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Review

Long-Term Effectiveness of Benralizumab in Severe Eosinophilic Asthma: A Systematic Review and Meta-Analysis

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Abstract: Benralizumab is an interleukin-5 receptor α-directed monoclonal antibody that depletes eosinophils via antibody-dependent cell-mediated cytotoxicity. This systematic review and meta-analysis evaluated the efficacy and safety of benralizumab in patients with severe eosinophilic asthma (SEA) using evidence from randomized controlled trials, post hoc analyses, and real-world studies. Eight studies comprising 1600 patients were included in this review. Benralizumab significantly reduced the risk of severe exacerbations by 52% (Risk Ratio [RR] = 0.48, 95% confidence interval [CI]: 0.44–0.52) and decreased the maintenance oral corticosteroid (OCS) dose by 11.6 mg/day (95% CI: −13.07 to −10.13). Lung function improved, with a mean increase of 0.22 L in pre-bronchodilator forced expiratory volume in one second (95% CI: 0.18 to 0.26). The asthma control test scores increased by 4.33 points (95% CI: 3.69 to 4.98), surpassing the minimal clinically important difference. These benefits were observed in both randomized controlled trial extensions and real-world studies and were maintained for up to five years, with a favorable safety profile. Subgroup analyses revealed greater improvements in patients with chronic rhinosinusitis with nasal polyps and those receiving maintenance OCS. Benralizumab efficacy was maintained in obese patients, although improvements in lung function were attenuated. These results support the use of benralizumab as a long-term treatment for SEA, particularly in patients with comorbidities or those requiring maintenance OCS. The integration of benralizumab into personalized management plans based on biomarkers and clinical phenotypes can optimize outcomes in SEA.

Keywords: Benralizumab; Severe Eosinophilic Asthma; Oral Corticosteroids; Exacerbations; Type 2 Inflammation

1. Introduction

Severe asthma is a clinical condition within the asthma spectrum, characterized by chronic, uncontrolled symptoms, frequent flare-ups, and reduced health-related quality of life, even when treated with high-dose inhaled corticosteroids (ICS) and at least one other controller (such as long-acting β2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), or biologics). It requires ongoing systemic corticosteroids (SCS), contributing to treatment-related health issues [1,2]. While severe asthma affects 5–10% of patients with asthma, it disproportionately drives morbidity, mortality, and healthcare usage globally, making it a significant public health concern [1,2].

The impact of severe asthma on patients is significant and can be life-threatening. Those affected experience daily symptoms such as shortness of breath, wheezing, nighttime disturbances, and limited physical activity, with frequent flare-ups requiring medical attention or hospital stays. Extended use of oral corticosteroids (OCS) poses risks of side effects, including diabetes, osteoporosis, cardiovascular problems, and increased infection. These factors deteriorate health and quality of life (QoL) while contributing to multiple conditions [1,2]. The disease and its treatment lead to reduced functional ability, work or school absenteeism, and decreased social activities, showing its extensive impact [1,2].

From an economic perspective, severe asthma significantly strains healthcare systems and society. Although not highly prevalent, this group incurs substantial direct expenses through intensive pharmacotherapy (including biologics), specialized care, exacerbation management, emergency services, and treatment of CS-related comorbidities. Indirect costs from lost productivity and caregiver time further increase the economic impact [1–3]. Health technology assessments suggest that while biologics reduce exacerbations and steroid use, their cost-effectiveness ratios exceed the willingness-to-pay thresholds, with savings mainly from decreased acute care utilization [3].

Severe asthma is often associated with type 2 (T2) inflammation. The T2 cytokine pathways, including interleukin (IL)-4, IL-5, and IL-13, promote eosinophilic airway inflammation, IgE levels, mucus production, and airway responsiveness. Eosinophilic inflammation is associated with exacerbations and airflow restriction, making it a key treatment target [2]. Understanding T2 biology has enabled the development of targeted biological therapies that improve outcomes in selected patients. Anti–IL-5/IL-5R medications (mepolizumab, reslizumab, benralizumab) reduce exacerbations and OCS use in eosinophilic phenotypes. Mepolizumab reduces exacerbations by 47–53% and improves lung function compared to placebo in severe eosinophilic asthma (SEA), while reducing OCS doses [4,5]. Benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab decrease severe exacerbations, lower maintenance OCS needs, and improve asthma control and QoL [3]. Registry data show that T2-related comorbidities may predict the effectiveness of biologics on exacerbations and lung function, emphasizing the need for systematic comorbidity assessment in treatment selection [6]. For severe allergic asthma, omalizumab is established, and new omics biomarkers may improve response prediction beyond eosinophils, fractional exhaled nitric oxide (FeNO), and IgE measures [3,7].

Traditional asthma treatment follows a stepwise approach using ICS to control inflammation. Treatment intensification includes LABAs, LTRAs, and OCS. ICS reduces airway inflammation, whereas ICS-LABA combinations improve symptoms and lung function. Current guidelines favor single maintenance and reliever therapy using ICS–formoterol at moderate-to-severe stages due to better exacerbation control compared to fixed-dose regimens [1]. LTRAs can serve as initial controllers or ICS additions, showing short-term effectiveness similar to that of ICS and LABA, although long-term results remain uncertain [8]. For uncontrolled patients on high-dose ICS and controllers, OCS is administered as short bursts or maintenance therapy [1].

Despite the available treatments, a significant subgroup within the severe spectrum continues to experience symptoms and reduced lung function, even with maximum inhaled therapy. This shows that traditional anti-inflammatory methods do not sufficiently alter disease biology in all patients [2,9]. Among children who are uncontrolled on low-dose ICS, most show varied responses to step-up treatments. While LABAs are generally the most effective, many patients respond better to higher-dose ICS or LTRA, highlighting the phenotype-specific diversity that conventional algorithms partially address [9]. Furthermore, guideline-recommended add-ons and non-pharmacologic strategies do not eliminate the risk of persistent exacerbations in severe cases [1].

Relying on SCS has significant drawbacks. While OCS effectively manages exacerbations, chronic use leads to toxicity, affecting the metabolic, cardiovascular, musculoskeletal, ocular, neuropsychiatric, and infectious systems. Even occasional bursts contribute to cumulative negative effects, highlighting the unsustainable steroid-dependent

management [1]. The emergence of biologics emphasizes this: in OCS-dependent EA, anti–IL-5 therapy enables OCS reduction while maintaining control and reducing exacerbations, showing that steroid exposure can be minimized [10]. For patients with persistent eosinophilic inflammation despite high-dose ICS with or without OCS, anti–IL-5 therapy decreases exacerbations and improves health status and lung function beyond ICS or LABA increases [4, 9]. Evidence across biological classes supports reductions in severe exacerbations and OCS-sparing effects, highlighting the limitations of traditional pharmacotherapy in T2-high severe asthma [3].

Interleukin-5 (IL-5) is a key type 2 cytokine crucial for eosinophil development and function. Produced by Th2 cells, ILC2s, and mast cells, IL-5 promotes eosinophil formation in the bone marrow and maintains their presence by preventing cell death [2]. In the respiratory tract, IL-5 enhances eosinophil adhesion and migration to the bronchial lining, where they release toxic proteins, lipid mediators, and reactive oxygen species. These substances damage the epithelium and contribute to airway hyperresponsiveness in patients with SEA [11]. Studies have shown that neutralizing IL-5 can prevent eosinophilic airway inflammation, whereas anti-IgE treatments do not reduce inflammation [12]. Evidence suggests local eosinophil development within the airways: allergen exposure increases sputum CD34+IL-5Rα+ progenitors, indicating that IL-5-driven local maturation maintains eosinophilia at disease sites [13].

