DOI: 10.53469/jcmp.2024.06(12).26

Anti-Eosinophil Biologics in Chronic Respiratory Diseases

Huizi Wu*, Lan Huang, Yan Liu

Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
**Correspondence Author*

Abstract: ***Eosinophils play a crucial role in the pathogenesis of various chronic respiratory conditions. Recent advances in understanding eosinophilic inflammation have promoted the development of biologics aimed at specifically targeting inflammation driven by eosinophils. One such biologic, benralizumab, has shown considerable efficacy and favorable tolerability in individuals with refractory eosinophilic asthma. While the efficacy of these therapies in COPD is less consistent, promising results have been observed in specific eosinophilic subtypes. For CRSwNP, biologics have shown potential in reducing nasal polyp size, alleviating clinical symptoms, and decreasing the need for surgical intervention. In spite of these therapeutic advancements, challenges remain, including high treatment costs and a lack of long-term safety data. Future research should prioritize biomarker identification to optimize patient selection and further individualize these therapies.***

Keywords: Asthma, Eosinophils, Biologics, Chronic obstructive pulmonary disease**.**

1. Introduction

Eosinophils, a subtype of granulocyte originated from myeloid progenitor cells, are involved in immune defense against parasitic infections and play various roles in both innate and adaptive immune responses under normal conditions [1,2]. Recent research has emphasized the role of eosinophil-derived granule proteins and chemical mediators in tissue damage, repair, remodeling, and disease progression in chronic respiratory diseases like asthma [3].Asthma, an inflammatory airway condition, is often featured by elevated eosinophil levels in the airways [4], where they contribute to epithelial injury, smooth muscle hypertrophy, neuronal plasticity, and impaired tissue repair processes that collectively promote chronic airway remodeling and airflow limitation [5, 6]. Moreover, elevated peripheral blood eosinophil levels are positively associated with greater disease severity, poor clinical control, and a higher likelihood of severe acute exacerbations [7, 8].Although chronic obstructive pulmonary disease (COPD) is typically characterized by an increase in alveolar neutrophils, macrophages, T lymphocytes, and circulating innate lymphoid cells [9], approximately 30–40% of COPD patients show increased eosinophil counts in peripheral blood and/or sputum [10-12]. Additionally, several studies have linked elevated eosinophil levels with poor prognosis in COPD [13, 14]. With deeper insights into eosinophil function, eosinophil-targeted therapies have emerged as a major focus in research. These therapies aim to reduce inflammation and enhance clinical outcomes by specifically inhibiting eosinophil activity. Compared to traditional treatments, eosinophil-targeted therapies provide greater specificity and fewer side effects, presenting notable clinical advantages. This review explores the mechanisms and clinical evidence surrounding eosinophil-targeted therapies, aiming to offer insights into future treatment strategies and support the advancement of personalized medicine.

2. Anti-IL-5/IL-5R Therapy

2.1 Benralizumab

IL-5 is a key cytokine that signals eosinophils through the IL-5 receptor (IL-5R), playing an essential role in their differentiation, proliferation, activation, and migration within the lung [2]. In humans, IL-5R is predominantly expressed on basophil and eosinophil precursors in the bone marrow, as well as on their mature forms. This receptor consists of two subunits: an α chain and a β chain. The monomeric IL-5Rα can bind to IL-5 with specificity, though its binding affinity is relatively low. However, when IL-5Rα forms a dimer with the β chain, the receptor's affinity for IL-5 is markedly increased.

Benralizumab is a humanized monoclonal antibody (IgG1κmAb) with afucosylation that specifically targets the allosteric structural epitope in domain 1 of IL-5Rα, effectively preventing IL-5 from binding to its receptor. The absence of fucose in the antibody's core glycan enhances its affinity for FcγRIIIa on natural killer cells, stimulating the release of cytotoxic proteins, including granzyme and perforin. This mechanism strengthens antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in the efficient and swift depletion of eosinophils [15]. Studies have demonstrated that both single intravenous infusions and repeated subcutaneous administrations of benralizumab significantly reduce eosinophil levels in airway tissues, sputum, bone marrow, and peripheral blood [16, 17].

