show alarming adverse events. The most frequently reported adverse events include headache, nasopharyngitis, upper respiratory tract infection, bronchitis, and

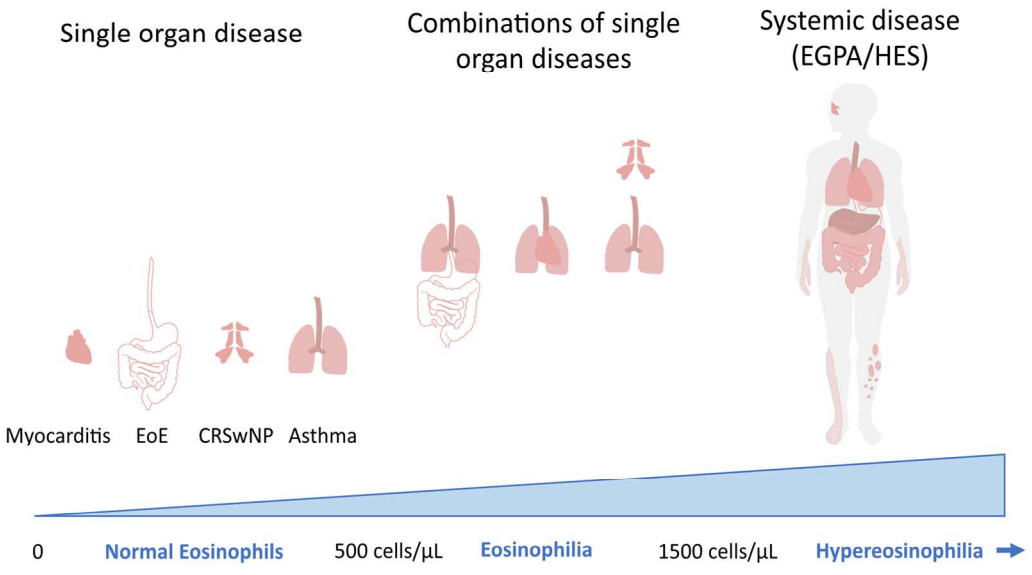

Fig. 1 Eosinophilic-associated disorders and eosinophil blood levels. Single-organ disease has usually (but not always) lower circulating eosinophil levels than systemic diseases. Accordingly, the combination of two or more single organ disease, as the explanatory cases of asthma with comorbidities (e.g., asthma complicated by chronic rhinosinusitis with nasal polyposis [CRSwNP]) which is reported in the figures, has usually higher circulating eosinophil levels than single-organ disease (e.g., asthma or CRSwNP alone), but usually lower than systemic diseases, as eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES). *EOE* eosinophilic esophagitis. Part of the figure was created with BioRender.com

asthma exacerbation [7, 8]. According to FDA data, the proportion of serious adverse events with mepolizumab seems to be greater than benralizumab in each age group (≤20, 20–65, and ≥65 years); however, such data also include self-reports from patients and other confounding factors [8]. Immunogenicity was tested for these drugs in phase III randomized controlled trials (RCTs), testing positive for anti-drug antibodies in 4% of patients for mepolizumab (in most cases non-neutralizing) [9], in 4.8–5.4% for reslizumab (with no impact on exposure, blood eosinophils, clinical efficacy and safety) [10], and in 11–13% for benralizumab (with no associated adverse clinical outcomes) [11, 12]. This review article summarizes current evidence on licensed anti-IL-5 agents (mepolizumab, reslizumab and bernalizumab) used for the main recognized eosinophil-associated disorders, i.e., eosinophilic asthma, CRwNP, EoE, EGPA, and HES, analyzing the data by age groups.

2 Eosinophilic Asthma

Roughly 5% of asthmatic patients have severe asthma, which is associated with reduced quality of life, increased healthcare costs, and mortality [13]. Patients with severe disease experience refractory symptoms despite high-intensity therapy, resulting in a lack of response to conventional inhaled therapy. Luckily, recent improvements in our understanding of the molecular biology and pathophysiologic mechanisms of asthma have facilitated the discovery of new treatment options targeting different mechanisms. From a biological perspective, asthma can be subdivided into two endotypes: T2-high and T2-low endotypes. The T2-high endotype, in which activated type 2 T-helper cells produce IL-5, along with IL-4 and IL-13, acting as the main drivers of eosinophilic inflammation, is the endotype that represents 50% of mild-to-moderate asthma and up to 80% of severe asthma [14]. Mepolizumab, benralizumab, and reslizumab are currently licensed for eosinophilic severe asthma. Compared with the standard of care, these biologics have been shown to

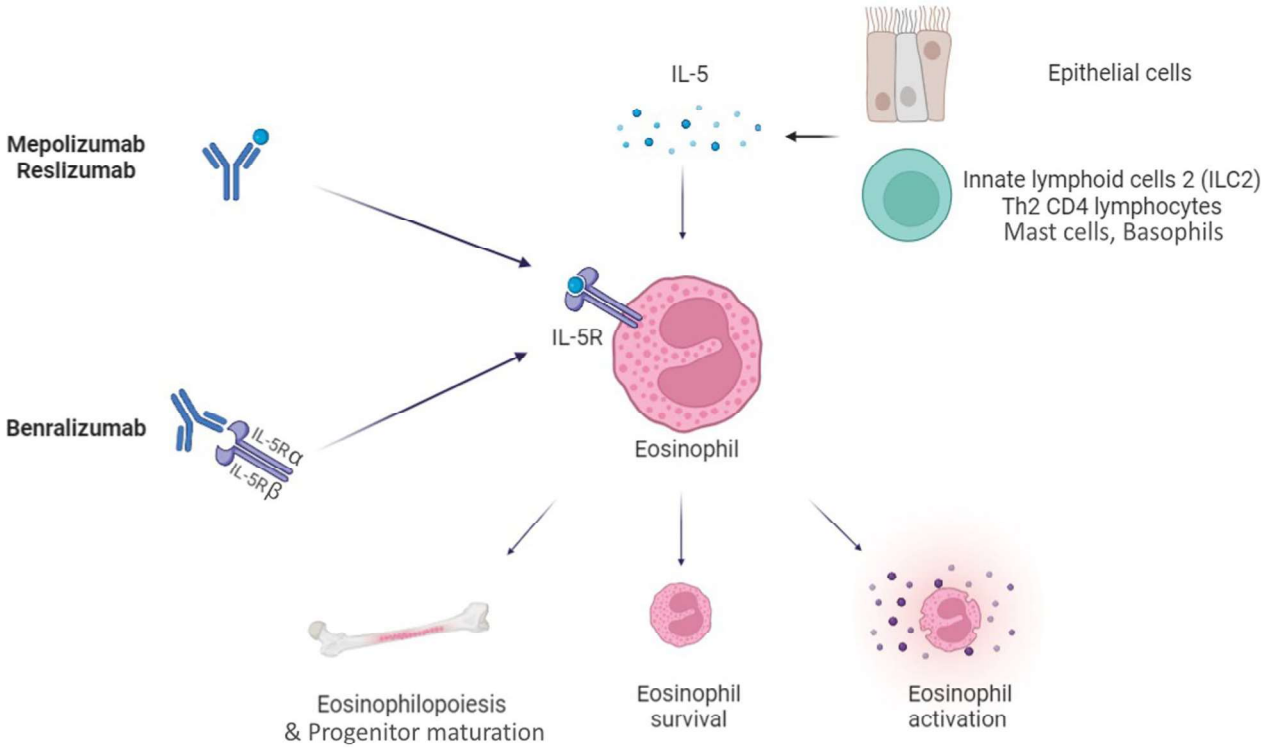

Fig. 2 Interleukin-5 (IL-5) and biological agents interfering with the IL-5 pathway (anti-IL-5 agents), thus negatively modulating the growth, survival, recruitment in inflamed tissues and function of eosinophils. Activated CD4 type 2 T helper lymphocytes produce IL-5. Innate lymphoid cells 2 (ILC2) cells are another relevant source of IL-5; these cells are activated by alarmins (thymic stromal lymphopoietin, IL-33, and IL-25) produced by surrounding cells, as epithelial cells for airways, in response to various triggers. Epithelial cells, in the context of eosinophilic inflammation, could also produce IL-5. Interleukin-5 is a crucial mediator responsible for eosinophilopoiesis, eosinophil survival, and activation. Mepolizumab, reslizumab, and bernalizumab target eosinophils through the targeting of IL-5 pathway. There is another monoclonal antibody with an anti-IL-5 effect named depemokimab, which is currently under development (not reported in the figure, since not licensed yet). *Th2* T-helper 2. Part of the figure was created with BioRender.com

reduce exacerbation rates [15, 16], long-term corticosteroid use and asthma-related hospitalizations [17], health-related quality of life and lung function in adults and children [18, 19].