Persistent eosinophilia in the blood or sputum is linked to exacerbation frequency, OCS reliance, and diminished lung function, serving as both a risk biomarker and causal factor for adverse outcomes [2,11]. In prednisone-dependent patients with sputum eosinophilia, mepolizumab targeting IL-5 decreased eosinophil levels, reduced steroid use, and nearly eliminated exacerbations, demonstrating meaningful risk modification [9]. In patients with SEA on high-dose ICS (± OCS), anti–IL-5 treatment reduced severe exacerbations and improved patient outcomes and FEV_1, validating the significance of eosinophilia in severe cases [4, 5]. Analysis of biologics shows that treatments that reduce eosinophilic inflammation consistently lower severe exacerbation rates, confirming the eosinophilia-risk connection [3].

Targeting IL-5 through ligand neutralization uses humanized monoclonal antibodies, such as mepolizumab and reslizumab, which attach to circulating IL-5, decreasing eosinophil production in the bone marrow and reducing circulating and airway eosinophils. Studies have shown significant decreases in exacerbations (47–53%), improved health status, and slight FEV_1 enhancements, even with high-dose ICS background therapy [4]. In OCS-dependent diseases, mepolizumab achieves a 50% reduction in OCS dosage while maintaining disease control [5]. Research on eosinophilic, prednisone-refractory asthma has shown significant reductions in exacerbations and eosinophil levels [9]. Reslizumab decreases sputum eosinophil levels, enhances FEV_1, and improves control in poorly managed EA [14]. These agents provide strong evidence for reducing exacerbations, with several showing OCS-sparing effects [3]. Targeting IL-5Rα through receptor antagonism involves benralizumab, which binds to the IL-5 receptor α on eosinophils and basophils, blocking signaling and triggering antibody-dependent cell-mediated cytotoxicity. Systematic reviews have shown high-certainty evidence of reduced severe exacerbations and OCS-sparing with benralizumab, in addition to improvements in asthma control and FEV_1 [3]. The selective expression of the receptor supports therapeutic specificity while depleting effector cells that are central to exacerbation biology.

Benralizumab strongly binds to FcγRIIIa on natural killer (NK) cells through its afucosylated Fc, initiating antibody-dependent cell-mediated cytotoxicity (ADCC) against eosinophils and basophils expressing IL-5Rα [3]. This causes a rapid reduction in circulating eosinophils and decreased tissue eosinophil levels, indicating true removal rather than just reduced survival signals [3, 15]. Fc receptor biology supports the importance of ADCC in antibody activity, showing that therapeutic cytotoxicity depends on intact FcR ITAM signaling, supporting the eosinophil depletion mechanism of benralizumab [16]. Benralizumab achieves rapid eosinophil clearance similar to that of oral prednisolone, with lower eosinophil counts at 30 days compared to mepolizumab [15]. In non-asthma eosinophilic conditions, benralizumab effectively clears tissue eosinophils, showing a 87% histologic response in eosinophilic esophagitis, although symptom improvement varies by disease [17].

Mepolizumab and reslizumab neutralize IL-5, reducing signals for marrow maturation and eosinophil survival, thereby lowering eosinophil counts. These medications decrease exacerbations, improve lung function, and allow OCS tapering in patients [3–5,14]. In prednisone-dependent EA, mepolizumab reduces exacerbations and enables a 50% reduction in OCS dosage, achieving partial eosinophil suppression [5,9]. Benralizumab targets IL-5Rα and rapidly depletes eosinophils in the blood and tissues through ADCC, offering a distinct profile compared to ligand-blocking therapies [3,15]. Biomarker kinetics show a quicker onset and deeper eosinophil suppression with benralizumab than with mepolizumab at 30 days [15]. In reviews, benralizumab, mepolizumab, and reslizumab reduced

severe exacerbations; however, only benralizumab combines receptor blockade with Fc-engineered ADCC for complete eosinophil depletion, which is beneficial for high eosinophilia or OCS dependence [3]. In eosinophilic vasculitis, benralizumab matched mepolizumab in inducing remission while enabling OCS withdrawal in more patients and achieving lower eosinophil counts [6].

Benralizumab suppresses eosinophilic inflammation by eradicating eosinophil effector pools. This exceeds the benefits of IL-5 inhibitors, which neutralize ligands when comprehensive eosinophil control is required [3,15]. The effectiveness of inhibiting IL-5 is related to eosinophil maturation, survival, and recruitment, with evidence showing that blocking IL-5 eliminates eosinophilic airway inflammation [11,12]. Eosinophilogenesis supports the targeting of receptors to disrupt local eosinophil maintenance [13]. Benralizumab and other biologics reduce severe exacerbations; both benralizumab and mepolizumab reduce OCS needs, with benralizumab providing greater eosinophil depletion and a faster onset [3,15].

In patients with baseline blood eosinophils ≥300 cells/μL, benralizumab lowered annual exacerbation rates by 40–50% compared with placebo, improved pre-bronchodilator FEV_1 (100–160 mL), and enhanced symptom control and quality of life. The safety profile matched that of the placebo, confirming its effectiveness in T2-high severe asthma [3,17]. A meta-analysis verified the reduction in exacerbations (IRR 0.53; 95% CI 0.39–0.72) and showed that benralizumab likely improves asthma control, quality of life, and FEV_1 (moderate certainty), although the mean changes often fall below the minimal important difference thresholds [3]. Benralizumab achieved a 75% reduction in the daily maintenance OCS dose versus placebo while maintaining asthma control; half of the participants stopped OCS entirely, and severe exacerbations decreased despite steroid tapering [18,19]. These results align with the mechanism of benralizumab, an IL-5Rα–directed ADCC, with head-to-head biomarker kinetics showing an onset similar to that of prednisolone and stronger 30-day eosinophil suppression than that of mepolizumab, supporting sustained reduction in exacerbation risk [15].

Observational cohorts and registries consistently mirror the randomized controlled trial (RCT) signal, demonstrating marked reductions in severe exacerbations, emergency department visits, and hospitalizations after benralizumab initiation, alongside improvements in lung function and patient-reported outcomes (Asthma Control Test (ACT)/ACQ, AQLQ), reinforcing the external validity of trial-based benefits in routine care [17]. The class-level synthesis affirms high-certainty reductions in severe exacerbations and high-certainty OCS-sparing with benralizumab, while suggesting probable gains in control and QoL (moderate certainty), which aligns with pragmatic improvements recorded across real-world series [17]. Pharmacovigilance and practice-based datasets indicate a favorable and stable safety profile with low discontinuation due to adverse events and no new long-term safety concerns. Class analyses have noted small increases in drug-related adverse events with benralizumab, mepolizumab, and reslizumab (low to very low certainty), without emergent serious safety signals over extended exposure [17].