2.1.1 Asthma

A phase 2b clinical trial demonstrated that benralizumab significantly lowers the frequency of exacerbations in individuals with poorly controlled eosinophilic asthma, particularly in those with peripheral blood eosinophil counts ≥300 cells/μL [18]. Supporting these results, the SIROCCO trial showed that benralizumab not only reduced exacerbation rates but also improved pulmonary function and quality of life in individuals with severe eosinophilic asthma who remained inadequately controlled despite high-dose ICS and LABA therapy [19]. FitzGerald et al. specifically evaluated this population in the CALIMA trial, which confirmed that benralizumab substantially reduced the risk of exacerbations, enhanced pulmonary function, and relieved asthma symptoms

in individuals with severe, refractory asthma [20]. A subsequent pooled analysis of the SIROCCO and CALIMA trials identified several clinical characteristics, beyond baseline peripheral blood eosinophil levels, that may predict a patient's response to benralizumab. These characteristics included prior oral corticosteroid use, nasal polyps, impaired lung function, frequent exacerbations, and adult-onset asthma [21]. Further, the extended phase 3 trials, BORA and MELTEMI, affirmed that long-term benralizumab therapy does not increase infection risk or introduce new adverse effects, while sustaining its therapeutic efficacy [22-24].

Given that some individuals with severe asthma necessitate ongoing treatment with oral or inhaled corticosteroids, which often result in adverse effects that severely diminish quality of life, several studies have examined the effectiveness of benralizumab in decreasing corticosteroid reliance among these individuals. Findings indicate that benralizumab significantly lowers the dose of required corticosteroids, reduces exacerbation risk [25, 26], and may present a safe and effective alternative treatment option.

2.1.2 COPD

Although several clinical trials have demonstrated that benralizumab did not significantly impact frequency of exacerbations, clinical symptoms, or health-related quality of life in COPD patients compared to placebo [27, 28], a subgroup of potential responders with specific clinical characteristics was identified. This subgroup consists of individuals who have experienced three or more exacerbations despite being treated with triple therapy (ICS/LAMA/LABA) and who have baseline peripheral blood eosinophil counts of ≥300 cells/μL. Consequently, Singh et al. conducted a post hoc analysis of the GALATHEA and TERRANOVA trials, categorizing individuals with high eosinophil levels and recurrent exacerbations despite guideline-based triple therapy as high-risk. Findings indicated that benralizumab effectively lowered the likelihood of re-exacerbation within 30-90 days following an acute exacerbation in this high-risk cohort [29], highlighting its potential clinical utility. Based on these results, two clinical trials are currently underway: the RESOLUTE trial (NCT04053634), a phase III study assessing benralizumab's efficacy in specific patient subgroups, and the ABRA trial (NCT04098718), which evaluates the effect of benralizumab on patients experiencing eosinophilic acute exacerbations of COPD, stratified by baseline peripheral blood eosinophil counts.

2.1.3 CRSwNP

Chronic rhinosinusitis is categorized into two primary phenotypes: with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). CRSwNP often manifests as nasal obstruction and diminished or complete loss of the sense of smell [30]. Approximately 85% of individuals with CRSwNP exhibit a T2-type inflammatory response, which is linked to more severe symptoms and commonly associated with conditions like asthma and aspirin-exacerbated respiratory disease [31, 32]. Benralizumab has been shown to rapidly and almost entirely deplete eosinophils in both the blood and nasal polyp tissue of individuals with CRSwNP [33]. An early subgroup analysis of the ANDHI trial indicated that, among indivoduals with severe eosinophilic asthma and concomitant nasal polyps, benralizumab led to a significant reduction in sinusitis symptoms, as measured by the SNOT-22 score [34]. A phase II clinical trial found that, although nasal polyp scores at 12 weeks did not show a significant difference between the benralizumab and placebo groups, further analysis revealed that Among patients with eosinophilic CRSwNP (ECRS), 42.2% demonstrated a reduction of at least 2 points in their nasal polyp score. Remarkably, a more pronounced response was noted in those with elevated eosinophil levels [35]. In a randomized controlled phase II trial involving severe ECRS patients, 20-week benralizumab treatment led to significant reductions in polyp size, improvement in nasal obstruction scores, and recovery of smell from baseline, with a favorable safety profile [36]. These findings were subsequently validated by the OSTRO trial, which reinforced the effectiveness and tolerability of benralizumab in managing severe CRSwNP patients [37].

2.2 Mepolizumab

Mepolizumab, a humanized monoclonal antibody, mitigates type 2 inflammation by binding to and neutralizing IL-5, thereby decreasing eosinophils in peripheral blood and tissues [38, 39]. A clinical study also demonstrated that mepolizumab decreased eosinophil counts in both bone marrow and bronchial mucosa [40], potentially through a mechanism that induces partial maturation arrest of the eosinophil lineage within the bone marrow [41].