2.1 Pediatric

Currently, two biological therapies that target IL-5 are approved for the treatment of severe eosinophilic asthma in pediatric patients: mepolizumab and benralizumab (Table 1).

2.1.1 Mepolizumab

Phase II/III clinical trials have demonstrated that mepolizumab reduces severe exacerbations by 50% in adults and adolescents with severe asthma prone to exacerbations and with blood eosinophil counts of ≥150 cells/mm^3. Additionally, these trials indicate that the therapeutic effect becomes more pronounced with higher blood eosinophil counts [20, 21].

Notably, adolescents aged 12–17 years constituted only 2% of the overall population in phase II/III mepolizumab trials (n = 37/1878) [22]. A post-hoc meta-analysis of these trials revealed that mepolizumab exhibited comparable efficacy and safety in adolescents compared to the overall population. Adolescents showed similar exacerbation rate ratios relative to the placebo when compared to adults (0.60 vs 0.46). However, this similarity came with significantly wider confidence intervals (CIs) [95% CI 0.17–2.10 for adolescents compared to 95% CI 0.38–0.56 for adults) because of the small sample size [22].

Recently, the license for mepolizumab was extended in the USA and Europe to include children aged 6–11 years with severe eosinophilic asthma. The recommended dose is 40 mg/month for children aged 6–11 years versus 100 mg/month in patients aged 12 years and older. This license extension was based on findings from an open-label non-randomized study in which 36 children with severe asthma were treated with mepolizumab for 12 weeks. This treatment resulted in similar reductions in blood eosinophils as observed in adults, along with comparable safety profiles [23] (Fig. 3). Subsequently, these children were followed up for 1 year in an open-label uncontrolled study, which reported a positive safety profile and improvements in the exacerbation rate and asthma control, akin to those seen in adults [24]. Jackson et al. [25] recently reported the results of the first randomized placebo-controlled trial of mepolizumab in children and adolescents (n = 290; age 6–17 years) with severe eosinophilic asthma. Participants treated with mepolizumab for 12 months exhibited a 27% relative reduction in the rate of severe exacerbations, particularly those occurring in the fall season, compared with the placebo. Nevertheless, mepolizumab did not yield significant benefits in terms of asthma control and lung function (as measured by spirometry and impulse oscillometry) when compared to the placebo. Furthermore, fractional exhaled nitric oxide levels were not significantly affected by mepolizumab. Interestingly, this study found that the overall effect of mepolizumab on asthma exacerbations was less pronounced than what was observed in prior mepolizumab studies in adults and pediatric patients, despite a similar reduction in blood eosinophils in the active group [23]. However, it is worth noting that this study included predominantly Black and Hispanic children living in urban communities, who might have different airway inflammation patterns compared to Caucasian children [26, 27]. Additionally, eosinophilic asthma and related exacerbations may be influenced by different factors in children and adults, as well as in adults with childhood-onset versus adult-onset asthma. Severe asthma diagnosed in adulthood is associated with a low rate of atopy, reduced lung function, and predictive factors for mepolizumab response, including elevated blood eosinophil counts (>500 cells/mm^3) and high rates of exacerbations and comorbidities such as nasal polyposis [28, 29].

2.1.2 Benralizumab

Two phase III, randomized, placebo-controlled trials (SIROCCO and CALIMA) enrolled a total of 108 adolescents (aged 12–17 years), with 40 of them receiving benralizumab administered every 8 weeks (with the first three doses every 4 weeks) [11, 12]. In adolescents with blood eosinophil counts ≥300 cells/mm^3, the annual exacerbation rate ratios versus placebo were 1.77 (95% CI 0.40–7.78) in SIROCCO and 1.57 (95% CI 0.13–13.96) in CALIMA [11, 12] (Fig. 4). However, the limited number of participants and the wide CIs make it challenging to interpret these results [21]. Concerning safety, adolescents from the SIROCCO and CALIMA trials who continued treatment for the second and third years exhibited a positive safety profile consistent with previous findings [30].

A recent open-label study in 28 children with severe eosinophilic asthma, who received benralizumab for 40 weeks, showed that the time to reach the maximum serum concentration, the reduction in the blood eosinophil count, and immunogenicity profile of benralizumab were consistent with prior adolescent and adult studies. Adverse events were frequent (mostly nasopharyngitis, pyrexia, and viral upper respiratory tract infections), but not serious to lead to discontinuation of the treatment [31]. These findings led to the recent FDA's approval of benralizumab as add-on maintenance therapy in patients aged 6–11 years, with a recommended specific dosage of 10 mg for children in

Table 1 Indication, doses, administration routes, and approval by the FDA/EMA for anti-interleukin-5 biologic agents in eosinophilic-associated conditions

	Mepolizumab				
	Dose, frequency	Administration route	Age range approved	Currently approved by	Relevant trials for treatment registration
Eosinophilic severe asthma	100 mg, Q4W	SC	≥11 years	FDA, EMA	DREAM [44] MENSA [45] MUSCA [46] SIRIUS [9]
	40 mg, Q4W	SC	≥6–11 years	FDA, EMA	Gupta et al. [23] Gupta et al. [24]
CRSwNP	100 mg, Q4W	SC	≥18 years	FDA, EMA	SYNAPSE [85]
EGPA	300mg Q4W	SC	≥12 years	FDA, EMA	MIRRA [118, 119]
	200 mg Q4W	SC	≥6–11 years, ≥40 kg	FDA, EMA	–
	100 mg Q4W	SC	≥6–11 years, <40 kg	FDA, EMA	–
HES	300 mg Q4W	SC	≥18 years	FDA, EMA	"HES Mepolizumab studies [131–137]"
	Benralizumab				
	Dose, frequency	Administration route	Age range approved	Currently approved by	Relevant trials for treatment registration
Eosinophilic severe asthma	10 mg, Q4W for the first 3 doses and Q8W thereafter	SC	6–11 years <35 kg	FDA	TATE [31]
	30 mg, Q4W for the first 3 doses and Q8W thereafter	SC	≥6 years and ≥35 kg (FDA) ≥18 years (EMA)	FDA EMA	SIROCCO [11] CALIMA [12] ZONDA [55]
	Reslizumab				
	Dose, frequency	Administration route	Age range approved	Currently approved by	Relevant trials for treatment registration
Eosinophilic severe asthma	3 mg/kg, Q4W	IV	≥18 years	FDA, EMA	Castro et al. [59] Castro et al. [60] Bjermer et al. [61] Bernstein et al. [62]

CRSwNP chronic rhinosinusitis with nasal polyposis, *FDA* US Food and Drug Administration, *EMA* European Medicines Agency, *IV* intravenous infusion, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous injection

this age range who weigh less than 35 kg (Table 1). Additionally, a randomized, double-blind, placebo-controlled trial is actively recruiting to assess the safety and efficacy of benralizumab in children aged 6–17 years (NCT05692180). The age of asthma onset appears to influence the therapeutic response to benralizumab, with patients diagnosed with asthma in adulthood showing greater responsiveness to this biological therapy compared with those with childhood-onset asthma [32].

2.1.3 Reslizumab

Early clinical trials involving a small group of adolescents with severe eosinophilic asthma ($n = 39$; aged 12–17 years) showed no significant effect of reslizumab on asthma exacerbations. Following this, no other studies evaluated the impact of reslizumab in children and adolescents with severe asthma [33].

Overall, there is still a scarcity of data regarding the efficacy, safety, and long-term effects of anti-IL-5 biological therapies in adolescents and children with severe asthma. Studies involving biomarkers, such as the recent analysis of

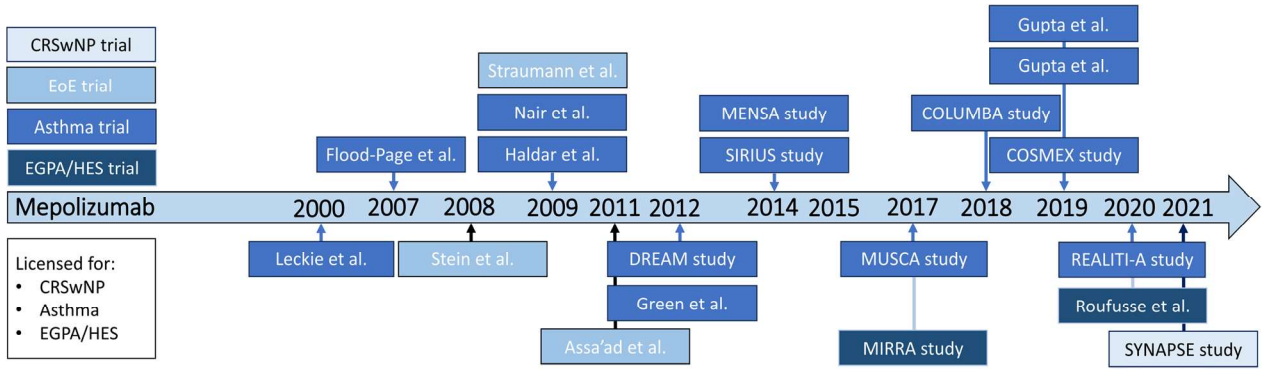

Fig. 3 Clinical development of mepolizumab. Here are reported the more relevant clinical trials for mepolizumab for eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRwNP), eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES). Mepolizumab is presently licensed for asthma, CRSwNP, EGPA, and HES