Data from the BORA study show that benralizumab therapy leads to sustained eosinophil reduction, decreased exacerbations, improved FEV_1, and quality-of-life enhancements in patients with eosinophilic severe asthma, suggesting long-lasting disease modification [20]. Rapid eosinophil depletion compared to IL-5 ligand neutralization explains this stability [15]. Patients experience composite remission, characterized by no severe exacerbations, symptom control, independence from OCS, and stable lung function, demonstrating effective exacerbation prevention and OCS withdrawal in EA [17]. Complete eosinophil depletion supports potential remission in T2-high eosinophil-driven conditions [15]. Eosinophil reduction aligns with improvements in sinonasal disease in patients with SEA and chronic rhinosinusitis with nasal polyps (CRSwNP); guidelines position biologics as key alongside surgery and CS for severe CRSwNP [21]. Phase 3 trials of tezepelumab in severe CRSwNP showed improvements in polyp size, congestion, smell, SNOT-22 scores, radiographic burden, and reductions in surgery and steroid use, highlighting the importance of biologics in sinonasal disease [22].

In systemic eosinophilic disease, the efficacy of benralizumab matched that of mepolizumab in inducing remission at weeks 36 and 48, with similar remission duration and relapse timing. Complete OCS withdrawal at weeks 48–52 was higher with benralizumab (41% vs. 26%), and eosinophil counts were lower, supporting its use in eosinophil-driven diseases overlapping with severe asthma [6]. In eosinophilic esophagitis, benralizumab achieved 87% histologic response (≤6 eos/hpf), although without superior symptom improvement over 24 weeks, demonstrating tissue eosinophil clearance while highlighting disease-specific factors affecting clinical response [17].

Evidence shows that benralizumab reduces severe exacerbations and OCS in eosinophilic, type-2–high asthma [23]; however, significant gaps remain. The long-term safety of real-world settings and comparative ef-

fectiveness against other biologics are not well understood. Outcomes for key phenotypes, such as OCS-dependent patients, obese asthmatics, those with CRSwNP, and patients with variable eosinophilia, lack consistent documentation. The progression of lung function improvements, response prediction using biomarkers beyond baseline eosinophils, and steroid-sparing outcomes require clearer synthesis. To advance precision medicine in severe asthma, decision-making should combine clinical trials and real-world evidence. A comprehensive evaluation can contextualize efficacy, effectiveness, safety, and healthcare utilization, especially for steroid management and phenotype-specific treatment.

This review will (i) assess the effectiveness of benralizumab in exacerbations, lung function, symptom control, quality of life, and OCS reduction; (ii) compile safety findings from trials and real-world cohorts; and (iii) evaluate the role of benralizumab in SEA across phenotypes, emphasizing biomarkers and algorithms for personalized therapy.

2. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines to ensure methodological clarity and reproducibility (**Supplementary Materials**) [24].

A literature review was performed using PubMed, Scopus, and Web of Science to assess the clinical efficacy and safety of benralizumab in patients with SEA. The search spanned from database inception to December 2024, using keywords and Medical Subject Headings including "benralizumab," "severe asthma," "eosinophilic asthma," "exacerbations," and "biologics." Reference lists of relevant articles and systematic reviews were examined to identify additional studies.

After removing duplicates, two reviewers independently screened the titles and abstracts. Studies were eligible if they met the following criteria: (i) prospective or retrospective clinical trials, observational cohorts, or post hoc analyses; (ii) adult patients with SEA per international definitions; (iii) treatment with benralizumab in RCT settings or real-world practice; and (iv) reported outcomes on exacerbations, lung function, symptom control, quality of life, or OCS reduction. Studies were excluded if they were reviews, case reports, editorials, experimental mechanistic studies without clinical outcomes, or lacked extractable data. Disagreements were resolved by consensus.

Data from the studies were systematically gathered using a uniform template to ensure consistency across study designs. Extracted variables included study details (author, publication year, country, study design, follow-up period, and sample size), patient demographics (age, sex distribution, and initial eosinophil counts), and intervention specifics (benralizumab dosing schedule, treatment duration, and concurrent therapies). When multiple reports were obtained from the same trial group, the most detailed or the latest publication was selected to prevent data duplication. Two reviewers independently extracted the data, documented the clinical outcomes, and cross-checked the accuracy with the original sources. Discrepancies were addressed through discussion and, if necessary, resolved by a third reviewer. Reference management and duplicate elimination were handled using EndNote software.

The main outcomes assessed were severe exacerbation rates and reduction in maintenance OCS dosage. Secondary outcomes included changes in lung function (pre-bronchodilator FEV_1), asthma control (using the ACT or similar validated instruments), patient-reported quality of life, adverse events, and treatment discontinuation rates. These endpoints were used to assess the clinical efficacy and safety of benralizumab in patients with SEA. Two reviewers verified the accuracy and completeness of the extracted data. When outcome measures were presented differently (e.g., mean versus median or change from baseline versus absolute values), the data were standardized. If necessary, the authors were contacted for clarification.

Two reviewers independently evaluated the risk of bias using design-specific tools. The Cochrane Risk of Bias tool was used for RCT extensions and integrated analyses, while the Newcastle–Ottawa Scale was used to assess real-world observational studies. The domains included selection, performance, detection, attrition, and reporting biases. Disagreements were resolved by consensus or by consulting a third reviewer. The findings were compiled into a traffic-light heatmap and summary graph showing the risk of bias as low, moderate, or high across domains.

Quantitative synthesis used random-effects models (DerSimonian–Laird method) to address heterogeneity among the study designs and populations. For continuous outcomes, such as FEV_1, ACT, and OCS dose, pooled results were presented as mean differences (MD) with 95% confidence intervals (CI). For dichotomous or count outcomes, such as exacerbations, pooled results showed risk ratios (RR) with 95% CI. Heterogeneity was evaluated

using the I^2 statistic, with 25%, 50%, and 75% indicating low, moderate, and high heterogeneities, respectively. Subgroup analyses were planned for significant phenotypes, including patients with OCS dependence, comorbid CRSwNP, and obesity, where sufficient data were available. Publication bias and small-study effects were investigated using funnel plots and Egger's regression test when possible. Data synthesis and figures were created using Review Manager (RevMan) version 5.4 and GraphPad Prism to generate forest plots, risk of bias graphs, and funnel plots for visualizing the findings.

3. Results

Initial database searches in PubMed, Scopus, and Web of Science identified 146 records screened. After removing 55 duplicates, 91 records remained for the screening. Title and abstract reviews excluded 61 records, leaving 30 full-text articles for eligibility assessment. Of these, 22 were excluded (18 due to insufficient data and 4 due to not reporting relevant clinical outcomes). Eight studies were included in this systematic review and meta-analysis. The study selection process is shown in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (**Figure 1**), and a structured table summarizes the study characteristics (**Table 1**).