2.2.1 Asthma

Initially, a randomized controlled trial evaluated the tolerability and effectiveness of mepolizumab in individuals with persistent moderate asthma, showing that it significantly lowered eosinophil levels in blood and sputum, though its effect on pulmonary function and overall quality of life was limited [42]. However, subsequent studies found that at higher doses, mepolizumab could reduce the frequency of asthma exacerbations, particularly in individuals with steroid-dependent and uncontrolled eosinophilic asthma, significantly lowering eosinophil counts and improving clinical outcomes during treatment [43-45]. The large Phase II DREAM trial further validated its efficacy, showing a notable decrease in acute exacerbation rates in individuals with severe eosinophilic asthma [46]. Later MENSA and MUSCA, confirmed that mepolizumab lowers the risk of acute exacerbations and enhances health-related quality of life (HRQOL) [47, 48]. Furthermore, the SIRIUS trial demonstrated that mepolizumab reduces the need for oral corticosteroids in patients with severe eosinophilic asthma, thus mitigating the long-term side effects associated with steroid use [49]. Several long-term clinical trials have further validated the safety profile and clinical effectiveness of mepolizumab [50-52]. Additionally, multiple real-world studies have corroborated these findings, demonstrating the drug's effectiveness and tolerability in patients with severe eosinophilic asthma. These studies show significant reductions in the risk of acute exacerbations, improvements in lung function, and a decreased reliance on oral steroids [53-56]. In summary, mepolizumab has proven to be both safe and effective in managing severe eosinophilic asthma,

particularly in patients with elevated peripheral blood eosinophil levels [57-59]. Furthermore, its efficacy has also been consistently observed in children and adolescents [60-62].

2.2.2 COPD

The METREX (mepolizumab 100mg vs placebo) and METREO (mepolizumab 100mg, 300mg vs placebo) trials were Phase III studies designed to assess the clinical effectiveness of mepolizumab in patients with COPD. These patients were on a stable ICS-based triple therapy regimen but continued to experience acute exacerbations. Both trials specifically enrolled COPD patients with an eosinophilic phenotype, defined as either an eosinophil count of ≥150 cells/μl in peripheral blood at screening or an eosinophil count of ≥300 cells/μl in the previous year. Results showed that in individuals with an eosinophilic phenotype, subcutaneous administration of mepolizumab led to an 18% and 20% reduction in the annual rate of moderate to severe acute exacerbations, respectively, compared to the placebo group [63]. Therefore, guiding mepolizumab use based on peripheral blood eosinophil counts can help more precisely and scientifically manage COPD patients who persistently experience frequent acute exacerbations despite ongoing maintenance therapy.

2.2.3 CRSwNP

Conventional treatment approaches for CRSwNP typically involve saline nasal irrigation, intranasal corticosteroids, and the short-term use of systemic corticosteroids. However, systemic corticosteroids can lead to a range of time- and dose-dependent side effects [64, 65]. For patients with severe refractory CRSwNP, surgical intervention may be necessary to remove nasal polyps and diseased nasal mucosa, while surgery carries risks such as bleeding, cerebrospinal fluid leaks, and recurrence requiring repeat surgeries [66]. The SYNAPSE trial demonstrated that mepolizumab can reduce polyp size, improve nasal obstruction symptoms [67-69], enhance olfactory function [70], decrease the dosage of systemic corticosteroids [71], and lower the risk of future surgeries in individuals with severe refractory CRSwNP [72]. Notably, the efficacy of mepolizumab remains significantly sustained for 24 weeks post-treatment [73], making it a promising alternative to surgery and systemic corticosteroid therapy for these patients.

3. Anti-IL-4 and IL-13 Therapy

IL-4, a crucial cytokine, significantly contributes to inflammation and tissue remodeling, facilitating processes such as goblet cell hypersecretion in the mucosa, fibrosis, alterations in smooth muscle cells, and heightened airway hyperreactivity. Furthermore, both IL-4 and IL-13 are capable of stimulating the production of factors that promote eosinophil activation, including IL-5 and eosinophil chemotactic agents, by Th2 cells and epithelial cells. This, in turn, triggers the migration of eosinophils from peripheral blood to inflamed tissues. Dupilumab, an effective fully human IgG4 monoclonal antibody, targets IL-4Rα specifically. By inhibiting the shared IL-4Rα receptor subunit, dupilumab disrupts the signaling of both IL-4 and IL-13, demonstrating significant clinical effectiveness in treating diseases associated with type 2 inflammation [74].

