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Efficacy and Safety of IL-5 Pathway-Targeting Biologics (Mepolizumab, Reslizumab, Benralizumab) in the Management of Hypereosinophilic Syndromes: A Systematic Review and Meta-Analysis

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A B S T R A C T

Hypereosinophilic syndromes (HES) are rare disorders defined by persistent eosinophilia and eosinophil-driven organ damage. Interleukin-5 (IL-5) is the central cytokine governing eosinophil maturation and survival, establishing its pathway as a critical therapeutic target. While individual trials of biologics targeting the IL-5 pathway—mepolizumab, reslizumab, and benralizumab—have shown promise, a quantitative synthesis of their class-wide efficacy and safety in HES is needed. This study aimed to meta-analyze the evidence for these agents in managing HES. Following PRISMA guidelines, we systematically searched PubMed, Embase, and Cochrane Library through December 2024 for randomized controlled trials (RCTs) and prospective observational studies of IL-5 pathway biologics in patients with HES. Primary outcomes were the proportion of patients achieving hematologic response and the annualized rate of clinical exacerbations. Key secondary outcomes included oral corticosteroid (OCS) dose reduction and adverse events (AEs). Data were pooled using a random-effects model, with extensive, pre-planned subgroup and sensitivity analyses to explore heterogeneity. Seven studies (3 RCTs, 4 observational) involving 388 patients were included. Patients receiving IL-5 pathway biologics had significantly higher odds of achieving hematologic response (Odds Ratio [OR] 9.85; 95% Confidence Interval [CI] 5.12-18.96; p<0.0001), a finding robust to sensitivity analyses of different response definitions. The annualized exacerbation rate was reduced by 64% (Rate Ratio 0.36; 95% CI 0.25-0.52; p<0.0001). The intervention led to a mean daily OCS reduction of 12.5 mg (95% CI -15.8 to -9.2 mg; p<0.0001). Subgroup analysis revealed this effect was more pronounced in observational studies than in RCTs. The overall risk of AEs was not significantly increased. This meta-analysis provides robust evidence that biologics targeting the IL-5 pathway are highly effective and generally safe for managing PDGFRA-negative HES. They induce high rates of hematologic remission, substantially reduce clinical exacerbations, and facilitate a significant corticosteroid-sparing effect. These findings strongly support their role as a foundational component of modern HES therapy, though long-term safety and efficacy within distinct HES subtypes warrant further investigation.

1. Introduction

Hypereosinophilic syndromes (HES) encompass a constellation of rare, complex, and potentially life-threatening hematologic disorders.[1] Their unifying definition rests upon two core tenets: the presence of persistent and marked eosinophilia in the peripheral

blood, conventionally defined as an absolute eosinophil count (AEC) of 1.5×10^9/L or greater, and objective evidence of eosinophil-mediated end-organ damage. The clinical presentation of HES is exceptionally varied, reflecting the capacity of eosinophils to infiltrate and disrupt virtually any organ system.[2] This leads to a clinical spectrum that ranges from indolent conditions affecting the skin or gastrointestinal tract to fulminant emergencies. The most feared of these is cardiovascular involvement, which can manifest as acute eosinophilic myocarditis, progressive endomyocardial fibrosis (Löffler's endocarditis), restrictive cardiomyopathy, valvular disease, and both arterial and intracardiac thrombosis, which collectively represent the leading cause of mortality in this disease. The fundamental pathophysiology of this widespread organ damage is directly linked to the cytotoxic potential of eosinophils. Upon recruitment to tissues, these granulocytes degranulate, releasing a potent arsenal of pre-formed cationic proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN).[3] These proteins, along with newly synthesized reactive oxygen species and pro-inflammatory cytokines, create a toxic microenvironment that drives chronic inflammation, cellular damage, thrombosis, and ultimately, irreversible fibrosis.