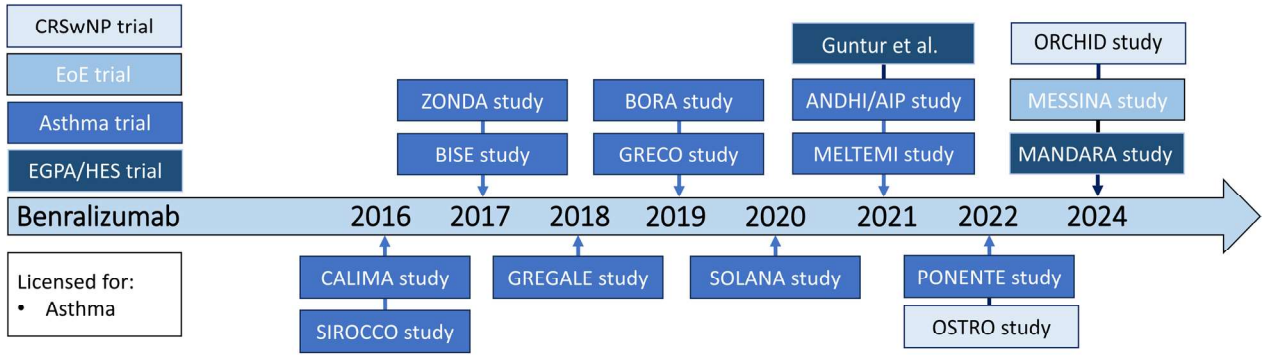

Fig. 4 Clinical development of benralizumab. Here are reported the more relevant clinical trials for benralizumab for eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRwNP), eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES). Bernalizumab is presently licensed for asthma

airway transcriptomics in relation to mepolizumab [25], are needed to better identify eligible patients and responders.

2.2 Adults

The clinical utility of biologics targeting the IL-5 pathway for severe asthma (mepolizumab 100 mg subcutaneously every 4 weeks; benralizumab 30 mg subcutaneously every 4 weeks for the first three doses and every 8 weeks thereafter; and reslizumab 3 mg per kg intravenously every 4 weeks) has been demonstrated in multiple RCTs in adults (Table 1). Even though only ~80% of patients with severe asthma in *real-life* settings would have been excluded from RCTs [34], the clinical efficacy obtained in RCTs has been widely replicated in *real-life* studies [35]. The annualized exacerbation rates were significantly reduced by −3.79, −3.17, and −6.72 with benralizumab, mepolizumab, and reslizumab, respectively. Likewise, significant improvements in forced expiratory volume in 1 second were observed with all three biologics (Table 2) [36]. In addition, the use of anti-IL-5 biologics in adults with severe asthma improved work productivity and activity (RAPSODI registry-based cohort study) [37].

2.2.1 Mepolizumab

Several studies contributed to accumulating evidence on the safety and efficacy of mepolizumab in eosinophilic adult asthma [9, 38–47]. The DREAM (Dose Ranging Efficacy And safety with Mepolizumab) trial took place in 2012 and demonstrated the effectiveness of intravenous mepolizumab in patients with severe asthma, high eosinophil inflammation, and a history of exacerbations (Fig. 3), showing a 54% reduction in exacerbation frequency. Notably, eligible patients were aged between 12 and 74 years [44]. Following DREAM, a phase III clinical trial named MENSA

(Mepolizumab as adjunctive therapy in patients with Severe Asthma) established a direct relationship between the reduction in eosinophil counts and the exacerbation rate [45], confirming the frequency in reduction in exacerbation rates (53%). Notably, eligible patients were aged between 12 and 82 years. This direct relationship was further validated in the MUSCA (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC Asthma) trial [46], and the SIRIUS (Steroid Reduction with Mepolizumab Study) trial [9], both enrolling patients aged ≥12 years. Additionally, the SIRIUS trial revealed that a reduced corticosteroid dosage in patients, when combined with mepolizumab, did not increase exacerbations. Finally, real-world observational studies, such as the REALITI-A (REAL world effectiveness of mepolizumab in patient care-Asthma) and the REDES (REal worlD Effectiveness and Safety of Mepolizumab), enrolling subjects aged ≥18 years, showed that mepolizumab significantly decreased annual asthma exacerbations and reduced patient reliance on corticosteroids, with no new safety concerns [47, 48].

2.2.2 Benralizumab

There is an extensive number of RCTs testing benralizumab in asthma, with several phase III trials including CALIMA, SIROCCO, SOLANA, BISE, PONENTE, GRECO, GREGALE, ZONDA, MELTEMI, ANDHI/AIP, and BORA (the WINDWARD program) (Fig. 4) [11, 12, 30, 49–56]. The three RCTs central for benralizumab approval are the CALIMA [12], SIROCCO [11], and ZONDA [55], which collectively demonstrated its efficacy as an add-on therapy in severe eosinophilic asthma. The CALIMA trial, enrolling patients between 12 and 75 years, significantly reduced the annual rate of asthma exacerbations by up to 36% and improved forced expiratory volume in 1 second throughout the treatment course [12]. The SIROCCO trial, enrolling individuals aged between 12 and 75 years using high doses of inhaled corticosteroids and long-acting β2 agonists still experiencing uncontrolled asthma. Over 48 weeks, benralizumab significantly reduced annual exacerbation rates by 51% and improved lung function (Table 2) [11]. The ZONDA trial, enrolled patients between 12 and 75 years, with a proportion of patients aged ≥65 years that was between 11% (placebo arm and benralizumab every 4 weeks arm) and 16% (benralizumab every 8 weeks arm); the trial showed an oral glucocorticoid-sparing effect in patients relying on oral glucocorticoids to manage severe asthma (by 75% from baseline in the benralizumab arms vs 25% in the placebo arm) [55].

2.2.3 Reslizumab

Several trials lead to the approval of reslizumab for eosinophilic asthma [57–63]. In the phase II trial of Castro et al. [59], adult patients receiving reslizumab showed a significant improvement in lung function (Table 2), and a reduction in blood and sputum eosinophil counts. However, a significant improvement in asthma control was seen only in those patients with nasal polyps (Fig. 5). While reslizumab significantly improved lung function in this study, it did not have a significant effect on asthma control. Subsequent to these findings, two phase III RCTs were conducted, enrolling patients aged between 12 and 75 years [60]. Across both studies, 477 patients received reslizumab in addition to their existing asthma treatments. The results showed significant improvements in asthma exacerbation rates and lung function when reslizumab was used in patients prescribed oral corticosteroids and with blood eosinophil counts higher than 400 cells/μL [60]. In another trial, reslizumab improved lung function, asthma control and symptoms, and quality of life, with the 3.0-mg/kg dose providing greater improvements in asthma outcomes versus the 0.3-mg/kg dose [61]. Finally, in a more recent analysis of two RCTs, fixed-dose subcutaneous reslizumab (110 mg/every 4 weeks) was not effective in reducing exacerbation frequency in patients with uncontrolled asthma and an increased blood eosinophil count (≥300 cells/μL), nor in reducing maintenance therapy with oral glucocorticoids [62].

2.3 Adults Aged >65 Years

Asthma in older adults is a public health problem recognized in many countries. The estimated lifetime prevalence of asthma above the age of 65 years was reported at 10.4% compared with 7.8% among all adults in the USA, with a higher prevalence in women [64]. At least two phenotypes exist among older patients with asthma: those with long-standing asthma (with a disease that is carried throughout a lifetime), exhibiting more severe airflow limitation and less complete reversibility, as compared with those with late-onset asthma [65]. Older individuals with asthma may also have severe/uncontrolled asthma, which overlaps with other diseases, such as chronic obstructive pulmonary disease, heart disease, chronic rhinosinusitis with nasal polyposis (CRSwNP), obstructive sleep apnea, diabetes mellitus, and other comorbidities [66], making both diagnostic and therapeutic approaches more complex. Older patients have also the highest reported asthma-related mortality [67].