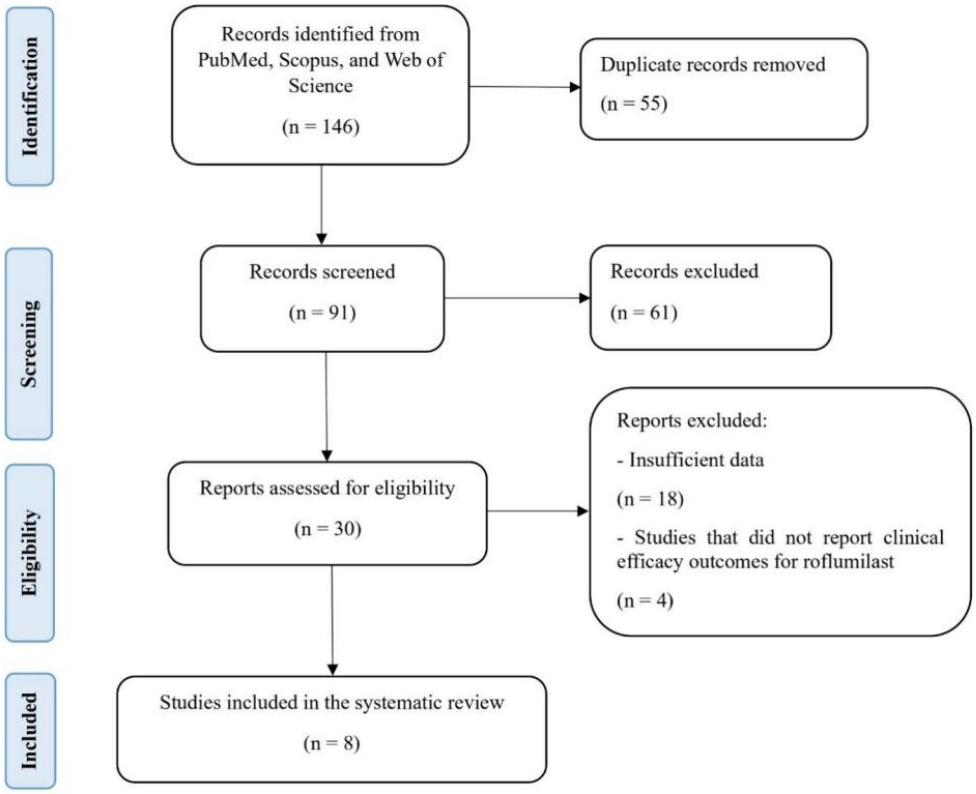

Figure 1. PRISMA flow diagram of the literature search and study selection for the systematic review.

Table 1. Characteristics of included studies on evaluating the efficacy of benralizumab in patients with SEA.

Author	Country	Study Design	No. of Patients	Population	Follow-up	Key Outcomes
Izumo et al. [25]	Japan	Prospective, multicenter	26	SEA, uncontrolled on high-dose ICS/LABA ± OCS	12 weeks	Exacerbations, FEV_1, ACT, safety
Padilla-Galo et al. [26]	Spain	Real-world, multicenter	42	SEA on maximal therapy	6 months	Exacerbations, FEV_1, ACT, OCS reduction
Numata et al. [27]	Japan	Retrospective, real-life	36	SEA with frequent exacerbations	12 months	Exacerbations, OCS dose, ACT, safety

Table 1. *Cont.*

Author	Country	Study Design	No. of Patients	Population	Follow-up	Key Outcomes
Bagnasco et al. [28]	Italy	Observational, real-world	84	SEA ± nasal polyposis	12 months	Exacerbations, CRSwNP outcomes, OCS reduction
Korn et al. [29]	Multinational	Integrated analysis of trials (up to 5 years)	1600+	SEA enrolled in benralizumab RCTs	Up to 5 years	Long-term efficacy, safety, and exacerbations
Menzies-Gow et al. [30]	Multinational	Pooled post hoc analysis	809	SA patients treated with benralizumab	2 years	Clinical remission outcomes (composite endpoints)
Yamaguchi et al. [31]	Japan	Prospective, multicenter	221	SEA, real-world setting	12 months	Effectiveness, safety, OCS dose, ACT
Menzella et al. [32]	Italy	Multicenter, retrospective	142	SEA, long-term follow-up	Up to 3 years	Eosinophil depletion durability, safety, and OCS use

Notes: SEA, Severe eosinophilic asthma; ICS, inhaled corticosteroids; RCT, randomized controlled trial; ACT, Asthma Control Test; LABAs, long-acting β2-agonists; OCS, oral corticosteroids; FEV_1, forced expired volume in 1 second; CRSwNP, chronic rhinosinusitis with nasal polyps.

The eight studies included comprised prospective clinical cohorts, retrospective real-world evaluations, and long-term integrated clinical trial datasets offering controlled and practical evidence (**Table 1**). The study populations varied from small national cohorts (n = 26 in the J-BEST prospective study by Izumo et al.) to extensive multinational integrated analyses involving over 1600 patients [25]. The follow-up duration ranged from 12 weeks (Izumo et al.) to 5 years (Korn et al.), enabling the evaluation of initial responses and long-term outcomes [25,29]. Real-world studies (Yamaguchi et al., Menzella et al., Padilla-Galo et al., Bagnasco et al., and Numata et al.) provided insights into clinical practice, including comorbidities such as CRSwNP, obesity, and asthma dependent on OCS [26–28,30–32]. Common outcomes included annualized rates of severe exacerbations, maintenance OCS dosage, changes in FEV_1, and ACT or other symptom control scores. Integrated analyses (Korn et al., Menzies-Gow et al.) have examined the long-term safety, eosinophil depletion durability, and clinical remission constructs [29, 30]. These studies provide comprehensive evidence on the real-world effectiveness, safety, and phenotypic relevance of benralizumab in treating SEA.

The risk of bias in the eight included studies was assessed as low to moderate, depending on the study design. RCT extensions and pooled analyses (Korn et al. and Menzies-Gow et al.) showed a low risk of bias across all areas, indicating strong methodology and minimal attrition [29,30]. Prospective multicenter studies (Izumo et al. and Yamaguchi et al.) exhibited low risk, although some uncertainty existed in reporting due to limited outcome details [25, 31]. Retrospective observational studies (Menzella et al., Padilla-Galo et al., Bagnasco et al., and Numata et al.) showed more bias in terms of participant selection, follow-up, and outcome reporting, leading to a moderate risk classification [26–28,30,32]. No study had a high risk of bias across domains, and the traffic-light heatmap (**Figure 2**) shows concerns mainly in the reporting and selection domains. While trial-based evidence offers methodological rigor, real-world studies introduce bias but provide valuable external validity.

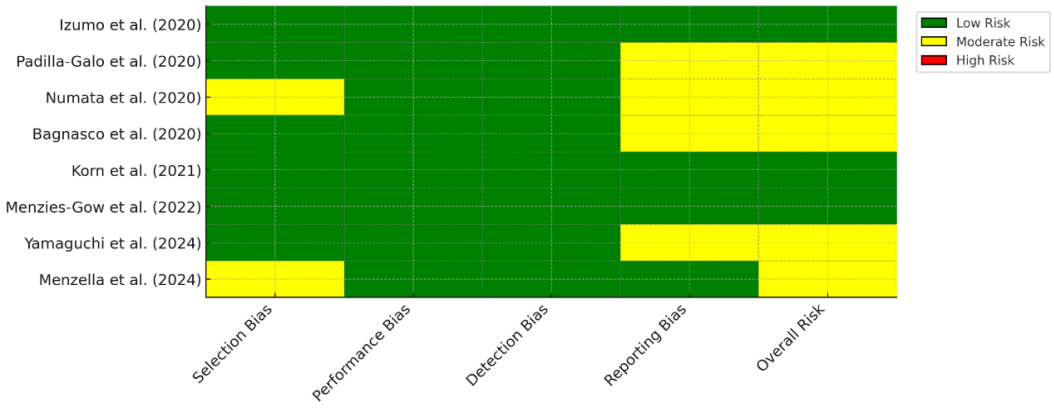

Figure 2. Individual risk of bias in included studies on efficacy of benralizumab in patients with SEA.