3.1 Asthma

To evaluate the effectiveness and tolerability of dupilumab in individuals with persistent moderate-to-severe asthma with elevated eosinophil levels, Wenzel et al. conducted a phase 2a clinical trial. The findings indicated a markedly lower rate of asthma exacerbations in the dupilumab group compared to the placebo group, along with significant enhancements in pulmonary function and asthma control metrics. Furthermore, the study observed a notable reduction in eosinophil-associated inflammatory biomarkers [75]. Subsequent larger-scale trials confirmed these results, demonstrating that dupilumab effectively lowered the risk of severe exacerbations in individuals with uncontrolled persistent asthma. These trials also reported improvements in lung function, symptoms, health outcomes, quality of life, and productivity [76]. Similar benefits were observed in pediatric populations [77, 78]. Long-term extension studies reinforced the sustained safety and efficacy of dupilumab [79], showing that its effectiveness was independent of baseline peripheral eosinophil levels [80-82], allergic asthma status [83], prior exacerbation history, or baseline ICS dosage [84]. However, patients with higher eosinophil counts exhibited more pronounced benefits [82]. For steroid-dependent individuals with severe asthma, dupilumab significantly reduced oral corticosteroid (OCS) usage, while concurrently lowering severe exacerbation rates and enhancing lung function [85], irrespective of baseline OCS dosage [86]. These effects were maintained over time [87], suggesting that dupilumab may serve as a viable alternative to oral corticosteroids. In addition to evidence from clinical trials, real-world studies corroborated these findings. Patients with severe asthma who received dupilumab treatment experienced notable improvements in asthma management and pulmonary function, along with reductions in OCS dependency and annual exacerbation rates [88].

3.2 COPD

To evaluate the effectiveness and tolerability of dupilumab in individuals with COPD and type 2 inflammation who remain symptomatic despite standard triple therapy, S.P. Bhatt et al. conducted a 52-week Phase III clinical trial. The study targeted high-risk COPD patients with type 2 inflammatory characteristics, such as elevated peripheral blood eosinophil levels (≥300/μL) and recurrent exacerbations, explicitly excluding those with asthma. The findings revealed that participants with type 2 inflammation, marked by high eosinophil counts, who were treated with dupilumab had fewer moderate-to-severe exacerbations, better respiratory function, improved quality of life, and reduced pulmonary symptoms compared to those receiving placebo [89, 90]. These outcomes were further supported by another large-scale Phase III trial, which confirmed both the clinical effectiveness and risk profile of dupilumab in COPD patients with elevated peripheral eosinophil counts [91].

3.3 CRSwNP

In individuals with CRSwNP unresponsive topical steroids, a

small-scale clinical trial demonstrated that subcutaneous dupilumab injections markedly reduced endoscopic nasal polyp scores after 16 weeks, while also enhancing olfactory function and improving quality of life [92]. Subsequent large-scale clinical trials have provided further evidence supporting the clinical effectiveness and tolerability of dupilumab in this population. These studies revealed that dupilumab significantly reduced the size of nasal polyps, alleviated symptoms such as nasal obstruction [93, 94], enhanced olfactory function [95, 96], improved quality of life [97, 98], and decreased the need for systemic corticosteroids and nasal polyp surgery [99, 100], regardless of baseline peripheral blood eosinophil counts [101]. Collectively, these findings position dupilumab as a well-tolerated and effective therapeutic alternative for individuals with severe, uncontrolled CRSwNP.

4. Anti-IL-33 Therapy

IL-33 is predominantly produced by barrier epithelial and endothelial cells [102] and functions as an "alarmin," passively released during tissue damage or necrosis triggered by factors such as cigarette smoke, environmental pollutants, or viral and bacterial infections [103]. Studies have shown that IL-33 plays a dual role in driving inflammatory responses of both type 1 and type 2 in vivo. For instance, in mouse models exposed to acute house dust mite allergens, an increase in pulmonary eosinophils, IL-5, IL-4, IL-13, goblet cell metaplasia, and IgE production has been observed [104]. Additionally, IL-33 has been found to enhance eosinophil maturation by stimulating IL-5 production and promoting the proliferation of IL-5Rα-expressing precursor cells in the bone marrow, thereby contributing to eosinophilic inflammation [105]. Itepekimab, a novel human IgG4P monoclonal antibody, is designed to specifically target IL-33.

4.1 Asthma

A study has demonstrated that Itepekimab shows both effective results and a favorable safety profile in individuals with moderate to severe asthma. Used alone or in combination with Dupilumab, it significantly reduces asthma exacerbation frequency while also improving pulmonary function and quality of life [106]. However, its capacity to reduce eosinophil levels and clinical efficacy appears comparatively weaker than that of Dupilumab, possibly due to the complex pathophysiology of asthma. Further research is required to elucidate this in greater depth.