Asthmatic patients aged ≥65 years have been included in registrational studies, and there are no RTCs specifically evaluating the impact of anti-IL-5 biological agents in this

Table 2 Double-blind, placebo-controlled, randomized clinical trials assessing the effect of anti-interleukin-5 biological therapies on pre-bronchodilator FEV1

Study, year (reference)	Biological agent	Patients	Age range (years)	Randomization	Doses and routes of administration	Mean prebronchodilator FEV1 improvement after treatment
DREAM, Pavord et al., 2012 [44]	Mepolizumab	$N = 621$	12–75	1:1:1:1 (placebo)	For 52 weeks • 75 mg IV Q4W • 250 mg IV Q4W • 750 mg IV Q4W	Difference from placebo • 61 mL (95% CI −39, 161; p = ns) • 81 mL (95% CI −19, 180; p = ns) • 56 mL (95% CI −43, 155; p = ns)
MENSA, Ortega et al., 2014 [45]	Mepolizumab	$N = 576$	12–82	1:1:1 (placebo)	For 32 weeks • 75 mg IV Q4W • 100 mg SCQ4W	Difference from placebo • 100 mL (95% CI 13, 187; $p = 0.02$) • 98 mL (95% CI 11, 184; $p = 0.03$)
MUSCA, Chupp et al., 2017 [46]	Mepolizumab	$N = 551$	12–75	1:1 (placebo)	For 24 weeks • 100 mg SC Q4W	Difference from placebo • 120 mL (95% CI 47, 192; $p = 0.001$)
SIRIUS, Bel et al., 2014 [9]	Mepolizumab	$N = 135$	12–75	1:1 (placebo)	For 20 weeks • 100 mg SC Q4W	Difference from placebo • 114 mL (p = 0.15)
MUPPITS-2, Jackson et al., 2022 [25]	Mepolizumab	$N = 290$	6–17	1:1 (placebo)	For 52 weeks • 40 mg SC (6–11 years) Q4W • 100 mg SC (12–17 years) Q4W	Difference from placebo • No significant differences for both doses
SIROCCO, Bleeker et al., 2016 [11]	Benralizumab	$N = 1205$	12–75	1:1:1 (placebo)	For 48 weeks • 30 mg SC Q4W • 30 mg SC Q8W	Least-square mean difference from placebo Subgroup with baseline blood eosinophils ≥300 cells per μL: • 106 mL (95% CI 16, 196; $p = 0.02$) Q4W • 159 mL (95% CI 68, 249; $p = 0.0006$) Q8W Subgroup with baseline blood eosinophils <300 cells per μL: • −25 mL (95% CI −134, 102; p = ns) Q4W • 102 mL (95% CI 3, 208; p = ns) Q8W
CALIMA, FitzGerald et al., 2016 [12]	Benralizumab	$N = 1306$	12–75	1:1:1 (placebo)	For 56 weeks • 30 mg SC Q4W • 30 mg SC Q8W	Least-square mean difference from placebo Subgroup with baseline blood eosinophils ≥300 cells per μL: • 125 mL (95% CI 37, 213; $p = 0.005$) Q4W • 116 mL (95% CI 28, 204; $p = 0.01$) Q8W Subgroup with baseline blood eosinophils <300 cells per μL: • 64 mL (95% CI −49, 176; p = ns) Q4W • −15 mL (95% CI −127, 96; p = ns) Q8W
ZONDA, Nair et al., 2017 [55]	Benralizumab	$N = 220$	18–75	1:1:1 (placebo)	For 28 weeks • 30 mg SC Q4W • 30 mg SC Q8W	Least square mean difference from placebo • 105 mL (95% CI −40, 251; p = ns) • 112 mL (95% CI −33, 258; p = ns)
Castro et al., 2011 [59]	Reslizumab	$N = 106$	18–75	1:1 (placebo)	For 15 weeks • 3 mg/kg IV Q4W	Least-square mean difference from placebo • 240 mL (95% CI 88, 392; $p = 0.002$)
Castro et al., 2015 [60]	Reslizumab	$N = 953$	12–75	1:1 (placebo)	For 52 weeks 3 mg/kg IV Q4W	Least-square mean difference from placebo • 110 mL (95% CI 67, 150; $p < 0.0001$)

Table 2 (continued)

Study, year (reference)	Biological agent	Patients	Age range (years)	Randomization	Doses and routes of administration	Mean prebronchodilator FEV1 improvement after treatment
Bjermer et al., 2016 [61]	Reslizumab	$N = 315$	12–75	1:1:1 (placebo)	For 16 weeks • 0.3 mg/kg IV Q4W • 3 mg/kg IV Q4W	Difference from placebo • 115 mL (95% CI 16, 215; $p = 0.0237$) • 160 mL (95% CI 60, 259; $p = 0$ .0018)
Bernstein et al., 2020 [62]	Reslizumab	$N = 645$	12–75	1:1 (placebo)	For 52 weeks • 110 mg SC Q4W	Least-square mean difference from placebo • 140 mL (95% CI 57, 230; minimal clinically important difference was change of 100 mL) Subgroup with baseline blood eosinophils >300 to <400 cells per μL • 130 mL (95% CI −53, 310; minimal clinically important difference was change of 100 mL) Subgroup with baseline blood eosinophils ≥400 cells per μL • 150 mL (95% CI 54, 250; minimal clinically important difference was change of 100 mL)

CI confidence interval, *FEV1* forced expiratory volume in 1 second, *IV* intravenous infusion, *ns* not significant ($p > 0.05$), *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous injection

subset of patients. From a biological perspective, asthma in elderly patients is more often T2-low rather than T2-high [68]. Nevertheless, limited *real-life* evidence confirms the clinical benefit of anti-IL-5 pathway in older adults.

2.3.1 Mepolizumab

In a single-center, retrospective, observational study, 20 patients (mean age of 77.5 ± 1.3 years) with severe asthma and overlapping chronic obstructive pulmonary disease were treated with mepolizumab, reducing a clinically significant exacerbation, glucocorticoid use, but did not improve lung function [69].

2.3.2 Mepolizumab, Benralizumab, and Reslizumab

A recent study performed a cross-sectional analysis to characterize patients from the Severe Heterogeneous Asthma Research Collaboration Patient-centred (SHARP Central) registry who were initiating an anti-IL-5 therapy [70]. This study demonstrated that patients with multiple comorbidities (related or not to asthma), older age, heavy smokers, and patients with airway remodeling appear to benefit from anti-IL-5 pathway treatments.

In a prospective cohort study from 22 countries enrolled in the International Severe Asthma Registry (ISAR) who were eligible for biological therapy, 16% of the patients (in the anti-IgE group) and 25% of the patients (in the anti-IL-5 pathway group) were aged ≥65 years [17]. Overall, the study concluded that patients treated with an anti-IL-5 therapy experienced fewer asthma exacerbations and used fewer oral corticosteroids.

Regarding safety, no specific study was performed to assess the safety of biologicals in older patients treated with anti-IL-5 pathway agents. A study on omalizumab, mepolizumab, benralizumab, and reslizumab (that included 21 older adults, over 147 patients), did not identify age as a risk factor for adverse events [71]. Notably, the liver and kidney are not directly involved in the degradation/excretion of monoclonal antibodies, thus it is unlikely that liver or kidney failure could modify the pharmacokinetics of the drug, and no dosage adjustment is required, also in the elderly population [72, 73]. In conclusion, there is no RCT focusing on anti-IL-5 therapy in individuals aged over 65 years, while real-world data are limited.

3 Chronic Rhinosinusitis with Nasal Polyps

Chronic rhinosinusitis with nasal polyposis affects 2.2–4.4% of the European population and is usually associated with asthma [74, 75] and, from a pathogenic perspective, is generally mediated by a type 2 inflammation pattern in adults [76]. In fact, in adults, nasal polyps are a marker of type 2 inflammation. In contrast, chronic rhinosinusitis in childhood is more likely related to the sub-acute/chronic immune response toward bacteria within adenoids, a source of pathogens, rather than idiopathic eosinophilic inflammation [77]. Consequently, most children with chronic rhinosinusitis do not develop nasal polyps and after the failure of

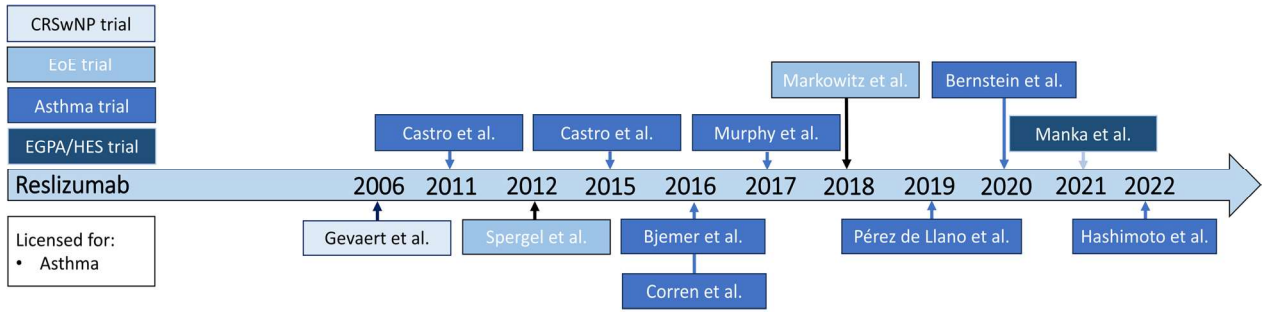

Fig. 5 Clinical development of reslizumab. Here are reported the more relevant clinical trials for reslizumab for eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRwNP), eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES). Reslizumab is presently licensed for asthma

adenoidectomy, pediatric sinus surgery is considered [78]. Chronic rhinosinusitis with nasal polyposis at age <10 years is rare and usually entails a systemic disease, such as cystic fibrosis or primary ciliary dyskinesia [79].