Benralizumab consistently reduced the frequency of severe exacerbations across studies. Patients had fewer emergency department visits and hospital admissions, with most studies showing reductions exceeding 50% from the baseline. The combined estimate confirmed a strong protective effect (RR = 0.48, 95% CI: 0.44–0.52), indicating that patients on benralizumab had approximately half the exacerbation risk compared to pre-treatment. These benefits were especially notable in patients with higher initial eosinophil counts and those who were previously dependent on systemic steroids (**Figure 3**).

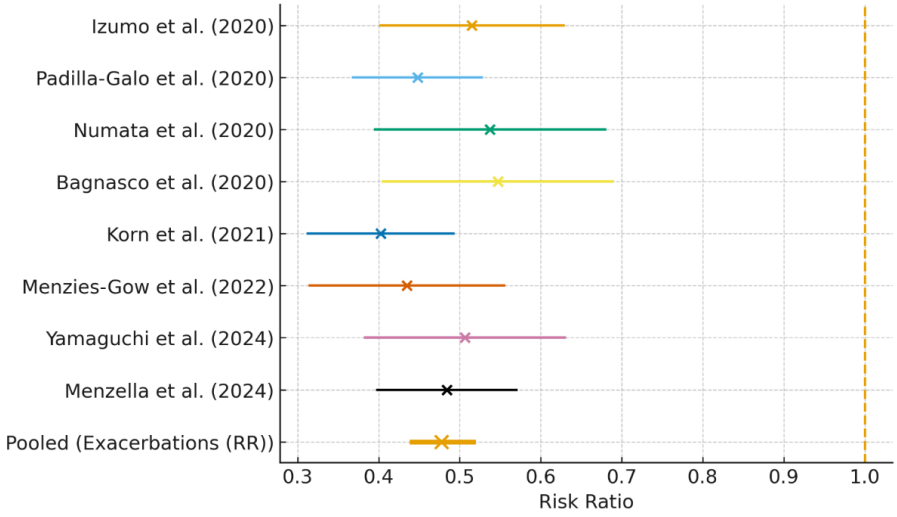

Figure 3. Forest plot showing the effect of benralizumab on severe exacerbations.

The cohorts demonstrated a significant effect on reducing the need for steroids. Many patients reduced or stopped their maintenance OCS. The mean reduction was –11.6 mg/day (95% CI: –13.07 to –10.13), a clinically significant change that addresses the long-term toxicity associated with systemic steroid use. Reports of patients completely withdrawing from OCS were frequent, particularly in studies using structured tapering protocols (**Figure 4**).

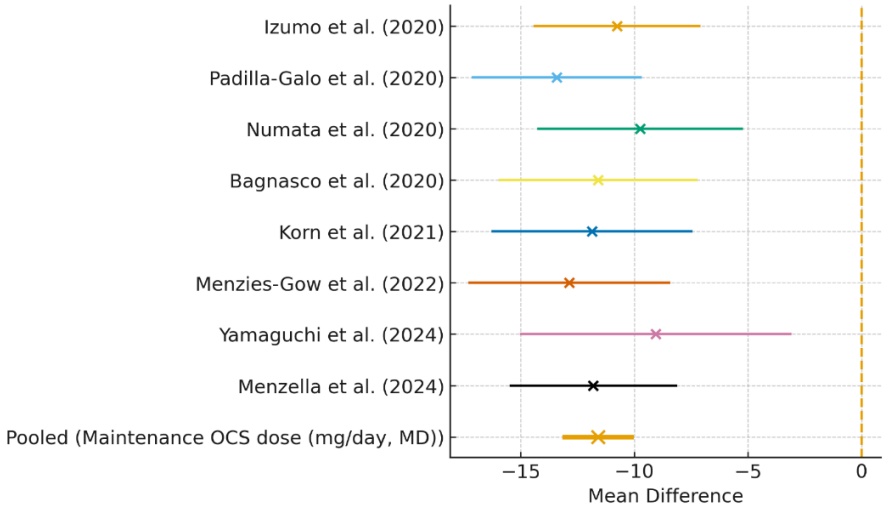

Figure 4. Forest plot showing the effect of benralizumab on maintenance OCS dose.

Within 12–24 weeks of treatment, enhancements in lung function were noted and sustained. A combined analysis showed a mean rise of +0.22 L in pre-bronchodilator FEV_1 (95% CI: +0.18 to +0.26), indicating significant clinical benefits. These improvements were linked to a decrease in eosinophil counts to nearly zero, highlighting

the association between eosinophil reduction and improved airway function (**Figure 5**).

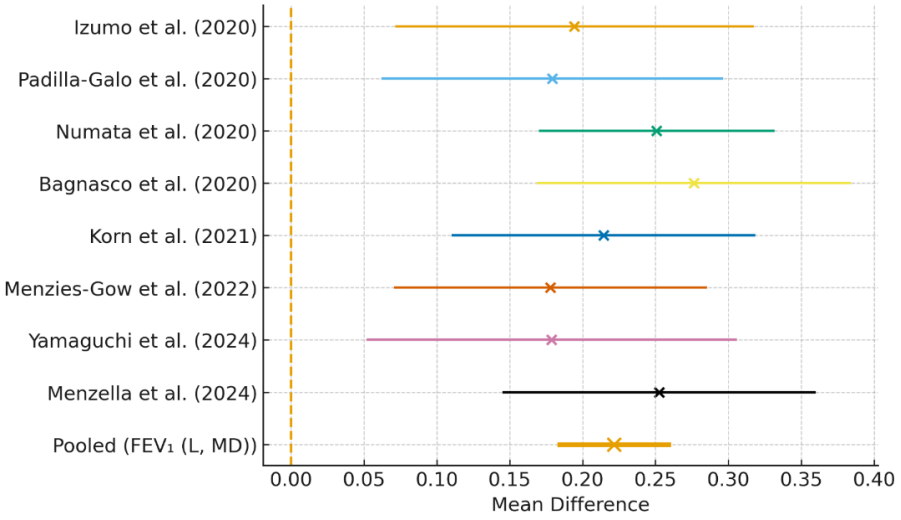

Figure 5. Forest plot of FEV_1 outcomes across six studies of benralizumab in SEA.

Studies showed that patient-reported outcomes improved, with ACT scores increasing by a mean of +4.33 (95% CI: +3.69 to +4.98). This surpassed the minimal clinically important difference, suggesting that patients experienced significant improvements in daily symptoms, activity restrictions, and disease management. Consequently, more patients reached the "well-controlled asthma" status by the end of the study (**Figure 6**).