4.2 COPD

Genetic analyses suggest that variations within the IL-33 signaling pathway are correlated with an increased risk of COPD. Subsequent clinical trials and subgroup analyses revealed that Itepekimab largely reduced acute exacerbation frequency and enhanced respiratory function in COPD patients with a smoking history, though primary outcomes did not achieve statistical significance in the overall population and current smokers [107].

5. Conclusions

In brief, anti-eosinophil biologics have substantially improved treatment options for severe asthma, eosinophilic COPD, and CRSwNP by offering targeted inflammatory control with fewer side effects than traditional therapies. These therapies have showed benefits in improving clinical outcomes. Although their impact is strongest in asthma, specific COPD and CRSwNP cases also demonstrate potential for these therapies. Despite the high costs and need for long-term safety data, anti-eosinophil biologics represent a valuable advancement toward personalized respiratory disease management.

References

[1] HUANG L, APPLETON J A. Eosinophils in Helminth Infection: Defenders and Dupes. Trends Parasitol 2016; 32: 798-807.

[2] ROSENBERG H F, DYER K D, FOSTER P S. Eosinophils: changing perspectives in health and disease. Nat Rev Immunol 2013; 13: 9-22.

[3] ABDALA-VALENCIA H, CODEN M E, CHIARELLA S E, et al. Shaping eosinophil identity in the tissue contexts of development, homeostasis, and disease. J Leukoc Biol 2018; 104: 95-108.

[4] CHUNG K F, WENZEL S E, BROZEK J L, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-73.

[5] MCBRIEN C N, MENZIES-GOW A. The Biology of Eosinophils and Their Role in Asthma. Front Med (Lausanne) 2017; 4: 93.

[6] DRAKE M G, LEBOLD K M, ROTH-CARTER Q R, et al. Eosinophil and airway nerve interactions in asthma. J Leukoc Biol 2018; 104:61-7.

[7] YANCEY S W, KEENE O N, ALBERS F C, et al. Biomarkers for severe eosinophilic asthma. J Allergy Clin Immunol 2017; 140:1509-18.

[8] PRICE D B, RIGAZIO A, CAMPBELL J D, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med 2015; 3:849-58.

[9] BARNES P J. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016; 138:16-27.

[10] LEIGH R, PIZZICHINI M M, MORRIS M M, et al. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J 2006; 27:964-71.

[11] SINGH D, KOLSUM U, BRIGHTLING C E, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014; 44:1697-700.

[12] NEGEWO N A, MCDONALD V M, BAINES K J, et al. Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. Int J Chron Obstruct Pulmon Dis 2016; 11:1495-504.

[13] ZEIGER R S, TRAN T N, BUTLER R K, et al. Relationship of Blood Eosinophil Count to Exacerbations in Chronic Obstructive Pulmonary Disease. J Allergy Clin Immunol Pract 2018; 6:944-54.e5.

[14] YUN J H, LAMB A, CHASE R, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2018; 141:2037-47.e10.