Finally, predictive factors have been identified in asthma to forecast super-responders, responders, and non-responders to biologics. However, such analyses are lacking in CRSwNP in both children and adults [80].

3.1 Pediatric

Reports specifically focusing on patients with CRSwNP in pediatric age (i.e., ≤18 years) are scant, and mostly case reports. Even if RCTs on CRSwNP usually include patients from 12 years of age or older, the participants are rarely adolescents [81]. Therefore, further studies are required for children (Table 1). There are no anti-IL-5 treatments licensed for CRSwNP aged <18 years.

3.2 Adults Aged >65 Years

The average age of onset of CRSwNP is 42 years, while the age of diagnosis ranges from 40 to 60 years [82]. Most papers on CRSwNP do not differentiate between adults and seniors (age >65 years), therefore preventing age-related considerations; specific studies are advocated. For CRSwNP, only mepolizumab has been licensed by the FDA/EMA among anti-IL-5 pathway agents (Table 1) [81]. Table 3 reports the main findings of RCTs of anti-IL-5 biological agents in adults with CRSwNP.

3.2.1 Mepolizumab

A preliminary study on 20 patients published in 2011, testing mepolizumab 750 mg given intravenously, proved that nasal function scores improved [83]. Following this study, a randomized trial demonstrated that intravenous mepolizumab 750 mg slightly reduced short-term (<6 months) sinus surgeries in patients with severe CRSwNP and improved the nasal polyp score (NPS), nasal polyposis severity visual analog scale score, and the Sinonasal Outcome Test (SNOT)-22 score [84]. In the Phase III SYNAPSE trial (Fig. 3), a recently published, larger clinical trial on mepolizumab in CRSwNP testing, the subcutaneous administration of mepolizumab 100 mg (in addition to intranasal mometasone), improved the nasal obstruction visual analog scale score, lowered the NPS, and reduced systemic corticosteroid use and the number of surgeries; without increased mepolizumab-related adverse events [85]. This study led to the approval of mepolizumab for CRSwNP by the FDA and EMA.

Finally, in a systematic review to inform the development of European Academy of Allergy and Clinical Immunology guidelines, mepolizumab reduced the need for surgery (relative risk: 0.78; 95% CI 0.64, 0.94), and improved quality of life (mean difference: −13.3; 95% CI −23.93, −2.67) and smell (mean difference: 0.7; 95% CI −0.48, 1.88), but with low levels of certainty according to the GRADE system [15].

3.2.2 Benralizumab

The phase III OSTRO study on benralizumab (given 30 mg subcutaneously vs placebo every 4 weeks for the first 3 doses and then every 8 weeks) reported an improvement in the NPS and long-term nasal blockage score, but no significant difference versus placebo in terms of improvements in SNOT-22 score at week 40, time to first nasal polyps surgery and/or systemic corticosteroid use for nasal polyps, and time to first nasal polyp surgery. Of note, patients aged >65 years were a minority of the 207 enrolled patients (Fig. 4) [86]. However, another double-blinded, multicenter, parallel-group, 56-week phase III trial named ORCHID (NCT04157335) to evaluate the effect of benralizumab on nasal polyp burden is ongoing, and results are waited for 2024.

In the ANDHI phase IIIb study [56, 87] conducted in patients with eosinophilic asthma, 92 CRSwNP-affected adults received benralizumab (given 30 mg subcutaneously, every 4 weeks for the first three doses and then every 8 weeks) with an improvement in SNOT-22 at 24 weeks, especially for those with higher scores at baseline (>30), with no significant difference of adverse events in both groups. Notably, severe adverse events in the benralizumab arm were lower than people in the placebo, both in the overall population of patients with CRSwNP [56]. A small clinical trial enrolling 24 patients with severe CRSwNP (NPS ≥5) who had already undergone nasal surgery, showed that a benralizumab 30-mg single dose improved NPS more than the placebo, although this did not reach statistical significance [88]. Moreover, 45% of drug-treated patients versus 17% of placebo-treated patients at week 20 had an improved NPS, Lund-Mackay computed tomographic scan score, SNOT-22 score, and smell test score, although the difference from placebo was not statistically significant [88].

A phase II RCT enrolled 56 Japanese adults (aged ≥20 years) who were randomized to either placebo or benralizumab 30 mg subcutaneously (single dose), or benralizumab 30 mg subcutaneously every 4 weeks (three doses) [89]. No significant difference regarding the NPS reduction at 12 weeks was seen between the three groups, although, in a post hoc analysis, patients with a higher blood eosinophil count (>10%) responded better to benralizumab [89]. However, as IL-5 is expressed in 80% of nasal polyps of European patients versus 20–60% of Asian patients, Japanese ethnicity may have influenced these results [76]. Significantly higher adverse events were observed: 56.5% and 72.7% in every 4 weeks and single-dose groups, respectively, versus 45.5% of the placebo group.

3.2.3 Reslizumab

To date, this biological agent is not registered for the treatment of CRSwNP. In a single, double-blind, placebo-controlled study designed to assess the safety and pharmacokinetic of reslizumab, 24 subjects affected by CRSwNP (either recurrent after surgery or with bilateral NPS ≥3) were randomized to either a single intravenous infusion of reslizumab (single dose of either 3 mg/kg or 1 mg/kg) or placebo (Fig. 5) [90]. No difference in the use of systemic nasal corticosteroids was observed and the efficacy results were conflicting (i.e., results on the median change from the baseline of the NPS were not straightforward, with "significant" change vs placebo for 1 mg/kg and "non-significant" change vs placebo for 3 mg/kg).

4 Eosionophilic Esophagitis

Eosinophilic esophagitis is an antigen-driven non-IgE-mediated disease, sustained by a type 2 inflammation, and defined by the presence of at least 15 eosinophils per high power field (HPF) on esophageal biopsies [91]. This condition is responsible for different clinical patterns, with a prevalence of dysphagia, food impaction, and chest pain in adults, and non-specific symptoms commonly present in children, such as vomiting, feeding difficulties, and failure to thrive [92]. Older patients (aged >65 years) are rarely affected, accounting for less than 10% of the adult population with EoE [93, 94], and performing no significant differences in clinical presentations, except for a lower recurrence of food allergy, asthma [93], and atopic dermatitis [94]. Moreover, a significantly higher prevalence of comorbidities requiring medical treatments has been described for them [94]. Given the limitations and possible side effects of the current therapeutic options for EoE (i.e., elimination diet, topical corticosteroid therapy, and proton pump inhibitor), biological agents could potentially be a relevant treatment strategy for this condition. However, current evidence regarding the efficacy of anti-IL-5 agents in patients with EoE is conflicting, and such therapies are not approved by the FDA or EMA for this condition (Table 4).

Interleukin-5 promotes the growth and survival of eosinophils, and eosinophil-derived IL-9 performs the same effects on mast cells. As a result of eosinophil and mast cell activation, the prolonged release of pro-fibrotic factors (i.e., transforming growth factor-β1, FGF-9) enhances the epithelial remodeling, resulting in basal zone hyperplasia, lamina propria fibrosis. and expansion of muscularis propria, thus leading to esophageal dysmotility and strictures [91]. In addition, a study performed on a multi-site cohort of more than 300 patients from 4 to 71 years of age, highlighted a higher expression of IL-5 in active cases of EoE (defined by histopathologic and endoscopic findings, and molecular profiling). Interestingly, such IL-5 expression did not increase linearly according to the natural evolution of the disease, but it underwent a transition from an IL-5 low phenotype to an IL-5 high phenotype after inflammatory or allergic insults, up to an IL-5 intermediate phenotype in a more advanced phase of the disease characterized by fibrostenosis [95]. Considering the lack of efficacy of the RCTs on anti-IL-5 agents, the role of IL-5 in orchestrating the inflammation in EoE should be carefully evaluated.