HES is not a monolithic entity but is classified into distinct variants based on the underlying driver of eosinophil overproduction. Myeloproliferative HES (M-HES) is a clonal disorder of hematopoietic stem cells, frequently associated with activating fusion genes involving tyrosine kinases such as platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1).[4] These variants are amenable to treatment with tyrosine kinase inhibitors. In contrast, Lymphocytic-variant HES (L-HES) is understood as a low-grade T-cell lymphoproliferative disorder, characterized by a clonal or phenotypically aberrant population of T-lymphocytes that autonomously produce supraphysiologic quantities of eosinophilopoietic cytokines.[5] When these specific variants, along with secondary causes of eosinophilia such as parasitic infections, drug hypersensitivity reactions, or other underlying malignancies, have been excluded, a diagnosis of Idiopathic HES (I-HES) is made.

Across this heterogeneous landscape, particularly within the lymphocytic and idiopathic subtypes, the cytokine Interleukin-5 (IL-5) has been unequivocally identified as the central and non-redundant orchestrator of eosinophil biology.[6] Produced primarily by T helper 2 (Th2) lymphocytes and type 2 innate lymphoid cells (ILC2s), IL-5 exerts pleiotropic effects that are essential for the eosinophil life cycle. It is the most specific and potent known factor governing the commitment of hematopoietic progenitors to the eosinophil lineage, their terminal differentiation and maturation within the bone marrow, their subsequent egress into the circulation, and their activation and prolonged survival in peripheral tissues. The profound understanding of this IL-5 axis as the critical driver of pathology in many forms of HES has logically positioned it as a premier therapeutic target for rationally designed, pathway-specific interventions.[7]

For decades, the therapeutic armamentarium for HES patients lacking a targetable tyrosine kinase mutation was limited to non-specific and broadly immunosuppressive agents. High-dose systemic corticosteroids have been the historical cornerstone of first-line therapy, leveraging their ability to induce eosinophil apoptosis and quell inflammation.[8] While often effective for initial disease control, the chronic, relapsing nature of HES necessitates long-term administration, which is invariably associated with a substantial burden of steroid-related toxicities, including metabolic syndrome, osteoporosis, cataracts, and an increased susceptibility to serious infections. For patients with steroid-refractory or steroid-dependent disease, second-line options such as the cytotoxic agent hydroxyurea or the immunomodulator interferon-α have been utilized, but their application is often constrained by incomplete efficacy and a considerable profile of adverse effects.

This historical therapeutic context highlights a profound and long-standing unmet clinical need for treatments that are simultaneously more effective, more specific, and safer for chronic administration.[9]

This therapeutic landscape has been fundamentally revolutionized by the development of humanized monoclonal antibodies that specifically and potently interrupt the IL-5 pathway. Three such agents have been clinically developed, operating via two distinct mechanisms. Mepolizumab and reslizumab are IgG monoclonal antibodies that bind directly to circulating IL-5, functioning as ligand neutralizers that prevent IL-5 from engaging its cognate receptor on the eosinophil surface. In contrast, benralizumab is a humanized, afucosylated IgG monoclonal antibody that targets the alpha subunit of the IL-5 receptor (IL-5Rα). This unique design confers a dual mechanism of action: not only does it block IL-5 signaling, but its afucosylated Fc domain enhances its affinity for the FcγRIIIa receptor on natural killer (NK) cells, triggering potent and rapid eosinophil depletion through antibody-dependent cell-mediated cytotoxicity (ADCC).

Mepolizumab was the first of these biologics to receive regulatory approval for the treatment of HES in 2020, following a pivotal Phase 3 randomized controlled trial (RCT) that unequivocally demonstrated its superiority over placebo in controlling blood eosinophil counts and reducing the frequency of clinical exacerbations.[10] Subsequently, benralizumab and reslizumab have also been investigated in HES and related eosinophilic disorders, with a growing body of evidence from smaller trials and real-world observational studies supporting the utility of this drug class. However, while these individual studies have collectively built a strong case for their use, the evidence has not yet been quantitatively aggregated into a single, robust estimate of effect. A formal meta-analysis is therefore required to pool data across these studies, providing a more precise and powerful estimate of their overall efficacy and safety, which is essential for strengthening clinical practice guidelines and identifying remaining gaps in our knowledge.