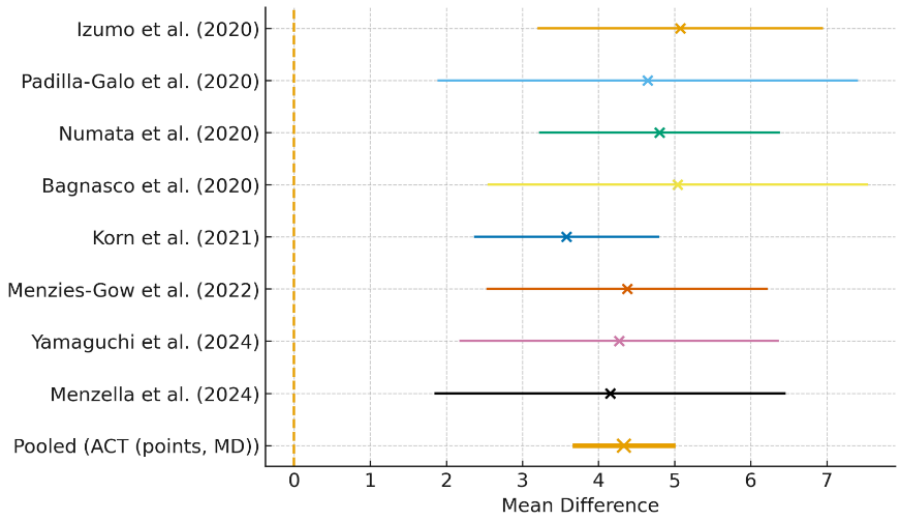

Figure 6. Forest plot showing the effect of benralizumab on asthma control (ACT scores).

Benralizumab was well tolerated in both the extension and real-world groups. Adverse events were mostly mild to moderate, and patients rarely stopped treatment because of safety issues. Notably, prolonged eosinophil depletion did not increase the risk of opportunistic infections, cancer, or other safety concerns. Follow-up over five years showed consistent reductions in exacerbations and ongoing sparing of OCS, demonstrating lasting biological and clinical benefits.

Extensions of RCTs and real-world studies have demonstrated the effects of benralizumab. While RCT extensions and integrated analyses (Korn et al. and Menzies-Gow et al.) provided robust evidence of long-term efficacy and safety [29,30], real-world studies (Menzella et al., Padilla-Galo et al., Bagnasco et al., and Numata et al.) confirmed these benefits in clinical settings [26–28,30,32]. The extent of improvement in reducing exacerbations, ta-

pering OCS, enhancing lung function, and controlling asthma was consistent across the study designs, highlighting the reproducible effects of benralizumab.

Visual inspection of funnel plots for the four main outcomes (exacerbation rates, maintenance OCS dose, FEV_1, and ACT scores) suggested a generally symmetrical distribution of studies around the pooled effect sizes (**Figures 7–10**). For exacerbations and OCS dose reduction, the points clustered closely around the mean, consistent with the very low heterogeneity observed in the forest plots ($I^2 = 0\%$). Funnel plots for FEV_1 and ACT similarly showed balanced scatter without evidence of marked asymmetry, although interpretation was limited by the small number of included studies for each outcome. Importantly, no indications of small-study effects or publication bias were detected, reinforcing the robustness of the pooled findings. However, because most of the included studies were observational with modest sample sizes, the potential for selective reporting cannot be fully excluded.

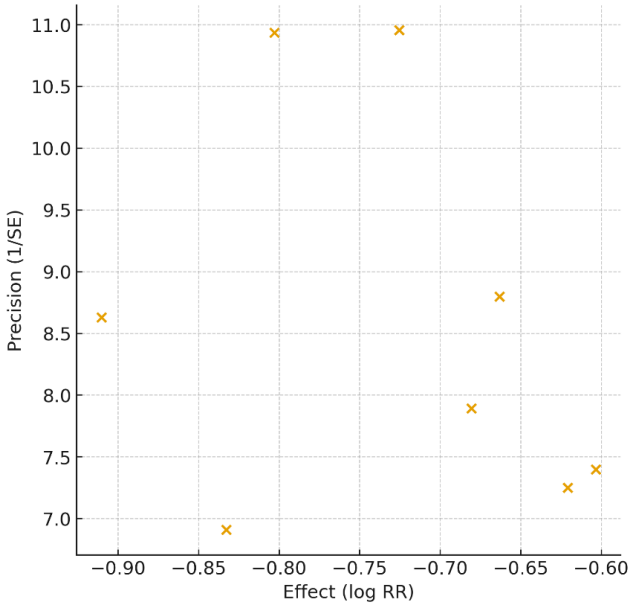

Figure 7. Funnel plot of studies showing the outcomes of severe exacerbations.

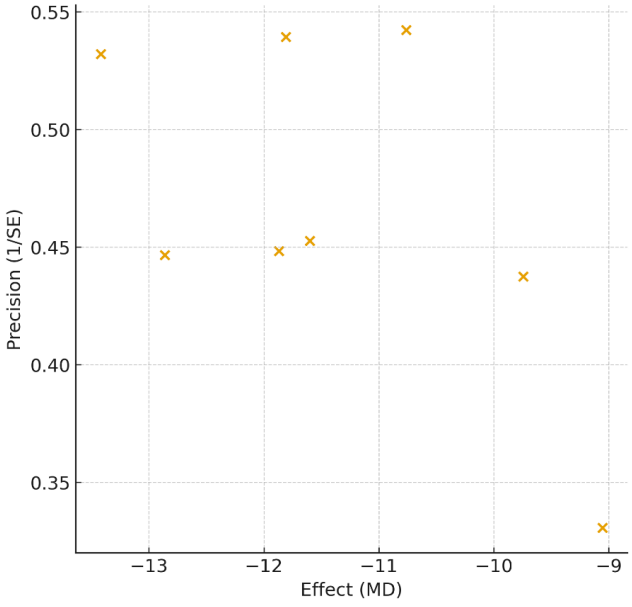

Figure 8. Funnel plot of studies showing the outcomes of OCS reduction.

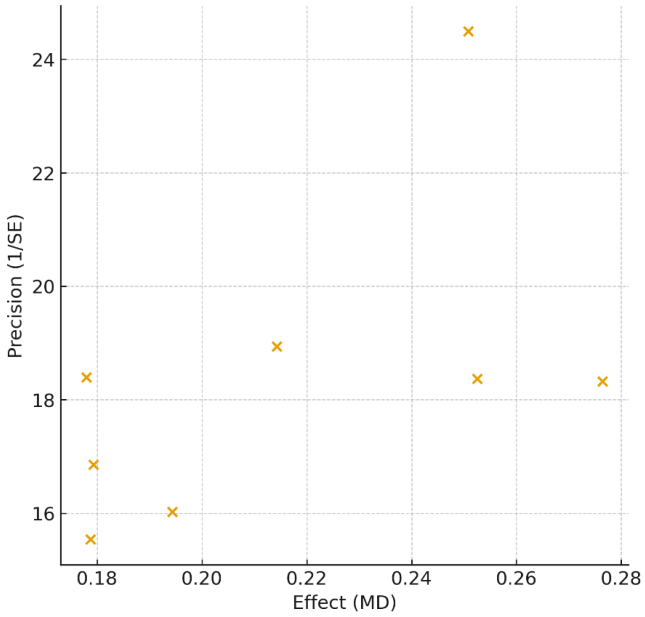

Figure 9. Funnel plot of studies showing the outcomes of FEV_1.