Table 3 Double-blind, placebo-controlled, randomized clinical trials of anti-interleukin-5 biologic agents in adults with chronic rhinosinusitis with nasal polyposis

Study (reference)	Biological agent	Patients	Randomization	Doses and routes of administration	Primary outcome	Reduction in the SNOT-22 after treatment	Need for nasal surgery after treatment
Gevaert et al., 2011 [83]	Mepolizumab	$n = 30$	$n = 20$ active $n = 10$ placebo	For 8 weeks • 750 mg IV Q4W	Change from baseline in total polyp score at week 8 • Difference from placebo: −1.30 (SD, 1.51; $p = 0.028$)	NA	At week 8 (primary time point) • 0% active vs 10% placebo; p = ns At week 48 (end of the follow-up) • 20% active vs 30% placebo; p = ns
Bachert et al., 2017 [84]	Mepolizumab	$n = 156$	$n = 105$ active $n = 51$ placebo	For 24 weeks • 750 mg IV Q4W	Number of patients no longer requiring surgery at week 25 • 30% active vs 10% placebo; $p = 0.006$	Difference from placebo: −13.2 (95% CI −22.2, −4.2; $p = 0.005$)	See primary outcome
SYNAPSE, Han et al., 2021 [85]	Mepolizumab	$n = 407$	$n = 206$ active $n = 201$ placebo	For 52 weeks • 100 mg SC Q4W	Change from baseline in total Endoscopic Nasal Polyp Score at week 52 • difference from placebo: −0.73, (95% CI −1.11, − 0.34; $p < 0.0001$) Change from baseline in mean nasal obstruction VAS score during weeks 49–52 • Difference from placebo: −3.14 (95% CI −4.09, −2.18; $p < 0.0001$)	Difference from placebo: −16.49 (95% CI −23.57, −9.42; $p = 0.0032$)	Proportion of patients having nasal surgery up to week 52 (time to first surgery) • 9% active vs 23% placebo; $p = 0.003$
Bachert et al., 2022 [86]	Benralizumab	$n = 413$	$n = 207$ active $n = 206$ placebo	For 40 weeks • 30 mg SC Q4W first 3 doses then Q8W	Change from baseline in Nasal Polyp Score • Difference from placebo: −0.570 (95% CI −0.852, −0.289; $p < 0.001$) Change from baseline in Nasal Blockage Score • difference from placebo: −0.270 (95% CI −0.458 to −0.083; $p = 0.005$)	Difference from placebo: −5.21 (95% CI −11.09, 0.66; p = ns)	Proportion of patients having nasal surgery up to week 40 (time to first surgery) • 15.9% active vs 18.2% placebo; p = ns
Canonica et al., 2022 [87]	Benralizumab	$n = 153$	$n = 96$ active $n = 57$ placebo	For 24 weeks • 30 mg SC Q4W first 3 doses then Q8W	Change from baseline in the SNOT-22 at week 24 • Difference from placebo: −10.44 (95% CI −19.02, −1.86; $p = 0.017$)	Proportion of patients with clinically meaningful improvements from baseline in SNOT-22 (at least ≤−8.9 at week 24) • 71.3% active vs 45.5% placebo ($p = 0.003$)	NA

Table 3 (continued)

Study (reference)	Biological agent	Patients	Randomization	Doses and routes of administration	Primary outcome	Reduction in the SNOT-22 after treatment	Need for nasal surgery after treatment
Tversky et al., 2021 [88]	Benralizumab	$n = 24$	$n = 12$ active $n = 12$ placebo	For 20 weeks • 30 mg SC Q4W first 3 doses then Q8W	Change from baseline in Endoscopic Nasal Polyp Score at week 20 • Difference from placebo −0.5 (± 0.3; p = ns) Change from baseline in CT score at week 20 • Difference from placebo −2.6 (± 1.2; p = ns)	Difference from placebo: −2.58 (±5.3; p = ns)	NA
Takabayashi et al., 2021 [89]	Benralizumab	$n = 56$	$n = 22$ active (A) $n = 23$ active (B) $n = 11$ placebo	• (A) 30 mg SC, 1 dose • (B) 30 mg SC Q4W, 3 doses	Change in Nasal Polyp Score from baseline at week 12 • (A) difference from placebo: 0.3 (95% CI −0.3, −0.9; p = ns) • (B) difference from placebo: 0 (95% CI −1, −1; p = ns)	No clinically relevant differences between either of the benralizumab groups and placebo	NA
Gevaert et al., 2006 [90]	Reslizumab	$n = 24$	$n = 8$ active (A) $n = 8$ active (B) $n = 8$ placebo	• (A) 1 mg/kg IV, 1 dose • (B) 3 mg/kg IV, 1 dose	This study was designed to evaluate safety and pharmacokinetics and not powered to detect treatment differences in efficacy variables	NA	At week 8: 0/16 active group vs 2/8 (25%) placebo (no statistical comparison; primary outcome was safety)

CI confidence interval, *CT* computed tomographic, *IV* intravenous infusion, *NA* not available, *ns* not significant ($p > 0.05$), *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneous injection, *SD* standard deviation, *SNOT-22* Sino-Nasal Outcome Test-22

4.1 Pediatric

4.1.1 Mepolizumab and Benralizumab

There are no trials for mepolizumab and benralizumab in children.

4.1.2 Reslizumab

For reslizumab, the only two trials assessing its effect in the treatment of EoE have been performed in populations of children and adolescents (Fig. 5, Table 4). The first one [96], assessing a period of therapy of 3 months, validates once again the role of anti-IL-5 in providing a significant reduction in intraepithelial esophageal eosinophilia, but still without a concomitant significance in clinical improvements. The more recent trial of Markowitz et al. [97] instead, offers a broader view by considering a longer time of follow-up (9 years) for 12 children. They all reported a considerable improvement in symptoms (absence of vomiting), a non-progression of the disease at the endoscopy (none of them developing esophageal narrowing or strictures), and a complete histopathologic remission (<2 eosinophils/HPF).

4.2 Adults Aged >65 Years

4.2.1 Mepolizumab

The first study testing anti-IL-5 in EoE is a small open-label trial of Stein et al., in which mepolizumab was administrated at a dose of 750 mg monthly for three times to four adult patients with a story of long-lasting EoE and esophageal narrowing (Fig. 3) [98]. A reduction of about nine-fold of mean esophageal eosinophilia has been reported, but never under the threshold level for the EoE remission (<5 eosinophils/HPF). Moreover, the patients reported improvements in clinical outcomes (i.e., dysphagia) and quality-of-life scores, but it is difficult to determine if they occurred for the biological treatment or the concomitant therapy, i.e., glucocorticoids, proton pump inhibitors, and an elimination diet, that they previously adhered to and never interrupted [98]. In a later double-blind placebo-controlled study by Straumann et al. [99], adult patients with EoE were treated only with mepolizumab and, despite the use of even higher doses compared with the previous study, they achieved only minimal improvements in symptoms (Fig. 3). A significant reduction in esophageal eosinophilia in terms of mean and peak was confirmed instead, although also in this case it never determined a histopathologic complete remission (<5 eosinophils/HPF). In this regard, mepolizumab seems to be slightly more effective in children, as shown in the trial of Assa'ad et al., where five of 57 patients reported complete histopathologic remission (Fig. 3) [100].

Another phase II recent study with mepolizumab administered through the subcutaneous route confirmed a dissociation between histopathologic enhancements in terms of eosinophilic infiltration of the esophagus and concrete positive effects on clinical manifestations [101]. This may suggest that the role of eosinophils might be less important than previously thought in the pathogenesis of EoE and consequently in its clinical presentation, in contrast to the effect of other inflammatory cells within the esophageal mucosa, such as T-regulatory cell, T-helper 2-like effectors, and mast cells.

4.2.2 Benralizumab

In recent years, several case reports have addressed their attention on benralizumab [102, 103], an anti-IL-5-receptor antibody, for which the FDA granted in 2019 the orphan drug status for use in EoE. Compared with the anti-IL-5 agents, benralizumab can count on a second mechanism beyond the block of the IL-5 bond to its receptor, which is the recruitment of natural killer cells, macrophages, and neutrophils through its Fc region, and the induction of antibody-dependent cell-mediated cytotoxicity for eosinophils and basophils [104]. Despite this, results of the MESSINA trial (NCT04543409), a recently completed phase III trial enrolling patients with EoE aged 12 years or older that will be likely published in 2024, did not show the improvement of dysphagia symptoms (one of the two primary endpoints, while demonstrating a significant improvement in histological disease remission) compared to placebo (Fig. 4).

4.2.3 Reslizumab

There are no trials for reslizumab in adults aged >65 years.