[15] KOLBECK R, KOZHICH A, KOIKE M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010; 125:1344-53.e2.
[16] LAVIOLETTE M, GOSSAGE D L, GAUVREAU G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 2013; 132:1086-96.e5.
[17] BUSSE W W, KATIAL R, GOSSAGE D, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol 2010; 125:1237-44.e2.
[18] CASTRO M, WENZEL S E, BLEECKER E R, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014; 2:879-90.
[19] BLEECKER E R, FITZGERALD J M, CHANEZ P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; 388: 2115-27.
[20] PARK H S, KIM M K, IMAI N, et al. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. Int Arch Allergy Immunol 2016; 169: 135-45.
[21] BLEECKER E R, WECHSLER M E, FITZGERALD J M, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018;52.
[22] BUSSE W W, BLEECKER E R, FITZGERALD J M, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med 2019; 7:46-59.
[23] BUSSE W W, BLEECKER E R, FITZGERALD J M, et al. Benralizumab for adolescent patients with severe, eosinophilic asthma: Safety and efficacy after 3 years of treatment. J Allergy Clin Immunol 2021; 148:266-71.e2.
[24] KORN S, BOURDIN A, CHUPP G, et al. Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years. J Allergy Clin Immunol Pract 2021; 9:4381-92.e4.
[25] NAIR P, WENZEL S, RABE K F, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med 2017; 376:2448-58.
[26] JACKSON D J, HEANEY L G, HUMBERT M, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. Lancet 2024; 403:271-81.
[27] BRIGHTLING C E, BLEECKER E R, PANETTIERI R A, JR., et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014; 2:891-901.
[28] CRINER G J, CELLI B R, BRIGHTLING C E, et al. Benralizumab for the Prevention of COPD Exacerbations. N Engl J Med 2019; 381:1023-34.
[29] SINGH D, CRINER G J, AGUSTí A, et al. Benralizumab Prevents Recurrent Exacerbations in Patients with Chronic Obstructive Pulmonary Disease: A Post Hoc Analysis. Int J Chron Obstruct Pulmon Dis 2023; 18:1595-9.
[30] WAUTLET A, BACHERT C, DESROSIERS M, et al. The Management of Chronic Rhinosinusitis With Nasal Polyps (CRSwNP) With Biologics. J Allergy Clin Immunol Pract 2023; 11:2642-51.
[31] DE PRINS L, RAAP U, MUELLER T, et al. White Paper on European Patient Needs and Suggestions on Chronic Type 2 Inflammation of Airways and Skin by EUFOREA. Front Allergy 2022; 3:889221.
[32] STEVENS W W, PETERS A T, HIRSCH A G, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract 2017; 5:1061-70.e3.
[33] EMSON C, HAN J K, HOPKINS C, et al. Pharmacokinetics/pharmacodynamics of benralizumab in chronic rhinosinusitis with nasal polyps: Phase III, randomized, placebo-controlled OSTRO trial. Br J Clin Pharmacol 2024; 90:1952-63.
[34] CANONICA G W, HARRISON T W, CHANEZ P, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. Allergy 2022; 77:150-61.
[35] TAKABAYASHI T, ASAKA D, OKAMOTO Y, et al. A Phase II, Multicenter, Randomized, Placebo-Controlled Study of Benralizumab, a Humanized Anti-IL-5R Alpha Monoclonal Antibody, in Patients With Eosinophilic Chronic Rhinosinusitis. Am J Rhinol Allergy 2021; 35:861-70.
[36] TVERSKY J, LANE A P, AZAR A. Benralizumab effect on severe chronic rhinosinusitis with nasal polyps (CRSwNP): A randomized double-blind placebo-controlled trial. Clin Exp Allergy 2021; 51: 836-44.
[37] BACHERT C, HAN J K, DESROSIERS M Y, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. J Allergy Clin Immunol 2022; 149: 1309-17.e12.
[38] HART T K, COOK R M, ZIA-AMIRHOSSEINI P, et al. Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. J Allergy Clin Immunol 2001; 108:250-7.
[39] BüTTNER C, LUN A, SPLETTSTOESSER T, et al. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions. Eur Respir J 2003; 21:799-803.
[40] FLOOD-PAGE P T, MENZIES-GOW A N, KAY A B, et al. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 2003; 167:199-204.
[41] MENZIES-GOW A, FLOOD-PAGE P, SEHMI R, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. J Allergy Clin Immunol 2003; 111:714-9.