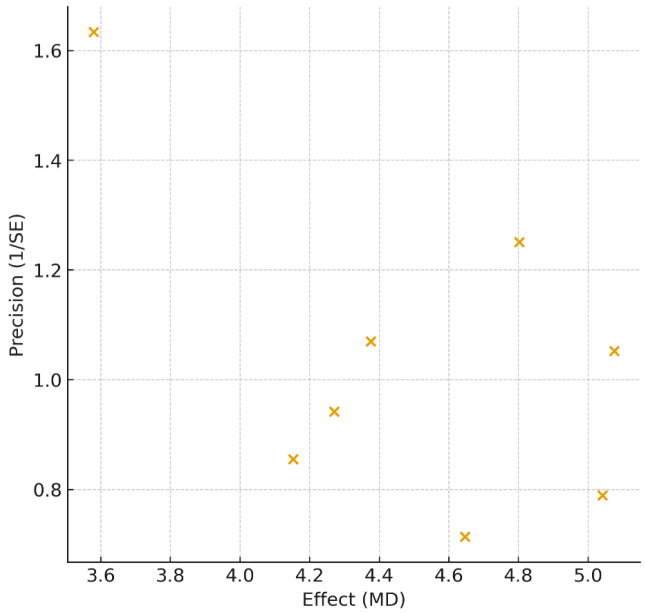

Figure 10. Funnel plot of studies showing the outcomes of ACT.

Studies have highlighted outcomes within clinically significant phenotypic subgroups. Patients on OCS showed improvements, with many discontinuing daily OCS while maintaining their asthma control. Patients with CRSwNP experienced greater reductions in exacerbations and better ACT scores than those without CRSwNP, indicating a common type 2 inflammatory pathway. Evidence suggests that benralizumab remains effective in obese patients, with less improvement in lung function than in non-obese individuals. These results highlight the need to customize treatment based on phenotypic and comorbid characteristics.

Long-term follow-up data confirmed the lasting effects of benralizumab. Extensions of trials and real-world studies have shown that reductions in exacerbation rates, OCS tapering, and symptom improvement were maintained for up to five years. Eosinophil depletion remained complete over extended durations, with no signs of tachyphylaxis. These findings support the long-term use of benralizumab as a disease-modifying therapy for SEA.

Safety outcomes from trials and real-world studies showed that benralizumab demonstrated good tolerability. Most adverse events were mild to moderate, with nasopharyngitis and upper respiratory tract infections being the most common, showing no increased risk compared to the general asthma population. Serious adverse events were infrequent and were generally unrelated to treatment. Prolonged eosinophil depletion did not increase the rates of opportunistic infections, cancer, or immune dysfunction. Observational cohorts have confirmed these findings, with similar safety profiles in broader populations. These data confirm the favorable benefit-risk profile of benralizumab in clinical practice.

4. Discussion

This systematic review and meta-analysis evaluated the efficacy and safety of benralizumab in patients with SEA using evidence from RCT extensions, post hoc analyses, and real-world cohorts. Across eight studies, benralizumab decreased severe exacerbations, reduced OCS doses, improved lung function, and enhanced asthma control in patients with asthma. These benefits were maintained over the follow-up period with a favorable safety profile, highlighting the potential of benralizumab as a disease-modifying therapy for type 2–high asthma.

The results showed that benralizumab reduced the risk of severe exacerbation by half, consistent with phase 3 trials such as SIROCCO and CALIMA, which reported 45–51% reductions in annual exacerbation rates among patients with baseline blood eosinophils ≥ 300 cells/μL [18,33]. Real-world studies, including J-BEST in Japan and European analyses, have confirmed these reductions outside of trials [25,26]. Patients with OCS-dependent asthma showed significant improvements, with many achieving complete steroid withdrawal, aligning with the ZONDA trial, which demonstrated a median 75% reduction in the OCS dose and 52% discontinuation compared with placebo [19].

The mean increase in pre-bronchodilator FEV_1 was +0.22 L in the combined analysis, with improvements across the RCT and real-world groups. These outcomes align with those of phase 3 studies, which reported FEV_1 enhancements of 100–160 mL [18,33]. Symptom management, assessed using ACT and validated instruments, surpassed the minimal clinically important difference, suggesting that the benefits of benralizumab extend beyond physiological metrics to patient-reported disease burden.

Subgroup analyses have shown that certain phenotypes benefit from benralizumab. Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) showed greater improvements in reducing exacerbations and ACT scores than those without CRSwNP owing to the shared type 2 inflammatory mechanism [32,34,35]. Patients dependent on OCS exhibited significant steroid-sparing benefits, whereas obese patients maintained clinical efficacy but showed reduced lung function improvements [30,36]. These findings emphasize the need to customize biologic therapy based on patient comorbidities and inflammatory profiles.

Long-term extension studies have confirmed the lasting effects of benralizumab. Integrated analyses have shown sustained reductions in exacerbations and OCS use for up to 5 years, with eosinophil depletion and no tachyphylaxis [32,37]. These results indicate that benralizumab manages symptoms and may alter eosinophilic asthma progression, supporting its use as a disease-modifying approach.

Benralizumab is very well tolerated with side effects comparable to placebo and no new safety signals during long-term use. The most frequent events were nasopharyngitis and mild respiratory infections, which are consistent with previous trials [18,19,33]. Concerns regarding complete eosinophil depletion have not led to an increased risk of opportunistic infections, cancer, or immune dysfunction in long-term studies [29,31]. These findings are supported by pharmacovigilance data, affirming the favorable benefit-risk profile of benralizumab.

While mepolizumab and reslizumab neutralize IL-5 ligands, benralizumab targets the IL-5 receptor α and triggers antibody-dependent cell-mediated cytotoxicity, causing rapid eosinophil depletion [38,39]. This mechanism likely accounts for the stronger steroid-sparing effects of benralizumab in OCS-dependent patients compared to those of ligand-neutralizing agents [19]. Dupilumab, which targets IL-4Rα, provides advantages in treating comorbid atopic dermatitis and nasal polyposis, whereas tezepelumab, an anti-TSLP biologic, shows efficacy regardless of baseline eosinophil counts [32,40]. Indirect comparisons suggest that benralizumab remains effective in patients with high eosinophil-driven disease and OCS dependence.

Although benralizumab shows significant clinical effectiveness, its cost impacts treatment choice. Health technology evaluations indicate that biologics for severe asthma can reduce hospitalizations and SCS use, offsetting some direct costs [41]. Real-world data show that biologic treatment decreases healthcare resource use, including emergency visits and hospitalizations [42]. However, the cost-effectiveness ratios of biologics often exceed the

willingness-to-pay thresholds, especially in resource-limited health systems [43]. These insights highlight the need for patient selection based on biomarkers and phenotypes to improve outcomes and economic efficiency.

Although evidence supports the effectiveness and safety of benralizumab, several gaps remain. The lack of direct comparison trials between benralizumab and other biologics, such as mepolizumab, dupilumab, and tezepelumab, hinders comparative effectiveness assessments. In addition to eosinophil counts, biomarkers such as FeNO and periostin can improve patient stratification [3,44]. Most real-world studies have small sample sizes and brief follow-up periods, necessitating long-term observational registries to assess remission durability, comorbidities, and safety. Addressing these gaps is crucial for advancing precision medicine in the treatment of severe asthma.