5 Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis is a rare systemic antineutrophilic cytoplasmatic antibody-associated vasculitis, even if antineutrophilic cytoplasmatic antibodies (most often against myeloperoxidase) are detectable up to 40% of patients [105]. It is characterized by a multi-systemic involvement (lung, nose and sinuses, heart, gastrointestinal tract, kidneys, and peripheral nerves), with a wide spectrum of clinical manifestations including asthma, chronic rhinosinusitis, peripheral eosinophilia and histologically characterized by tissue eosinophilia, necrotizing vasculitis, and eosinophil-rich granulomatous infiltration [106]. The onset of EGPA

Table 4 Randomized controlled trials of anti-interleukin-5 agents for eosinophilic esophagitis (none is currently approved by the European Medicines Agency or US Food and Drug Administration)

Study (reference)	Biological agent	Type of study	Patients	Age range (years)	Dose, and routes of administration	Histologic remission (peak eos count <5/HPF)	Reduction in esophageal eosinophilia	Endoscopic outcome	Clinical improvement
Straumann et al., 2009 [99]	Mepolizumab	DBPCRCT	$n = 11$ ($n = 5$ active; $n = 6$ placebo)	>18	2 IV infusions of 750 mg Q1W If non-complete histologic remission after 8 weeks: 2 more IV infusions of 1500 mg Q4W	No	Peak eos count: −65% compared to baseline ($p = 0.028$) Mean: −55% compared to baseline ($p = 0.011$)	Improved in 3/5 (60%)	No
Assa'ad et al., 2011 [100]	Mepolizumab	DBRCT	$n = 59$ (randomized to 3 different doses; no placebo)	2–17	3 IV infusions Q4W of • 0.55 mg/kg • 2.5 mg/kg • 10 mg/kg	5/57 (8.8%) No difference in the 3 doses	Peak eos count: −67% compared to baseline ($p < 0.0001$) Mean eos count −76% compared to baseline ($p < 0.0001$)	Improved in 18/57 (31.6%)	No
Spergel et al., 2012 [96]	Reslizumab	DBPCRCT	$n = 226$ ($n = 169$ randomized to 3 different doses; $n = 57$ placebo)	5–18	4 IV infusions Q4W of • 1 mg/kg • 2 mg/kg • 3 mg/kg	8/169 (4.7%)	Peak eos count: • −59% (1 mg/kg; $p < 0.001$) • −67% (2 mg/kg; $p < 0.001$) • −64% (3 mg/kg; $p < 0.001$) compared to baseline	NA	Improvement in physician's global assessment scores, without significant differences with placebo group
Markowitz et al., 2018 [97]	Reslizumab	DBPCRCT	First phase (DBPCRCT) $n = 12$ Second phase (open-label) $n = 8$ Third phase (compassionate use) $n = 4$	7–16	IV infusion Q4W • First phase: 1, 2, or 3 mg/kg or placebo for 3 months • Second phase: 1–3 mg/kg for 3.5 years • Third phase: up to 2 mg/kg for 5.5 years (interval: 4 weeks)	92% ($p < 0.001$)	Median: 2 eos/HPF (interquartile range, 0–4)	No disease progression; no narrowing or stricture	Symptoms improved on treatment: dysphagia (42%); abdominal pain (58%); heartburn (18%); reflux (58%); vomiting (67%); (absence of vomiting in second and third phases)

DBPCRCT double-blind, placebo-controlled, randomized clinical trial, *eos* eosinophils, *HPF* high-power field, *IV* intravenous, *NA* not available, *Q1W* every week, *Q4W* every 4 weeks

usually occurs in adults with a mean age at diagnosis of 50 years, but rare cases of EGPA are reported in children with predominant pulmonary and cardiac involvement compared to adults [107]. Because of typical relapses, systemic corticosteroids and immunosuppressive drugs are administered to achieve remission and disease control. Eosinophils are directly involved in tissue damage [108] and therefore targeting IL-5 in corticosteroid-dependent eosinophilic EGPA represents a growing field in current research [109].

5.1 Pediatrics

5.1.1 Mepolizumab

Currently, mepolizumab is the only biologic treatment approved by EMA and FDA for patients with EGPA, both in children (from age 6 years and above) and in adults (Table 1). Data on mepolizumab administration in the pediatric population are limited to only a few case reports that illustrate the efficacy of mepolizumab, at both doses of 100 mg and 300 mg every 4 weeks, as an add-on therapy in relapsing EGPA [110–112].

For adolescent patients aged ≥12 years with EGPA, the approved dose of mepolizumab is 300 mg every 4 weeks subcutaneously, as for adult patients (Table 1). For children aged 6–11 years, the dose of subcutaneous mepolizumab has been extrapolated from pharmacokinetic studies available for patients with severe asthma [23, 113]. This extrapolation led to the approval of mepolizumab for EGPA at a 100-mg dose for children aged 6–11 years weighing <40 kg and a 200-mg dose for those weighing ≥40 kg [114].

5.1.2 Benralizumab and Reslizumab

Only one case report describing the efficacy of benralizumab in a 16-year-old boy with antineutrophilic cytoplasmatic antibody-negative EGPA presenting with skin manifestations (eosinophilic infiltration and small-vessel and medium-vessel vasculitis) has been described [115]. With this exception, there are no studies available for reslizumab and benralizumab in patients aged ≤18 years and the MANDARA trial (NCT04157348), currently comparing mepolizumab versus benralizumab in EGPA excludes patients aged ≤18 years.

5.2 Adults

5.2.1 Mepolizumab

An open-label pilot study and a phase II investigator-initiated study, enrolling seven and ten young adults with EGPA respectively, confirmed the efficacy of intravenous mepolizumab 750 mg/every 4 weeks as a corticosteroid-sparing agent [116, 117]. Then, the efficacy and safety of mepolizumab in relapsing or refractory EGPA were confirmed in 2017 in a large phase III trial enrolling adults with relapsing or refractory EGPA [118]. This double-blind placebo-controlled trial (MIRRA study) was conducted on 136 patients with EGPA (mean age 49 ± 12 years), who were randomized to either subcutaneous mepolizumab 300 mg every 4 weeks or placebo for 52 weeks. No previous dose-finding study was performed, but the dose was extrapolated by a "dose meta-analysis" [113]. The two primary endpoints were both met, with mepolizumab leading to significantly more accrued weeks of remission than placebo (28% vs 3% of the participants had ≥24 weeks of accrued remission) and to a higher percentage of participants in remission at both week 36 and week 48 (32% vs 3%) (Table 1, Fig. 3). A post hoc analysis of this study showed that 87% of mepolizumab-treated patients achieved remission compared with 53% in the placebo group, using a less stringent definition as compared with the trial (i.e., EULAR remission criteria with Birmingham Vasculitis Activity Score = 0 and prednisone dose ≤7.5 mg/day, or a ≥50% reduction of glucocorticoid dose or relapse free) [119]. In addition, a multicenter retrospective study conducted on 191 patients treated with a stable dose of mepolizumab 100 mg or 300 mg per month confirms the efficacy of both dosages for the treatment of patients with EGPA, suggesting the need for a controlled trial to test is 100 mg could suffice to keep EGPA in remission [120]. However, it is worthy to mention that only the 300 mg per month is approved for EGPA. There is also an ongoing trial, the OCEAN study, that compares head-to-head mepolizumb 300 mg/every 4 weeks versus depemokimab (new biologic agent with high affinity to IL-5) 200 mg/every 26 weeks in patients with relapsing or refractory EGPA receiving standard of care (NCT05263934).

5.2.2 Benarlizumab

After a case report of a 63-year-old woman with asthma, chronic rhinosinusitis, pulmonary infiltrates, and hypereosinophilia successfully treated with benralizumab subcutaneously 30 mg/every 4 weeks [121], the first prospective 40-week open-label pilot study was published in 2021 and demonstrated the corticosteroid-sparing effect and the reduction of exacerbation rate in EGPA patients treated with benralizumab 30 mg monthly [122]. In February 2024, the MANDARA phase III trial (NCT04157348), comparing benralizumab with mepolizumab for EGPA has been published [123], demonstrating the non-inferiority in the efficacy of benralizumab 30 mg/every 4 weeks versus

mepolizumab 300 mg/every 4 weeks, while contributing to tapered off oral glucocorticoids in a higher proportion of patients (41.4% in benralizumab vs 25.8% in mepolizumab were fully tapered off). Given the positive results of benralizumab of this RCT, benralizumab will be soon approved by FDA/EMA for the treatment of EGPA.