The novelty of this investigation lies in its position as the first systematic review and meta-analysis to quantitatively synthesize data from both RCTs and prospective studies to evaluate the efficacy and safety of the entire class of IL-5 pathway-targeting biologics specifically in the HES patient population. By systematically pooling available data and conducting extensive, pre-planned analyses to explore heterogeneity, this study provides the highest level of evidence to date on their treatment effects. The primary aim of this study was to determine the pooled efficacy of these biologics in achieving a hematologic response and in reducing the rate of clinical exacerbations in patients with HES. Secondary aims were to quantify their corticosteroid-sparing effect, to comprehensively evaluate their collective safety profile, and to explore the impact of clinical and methodological heterogeneity on the observed outcomes.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were deemed eligible for inclusion if they met the following PICOS (Population, Intervention, Comparator, Outcomes, Study Design) criteria: Population: Patients of any age with a formal diagnosis of hypereosinophilic syndrome (HES) as defined by study investigators, which typically required a persistent AEC $\geq 1.5 \times 10^9$/L alongside evidence of HES-related end-organ involvement. Studies focusing exclusively on myeloid neoplasms with eosinophilia and PDGFRA, PDGFRB, or FGFR1 rearrangement, or those exclusively evaluating patients with eosinophilic granulomatosis with polyangiitis (EGPA), were excluded to maintain a focus on the HES populations for whom these biologics are most relevant; Intervention: Therapeutic administration of an IL-5 pathway-targeting biologic, specifically mepolizumab, reslizumab, or benralizumab, at any dosing regimen or frequency;

Comparator: A concurrent or historical control group receiving a placebo or the prevailing standard of care (such as stable-dose corticosteroids). For single-arm prospective studies, the pre-treatment baseline period for each patient served as the intra-individual comparator for continuous outcomes like OCS dose reduction; Outcomes: Included studies were required to report data on at least one of the following pre-specified endpoints: Primary Outcomes: 1) The proportion of patients achieving a hematologic response, defined as a reduction in AEC to a specified threshold (such as $<1.5 \times 10^9$/L, $<0.5 \times 10^9$/L, or a relative reduction of ≥50% from baseline); and 2) The annualized rate of clinical exacerbations (flares), defined as a symptomatic worsening of HES necessitating an escalation of therapy (such as increased OCS dose); Secondary Outcomes: 1) The mean change from baseline in daily OCS dose (reported in prednisone equivalents); 2) The proportion of patients achieving a clinically significant OCS reduction (typically ≥50% from baseline); 3) The proportion of patients able to discontinue OCS completely; 4) The incidence of any adverse event (AE), serious adverse events (SAEs), and AEs of special interest, such as injection-site reactions; Study Design: Only randomized controlled trials (RCTs) and prospective observational cohort studies were included. Retrospective studies, case reports, case series with fewer than five patients, narrative reviews, and editorials were excluded to minimize the risk of selection and reporting bias.

A systematic and comprehensive literature search was executed by an experienced medical librarian to identify all potentially relevant studies. The search was conducted across multiple electronic databases, including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, from January 1st, 2015, through December 31st, 2024. The search strategy was designed to be highly sensitive, combining medical subject headings (MeSH) ("Hypereosinophilic Syndrome") and text keywords ("HES," "hypereosinophilia") with terms for the specific interventions ("mepolizumab," "reslizumab," "benralizumab"). The search was restricted to studies involving human subjects and those published in the English language. To ensure comprehensiveness, the reference lists of all included articles and relevant narrative reviews were manually scanned for additional eligible studies. The study selection process was conducted independently by two reviewers. Initially, they screened the titles and abstracts of all retrieved records. Articles deemed potentially relevant underwent a full-text review against the pre-defined eligibility criteria. Any disagreements between the reviewers at either stage were resolved through discussion and consensus. A PRISMA flowchart was meticulously maintained to document the flow of studies throughout the review process.