[42] FLOOD-PAGE P, SWENSON C, FAIFERMAN I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176:1062-71.
[43] ANTONIU S A. Mepolizumab for difficult-to-control asthma with persistent sputum eosinophilia. Expert Opin Investig Drugs 2009; 18:869-71.
[44] HALDAR P, BRIGHTLING C E, HARGADON B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973-84.
[45] NAIR P, PIZZICHINI M M, KJARSGAARD M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009; 360:985-93.
[46] PAVORD I D, KORN S, HOWARTH P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380:651-9.
[47] ORTEGA H G, LIU M C, PAVORD I D, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371:1198-207.
[48] CHUPP G L, BRADFORD E S, ALBERS F C, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017; 5:390-400.
[49] BEL E H, WENZEL S E, THOMPSON P J, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371:1189-97.
[50] LUGOGO N, DOMINGO C, CHANEZ P, et al. Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study. Clin Ther 2016; 38:2058-70.e1.
[51] KHATRI S, MOORE W, GIBSON P G, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2019; 143:1742-51.e7.
[52] KHURANA S, BRUSSELLE G G, BEL E H, et al. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study. Clin Ther 2019; 41:2041-56.e5.
[53] PELAIA C, CRIMI C, PELAIA G, et al. Real-life evaluation of mepolizumab efficacy in patients with severe eosinophilic asthma, according to atopic trait and allergic phenotype. Clin Exp Allergy 2020; 50:780-8.
[54] KALLIERI M, ZERVAS E, KATSOULIS K, et al. Mepolizumab in Severe Eosinophilic Asthma: A 2-Year Follow-Up in Specialized Asthma Clinics in Greece: An Interim Analysis. Int Arch Allergy Immunol 2020; 181:613-7.
[55] SCHLEICH F, GRAFF S, NEKOEE H, et al. Real-word experience with mepolizumab: Does it deliver what it has promised? Clin Exp Allergy 2020; 50:687-95.
[56] DOMINGO RIBAS C, CARRILLO DíAZ T, BLANCO APARICIO M, et al. REal worlD Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils: The REDES Study. Drugs 2021; 81:1763-74.
[57] ORTEGA H G, YANCEY S W, MAYER B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med 2016; 4:549-56.
[58] ORTEGA H, MENZIES-GOW A, LLANOS J P, et al. Rapid and Consistent Improvements in Morning PEF in Patients with Severe Eosinophilic Asthma Treated with Mepolizumab. Adv Ther 2018; 35:1059-68.
[59] SHRIMANKER R, KEENE O, HYNES G, et al. Prognostic and Predictive Value of Blood Eosinophil Count, Fractional Exhaled Nitric Oxide, and Their Combination in Severe Asthma: A Post Hoc Analysis. Am J Respir Crit Care Med 2019; 200:1308-12.
[60] GUPTA A, IKEDA M, GENG B, et al. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol 2019; 144:1336-42.e7.
[61] JACKSON D J, BACHARIER L B, GERGEN P J, et al. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet 2022; 400: 502-11.
[62] GUPTA A, POULIQUEN I, AUSTIN D, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol 2019; 54:1957-67.
[63] PAVORD I D, CHANEZ P, CRINER G J, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med 2017; 377:1613-29.
[64] FOKKENS W J, LUND V J, HOPKINS C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58:1-464.
[65] HOX V, LOURIJSEN E, JORDENS A, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clin Transl Allergy 2020; 10:1.
[66] HOPKINS C, BROWNE J P, SLACK R, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: the results of a national audit in England and Wales. Laryngoscope 2006; 116:1494-9.
[67] BACHERT C, SOUSA A R, HAN J K, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps: Treatment efficacy by comorbidity and blood eosinophil count. J Allergy Clin Immunol 2022; 149: 1711-21.e6.
[68] HAN J K, BACHERT C, FOKKENS W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021; 9:1141-53.
[69] FOKKENS W, TRIGG A, LEE S E, et al. Mepolizumab improvements in health-related quality of life and disease symptoms in a patient population with very severe chronic rhinosinusitis with nasal polyps: psychometric and efficacy analyses from the SYNAPSE study. J Patient Rep Outcomes 2023; 7:4.
[70] MULLOL J, LUND V J, WAGENMANN M, et al. Mepolizumab improves sense of smell in severe chronic rhinosinusitis with nasal polyps: SYNAPSE. Rhinology 2024; 62:320-9.
[71] CHUPP G, ALOBID I, LUGOGO N L, et al. Mepolizumab Reduces Systemic Corticosteroid Use in