Real-life data on benralizumab in EGPA are accumulating. A multicenter retrospective study on 68 patients with EGPA (37 naïve, 31 previously treated with mepolizumab) showed that the off-label treatment with benralizumab every 8 weeks (asthma dose) was effective in inducing a complete response (reached by 49% of participants), in particular in those patients who were not previously treated with mepolizumab [124]. In another multicenter observational study, 26 patients with EGPA treated with benralizumab (asthma dose), showed a sustained remission in 61.5% [125]. These findings were confirmed by a recent study on 121 refractory patients treated with benralizumab (asthma dose), achieving complete remission in 46.4% of cases at 12 months [126].

5.2.3 Reslizumab

Reslizumab has not yet been approved for EGPA. Currently, there is only one ongoing pilot phase II study (RITE Study), including 10 adults treated with intravenous reslizumab 3 mg/kg in addition to their ongoing therapy every 4 weeks for a 28-week treatment [63]. From preliminary results, reslizumab led to a significant decrease in daily oral corticosteroid administration. Three subjects experienced disease relapse.

5.3 Adults Aged >65 Years

5.3.1 Mepolizumab, Benralizumab, and Reslizumab

There are no studies or clinical trials for mepolizumab, benralizumab, and reslizumab conducted exclusively in patients aged >65 years. Published and ongoing RCTs on EGPA did not set an age-upper limit for participation.

6 Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a rare heterogeneous condition characterized by persistent hypereosinophilia (eosinophils >1500/mm^3) and the demonstration of a tissue eosinophilic infiltration. When no identifiable causes are found (i.e., such as allergic, parasitic, and malignant disorders have been excluded), this condition is idiopathic HES. Patients are typically adults between 20 and 50 years of age, mostly male (4:9:1 ratio) but rare cases among children [127] and older adults [128] have been described. In children, primary immunodeficiency should be investigated, in particular in patients with severe hypereosinophilia (eosinophils >5000/mm^3) [129].

Eosinophil-related organ damage typically involves the skin, respiratory tract, gastrointestinal tract, cardiac tissue, and nervous system. It is a relapse-remitting disease and management consists of long-term treatment with oral corticosteroids, except for clonal myeloproliferative variants of HES that are generally treated with imatinib, specifically targeting tyrosine kinases as BCR-ABL, c-KIT, and FIPL1-PDGFRA (which can be mutated in malignant HES). During the last 20 years, eosinophilic drugs have been shown to be a safe and effective alternative in idiopathic HES and lymphocytic HES, in a subvariant of secondary HES characterized by overproduction of IL-5 by dysregulated T cells [130].

6.1 Pediatric

6.1.1 Mepolizumab

Currently, mepolizumab is the only biologic treatment approved by the EMA and FDA for adult HES patients (Table 1) [131–137], while is not currently approved for children. Data on mepolizumab in pediatric population are limited to only a few case reports that illustrate the efficacy of mepolizumab in HES in reducing disease relapse and the use of long-term corticosteroid treatment. A monthly dose of intravenous mepolizumab 10 mg/kg was successfully used in a 9-year-old boy with idiopathic HES who presented with asthma and eosinophilic cellulitis [138]. Schwarz et al. reported two cases: a clonal variant of HES and a lymphocytic HES successfully treated with mepolizumab [139]. Mepolizumab was recently used in a 4-year-old boy for lymphocytic HES [140]. One of the phase III trial tested mepolizumab 300 mg every 4 weeks enrolled patients aged ≥12 years, but only a minority were adolescents (with the youngest aged 15 years) [135]. A phase III trial study in children and adolescents (aged 6–17 years) with HES (SPHERE trial, NCT04965636) testing subcutaneous mepolizumab is ongoing.

6.1.2 Benralizumab

Only one case report describes the efficacy of a monthly dose of subcutaneous benralizumab 30 mg in an 8-year-old girl with severe idiopathic corticosteroid-dependent HES presenting with heart and skin manifestations, being able to become corticosteroid free without any exacerbation [141].

6.1.3 Reslizumab

Reslizumab treatment, given intravenously at a dose of 3 mg/kg, was successfully used in a 17-year-old Korean girl with lymphocytic HES presenting initially with episodic angioedema with eosinophilia, after failure of mepolizumab 100 mg monthly [142].

6.2 Adults

6.2.1 Mepolizumab

The first two open-label studies testing mepolizumab (10 mg/kg, maximum 750 mg/every 4 weeks) in three and four patients with HES, respectively, were published in 2003 [131] and 2004 [132], showing safety and efficacy in sparing glucocorticoids. Rothenberg et al. [133] published the first randomized, double-blind, placebo-controlled, international trial that evaluates the safety and efficacy of mepolizumab 750 mg given intravenously in 43 adults (age 47 ± 16.2 years) with idiopathic HES treated with prednisone 20–60 mg/day; a reduction in the corticosteroid dose under 10 mg/day was reached in 84% of patients in the active group. The efficacy of mepolizumab as a corticosteroid-sparing agent was then proved in a lymphocytic variant of HES [134]. The first phase III trial with mepolizumab 300 mg every 4 weeks by the subcutaneous route in FIP1L1-PDGFRA-negative ≥12-year-old patients with HES was published in 2020 by Roufosse et al. (Table 1, Fig. 3) [135]. The study demonstrated that mepolizumab 300 mg every 4 weeks was associated with a reduction in flares during the 32 weeks of treatment, irrespective of blood eosinophil count and IL-5 [136]. This result was confirmed in an open-label extension study by Gleich et al. [137], which also demonstrated the corticosteroid-sparing effect of mepolizumab 300 mg every 4 weeks. These studies led to the approval of mepolizumab 300 mg every 4 weeks in adults with HES. Of note, the phase II trial (DESTINY; NCT05334368) testing depemokimab versus standard of care is ongoing.

6.2.2 Benralizumab

In a small phase II study, Kuang et al. showed that 74% of the patients treated with benralizumab for 12 weeks had a sustained response at 48 weeks [143]. A phase IIa RCT to evaluate the safety and efficacy of subcutaneous benralizumab in reducing eosinophilia in subjects with HES (HESIL5R study, NCT02130882; primary endpoint 50% reduction in the blood eosinophil count on stable HES at 12 weeks) is ongoing and results are awaited.

6.2.3 Reslizumab

A few case reports have been described to illustrate the efficacy of reslizumab 3 mg/kg in idiopathic HES with skin and esophagus involvement [144] and in lymphocytic HES with skin involvement [145]. An open-label trial on four patients tested reslizumab 1 mg/kg, which was well tolerated and in two out of four patients signs and symptoms improved [146].

6.3 Aged Over 65 Years

6.3.1 Mepolizumab, Benralizumab, and Reslizumab

There are no studies or clinical trials for mepolizumab, benralizumab, and reslizumab conducted exclusively in patients aged >65 years in HES. Published and ongoing RCTs on HES did not set an age-upper limit for participation.

7 Conclusions

Current biologics targeting the IL-5 pathway, namely mepolizumab, benralizumab, and reslizumab, have changed expectations on the treatment of eosinophilic-associated conditions, leading to the general improvement of these diseases' burden. Eosinophilic asthma is currently the condition with most evidence across all age groups, with all the three biologics yet approved in adults (aged ≥18 years); mepolizumab is also approved for children (aged ≥6 years) both in Europe and in the USA, whereas benralizumab was recently approved for children (aged ≥6 years) in the USA.

In CRSwNP, mepolizumab, in addition to intranasal mometasone, is the only biological treatment approved (age ≥18 years), and is often utilized in patients with CRSwNP with asthma. Data for individuals aged under 18 years and above 65 years are limited.

In EoE, there is conflicting evidence on both intravenous mepolizumab and reslizumab, which did not end up in the FDA or EMA approval for this rare condition. Notably, less than 10% of EoE affects patients aged >65 years.

Finally, for both EGPA and HES, mepolizumab was recently approved at a dose three times higher than the one used for eosinophilic asthma in adults (i.e., 300 mg every 4 weeks, with lower doses for ages <12 years in EGPA). Benralizumab 30 mg every 4 weeks showed to be non-inferior to mepolizumb in adults with EGPA (but is not yet approved), while no phase III RCTs on reslizumab (nor depemokimab) were yet published in both these conditions. Overall, there is limited evidence for both the pediatric and elderly populations, as compared to adults, regarding the efficacy and safety of anti-IL-5 biologics in all these eosinophilic-associated disorders, which limits the application of such therapies in these two age groups.

Declarations

Funding Open access funding provided by Università degli Studi di Trento within the CRUI-CARE Agreement.

Conflicts of Interest/Competing Interests Alvise Berti received funding from GSK (advisory boards, speaker fees). Overall, the authors

declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Authors' Contributions AB, CL, and PC designed the study and harmonized each section. All the authors drafted the manuscript. AB prepared all the figures. All coauthors interpreted the results and analyzed critically the manuscript for important intellectual content and approved the final version.

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