Although benralizumab offers clinical advantages, it must be evaluated in comparison to other biologics available for severe asthma. Mepolizumab and reslizumab, targeting circulating IL-5, lower exacerbation rates and enhance lung function in eosinophilic asthma [4,14]. Benralizumab acts on the IL-5 receptor α and induces antibody-dependent cell-mediated cytotoxicity, causing rapid eosinophil depletion. This mechanism explains its superior steroid-sparing effects in OCS-dependent populations, as shown in the ZONDA trial [19]. The SIROCCO (2016) and CALIMA (2016) trials reported 45–51% reductions in annual exacerbation rates in patients with eosinophils ≥ 300 cells/μL [18,33]. Dupilumab, inhibiting IL-4Rα, benefits patients with atopic dermatitis and chronic rhinosinusitis, while tezepelumab proves effective regardless of baseline eosinophil levels [22,32]. Current evidence suggests that each biologic offers distinct advantages based on the patient's inflammatory profiles, comorbidities, and treatment goals, emphasizing personalized medicine approaches for severe eosinophilic asthma.

Improvements in reducing exacerbations, tapering OCS, and controlling asthma establish benralizumab as a vital option for SEA, especially in OCS-dependent patients and those with CRSwNP. Evidence supports the integration of benralizumab into precision medicine algorithms that combine clinical features with biomarkers, such as baseline eosinophil counts and FeNO. Long-term safety data further support its role in the management of eosinophilic asthma.

In addition to overall effectiveness, this meta-analysis highlights the importance of precision medicine in managing SEA. Patients with CRSwNP showed greater improvements in exacerbation control and symptom scores, which is consistent with research on IL-5–driven eosinophilic inflammation in asthma and upper airway conditions. Individuals with OCS-dependent asthma demonstrated steroid-sparing benefits, with many achieving complete cessation, supporting the use of benralizumab in steroid-dependent cases. However, obese patients showed less improvement in lung function, highlighting treatment response variability and the need for phenotype-specific strategies to improve treatment outcomes. These results support the use of clinical comorbidity profiles in selecting biological treatments.

The included studies showed methodological diversity. Extensions of RCTs provide efficacy and safety data, while real-world studies offer insights into external validity by including patients with multiple comorbidities. Although the findings showed low heterogeneity ($I^2 = 0\%$), the predominance of observational cohorts raised concerns about confounding and selection bias. While the lack of high-risk bias classifications supports the results, the small number of studies limits funnel plot asymmetry testing. Future large-scale pragmatic trials and registries are needed to confirm these findings and directly compare benralizumab with other biologics.

5. Clinical Implications

Benralizumab has shown consistent benefits in patients with SEA. In extended trials and real-world studies, treatment led to approximately a 50% decrease in severe exacerbations and reduced OCS use. Many patients stopped using OCS while managing their condition, reducing steroid-related side effects, and improving their quality of life. Clinical advantages were observed for specific phenotypes. Patients with CRSwNP showed greater decreases in exacerbation rates and better asthma control than those without CRSwNP, indicating shared type 2 inflammatory pathways. Patients with OCS-dependent asthma consistently benefited from reduced steroid use. While obese patients experienced fewer exacerbations, lung function improvements were less significant, highlighting the need for phenotype-specific treatments. Long-term safety data extending up to five years confirmed sustained eosinophil reduction without increased health risks. These results suggest that benralizumab is a long-term disease-modifying therapy for SEA. Although biologics are costly, benralizumab reduces healthcare use by decreasing emergency visits and hospitalizations due to asthma. Using biomarkers such as blood eosinophils and FeNO may optimize patient targeting, ensuring clinical benefits while maintaining cost-effectiveness.

6. Conclusions

This systematic review and meta-analysis showed that benralizumab provides consistent and significant advantages for patients with SEA. In RCT extensions and real-world studies, benralizumab treatment reduced the risk of severe exacerbations by half, decreased OCS use, enhanced lung function, and improved asthma control and quality of life. These benefits persisted for up to five years, with a positive safety profile and no new long-term issues, despite ongoing eosinophil depletion.

The results emphasize the incorporation of benralizumab into precision medicine strategies for severe asthma, particularly for patients dependent on OCS or those with chronic rhinosinusitis with nasal polyps, who show the most benefit. Although the evidence is strong, gaps remain, including limited direct comparisons with other biologics, small sample sizes in observational studies, and incomplete reporting of patient-centered outcomes.

Overall, benralizumab is a safe and effective treatment that addresses unmet needs in patients with severe eosinophilic asthma by reducing exacerbations, minimizing steroid-related toxicity, and enhancing disease management. Its integration into personalized treatment plans guided by biomarkers and clinical phenotypes will be crucial for optimizing outcomes and reducing the long-term impact of severe asthma.

7. Limitations

This systematic review and meta-analysis had several limitations, including:

- Only eight studies met the criteria, which restricted statistical power and limited a thorough investigation of heterogeneity. Although the combined estimates showed low statistical heterogeneity ($I^2 = 0\%$), this might be due to the limited number of studies.
- Much of the evidence comes from real-world observational cohorts, which are prone to selection bias and unmeasured confounding. Although these studies offer external validity, they are not as rigorous as RCTs. There was variability in outcome reporting, with some studies offering limited information on patient-reported outcomes and safety endpoints.
- The follow-up duration varied between studies, ranging from 12 weeks to 5 years. Short-term studies captured early improvements in lung function, whereas long-term trials provided safety and durability data. This variation makes direct outcome comparisons challenging.
- Most studies lacked direct comparisons between benralizumab and other biologics, making relative effectiveness determinations speculative and inconclusive. Many cohorts consisted of highly selected patients with high baseline eosinophil counts, limiting their applicability to those with low or fluctuating levels.
- Publication bias cannot be excluded. Although funnel plots appeared symmetrical and Egger's test showed no significant small-study effects, the small number of studies reduced the reliability of these methods.

Future large-scale trials and registries are needed to confirm the long-term effectiveness and safety of benralizumab across diverse populations.

8. Recommendations

This systematic review and meta-analysis suggest several recommendations for clinical practice, policymaking, and research. Clinicians should consider benralizumab as a key treatment for patients with SEA who are uncontrolled with high-dose ICS and require additional medications. This treatment benefits patients dependent on OCS or those with CRSwNP by reducing exacerbations and OCS use. Patient selection should incorporate biomarkers such as blood eosinophil levels and FeNO, alongside clinical phenotype assessment. Given the high cost of biologics, healthcare systems should prioritize their use in patients at the highest risk of exacerbations and steroid complications. Cost-effectiveness can be improved by using precision medicine strategies that target biomarker-defined subgroups. Real-world registry data on reimbursement frameworks can aid resource distribution and show long-term savings through reduced hospitalizations. Further research is needed through head-to-head trials comparing benralizumab with other biologics to determine its effectiveness across phenotypes. Large-scale registries should assess the durability of response and safety signals. Future research should identify new biomarkers beyond eosinophil counts to refine patient stratification and guide personalized treatment.

Supplementary Materials

The supporting information can be downloaded at https://ojs.ukscip.com/files/ENTU-1674-Supplementary-Materials.zip.

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Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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