Chronic Rhinosinusitis With Nasal Polyps. J Allergy Clin Immunol Pract 2023; 11:3504-12.e2.
[72] FOKKENS W J, MULLOL J, KENNEDY D, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): In-depth sinus surgery analysis. Allergy 2023; 78:812-21.
[73] DESROSIERS M, DIAMANT Z, CASTELNUOVO P, et al. Sustained efficacy of mepolizumab in patients with severe chronic rhinosinusitis with nasal polyps: SYNAPSE 24-week treatment-free follow-up. Int Forum Allergy Rhinol 2024; 14:18-31.
[74] LE FLOC'H A, ALLINNE J, NAGASHIMA K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy 2020; 75:1188-204.
[75] WENZEL S, FORD L, PEARLMAN D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013; 368:2455-66.
[76] CORREN J, CASTRO M, CHANEZ P, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. Ann Allergy Asthma Immunol 2019; 122:41-9.e2.
[77] BACHARIER L B, MASPERO J F, KATELARIS C H, et al. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N Engl J Med 2021; 385:2230-40.
[78] FIOCCHI A G, PHIPATANAKUL W, ZEIGER R S, et al. Dupilumab leads to better-controlled asthma and quality of life in children: the VOYAGE study. Eur Respir J 2023;62.
[79] WECHSLER M E, FORD L B, MASPERO J F, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med 2022; 10:11-25.
[80] WENZEL S, CASTRO M, CORREN J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016; 388:31-44.
[81] BUSSE W W, MASPERO J F, RABE K F, et al. Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma. Adv Ther 2018; 35:737-48.
[82] CASTRO M, CORREN J, PAVORD I D, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med 2018; 378:2486-96.
[83] CORREN J, CASTRO M, O'RIORDAN T, et al. Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma. J Allergy Clin Immunol Pract 2020; 8:516-26.
[84] CORREN J, KATELARIS C H, CASTRO M, et al. Effect of exacerbation history on clinical response to dupilumab in moderate-to-severe uncontrolled asthma. Eur Respir J 2021;58.
[85] RABE K F, NAIR P, BRUSSELLE G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med 2018; 378:2475-85.
[86] DOMINGO C, MASPERO J F, CASTRO M, et al. Dupilumab Efficacy in Steroid-Dependent Severe Asthma by Baseline Oral Corticosteroid Dose. J Allergy Clin Immunol Pract 2022; 10:1835-43.
[87] SHER L D, WECHSLER M E, RABE K F, et al. Dupilumab Reduces Oral Corticosteroid Use in Patients With Corticosteroid-Dependent Severe Asthma: An Analysis of the Phase 3, Open-Label Extension TRAVERSE Trial. Chest 2022; 162:46-55.
[88] DUPIN C, BELHADI D, GUILLEMINAULT L, et al. Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. Clin Exp Allergy 2020; 50:789-98.
[89] BHATT S P, RABE K F, HANANIA N A, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med 2023; 389:205-14.
[90] JAROENPUNTARUK V, PONGDEE T. A Phase 3 Trial of Dupilumab for People With Chronic Obstructive Pulmonary Disease and Elevated Peripheral Blood Eosinophil Counts. J Allergy Clin Immunol Pract 2024; 12:1394-6.
[91] BHATT S P, RABE K F, HANANIA N A, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med 2024; 390: 2274-83.
[92] BACHERT C, MANNENT L, NACLERIO R M, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. Jama 2016; 315:469-79.
[93] BACHERT C, HAN J K, DESROSIERS M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394:1638-50.
[94] BACHERT C, ZINREICH S J, HELLINGS P W, et al. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP. Rhinology 2020; 58:10-7.
[95] MULLOL J, BACHERT C, AMIN N, et al. Olfactory Outcomes With Dupilumab in Chronic Rhinosinusitis With Nasal Polyps. J Allergy Clin Immunol Pract 2022; 10:1086-95.e5.
[96] HOPKINS C, MULLOL J, KHAN A H, et al. Impact of Dupilumab on Sinonasal Symptoms and Outcomes in Severe Chronic Rhinosinusitis With Nasal Polyps. Otolaryngol Head Neck Surg 2024; 170:1173-82.
[97] BACHERT C, HELLINGS P W, MULLOL J, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. Allergy 2020; 75:148-57.
[98] LEE S E, HOPKINS C, MULLOL J, et al. Dupilumab improves health related quality of life: Results from the phase 3 SINUS studies. Allergy 2022; 77:2211-21.
[99] DESROSIERS M, MANNENT L P, AMIN N, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. Rhinology 2021; 59:301-11.
[100] HOPKINS C, WAGENMANN M, BACHERT C, et al. Efficacy of dupilumab in patients with a history of

prior sinus surgery for chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol 2021; 11:1087-101.
[101] FUJIEDA S, MATSUNE S, TAKENO S, et al. Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. Allergy 2022; 77:186-96.
[102] MOUSSION C, ORTEGA N, GIRARD J P. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? PLoS One 2008;3:e3331.
[103] SCOTT I C, MAJITHIYA J B, SANDEN C, et al. Interleukin-33 is activated by allergen- and necrosis-associated proteolytic activities to regulate its alarmin activity during epithelial damage. Sci Rep 2018; 8:3363.
[104] ALLINNE J, SCOTT G, LIM W K, et al. IL-33 blockade affects mediators of persistence and exacerbation in a model of chronic airway inflammation. J Allergy Clin Immunol 2019; 144:1624-37.e10.
[105] JOHNSTON L K, HSU C L, KRIER-BURRIS R A, et al. IL-33 Precedes IL-5 in Regulating Eosinophil Commitment and Is Required for Eosinophil Homeostasis. J Immunol 2016; 197:3445-53.
[106] WECHSLER M E, RUDDY M K, PAVORD I D, et al. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma. N Engl J Med 2021; 385:1656-68.
[107] RABE K F, CELLI B R, WECHSLER M E, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. Lancet Respir Med 2021; 9:1288-98.