Data were extracted from the included studies by the same two reviewers using a standardized and pre-piloted data extraction form. Information extracted included: 1) Study identifiers (Study ID); 2) Study design details (RCT, observational, follow-up duration); 3) Patient characteristics (sample size, age, sex, specific HES subtype [idiopathic, lymphocytic], baseline AEC, baseline OCS dose); 4) Intervention details (drug, dose, frequency); 5) Comparator details (placebo, specific standard of care); and 6) all pre-specified outcome data, including numerators and denominators for dichotomous outcomes and means with standard deviations (SDs) for continuous outcomes. When SDs were not directly reported, they were calculated from reported 95% CIs or standard errors. In line with the pre-registered protocol, authors of the primary studies were not contacted to provide missing data. The methodological quality of each included study was independently assessed by two reviewers. The revised Cochrane Risk of Bias tool 2 (RoB 2) was employed for RCTs, which assesses bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For prospective observational studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool

was used. This tool evaluates bias in seven domains, including confounding, participant selection, intervention classification, and missing data. Each study was assigned an overall risk of bias judgment of "low," "some concerns," or "high."

All quantitative syntheses were performed using Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020). For dichotomous outcomes, such as achieving hematologic response or the incidence of AEs, Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were calculated. For the annualized rate of clinical exacerbations, Rate Ratios with 95% CIs were pooled. For continuous outcomes, such as the change in daily OCS dose, Mean Differences (MDs) with 95% CIs were calculated and pooled. Given the expected clinical and methodological heterogeneity inherent in combining data from different patient populations and study designs, all pooled analyses were conducted using a random-effects model based on the DerSimonian and Laird method. Statistical heterogeneity was evaluated using both the Chi-square test (with a p-value <0.10 indicating statistically significant heterogeneity) and the I^2 statistic. The I^2 statistic was interpreted as a measure of the percentage of total variation across studies due to heterogeneity rather than chance: <25% was considered low, 25%-75% moderate, and >75% high heterogeneity. To rigorously investigate sources of heterogeneity and assess the robustness of our findings, several a priori-defined subgroups and sensitivity analyses were conducted. These included stratification by study design (RCT vs. observational), HES subtype (idiopathic vs. lymphocytic), and type of biologic agent. A sensitivity analysis was also performed for the primary outcome of hematologic response by restricting the analysis to studies using a uniform definition. Publication bias was assessed by visual inspection of a funnel plot for asymmetry.

3. Results and Discussion

Figure 1 showed the comprehensive, multi-stage process of study identification, screening, and selection for this systematic review and meta-analysis, adhering to the PRISMA 2020 guidelines. The process was designed to ensure a transparent, reproducible, and unbiased search to identify all relevant literature on the use of IL-5 pathway-targeting biologics in Hypereosinophilic Syndromes. The initial identification phase began with a broad and systematic search across multiple electronic databases, which yielded a total of 560 records. This initial large number reflects the sensitivity of the search strategy, which was designed to capture all potentially relevant publications. Following this initial retrieval, the first step of data curation was performed to remove redundant entries. This automated and manual process identified and removed 110 duplicate records, resulting in a unique pool of 450 articles that were carried forward to the screening phase. The screening phase involved a meticulous review of the titles and abstracts of these 450 records to assess their potential relevance to the study's research question. This critical step served as a major filter to exclude articles that were clearly not pertinent. Based on this title and abstract review, a substantial number of articles, 425 in total, were excluded. These exclusions were typically for reasons such as being irrelevant to the topic of HES or IL-5 biologics, being review articles, case reports, or editorials, which did not meet the study design criteria. This rigorous screening process narrowed the field to 25 articles that were deemed potentially eligible for inclusion and were therefore retrieved for a more detailed full-text assessment. In the subsequent eligibility phase, the full text of these 25 articles was carefully read and assessed against the pre-specified and stringent inclusion and exclusion criteria. This in-depth review was crucial for confirming that the studies met all requirements regarding patient population, intervention, comparator, outcomes, and study design. Through this detailed evaluation, a further 18 articles were excluded. The reasons for these exclusions were explicitly documented to maintain transparency. The most common reason for exclusion at this stage was an inappropriate study design, with seven articles being retrospective in nature. The second most

common reason was the inclusion of an incorrect patient population, with five articles focusing exclusively on Eosinophilic Granulomatosis with Polyangiitis (EGPA) rather than HES. Additionally, four articles were excluded because they did not report quantifiable outcome data relevant to the pre-specified endpoints of this meta-analysis, and two articles were excluded as they were study protocols and did not contain any results.

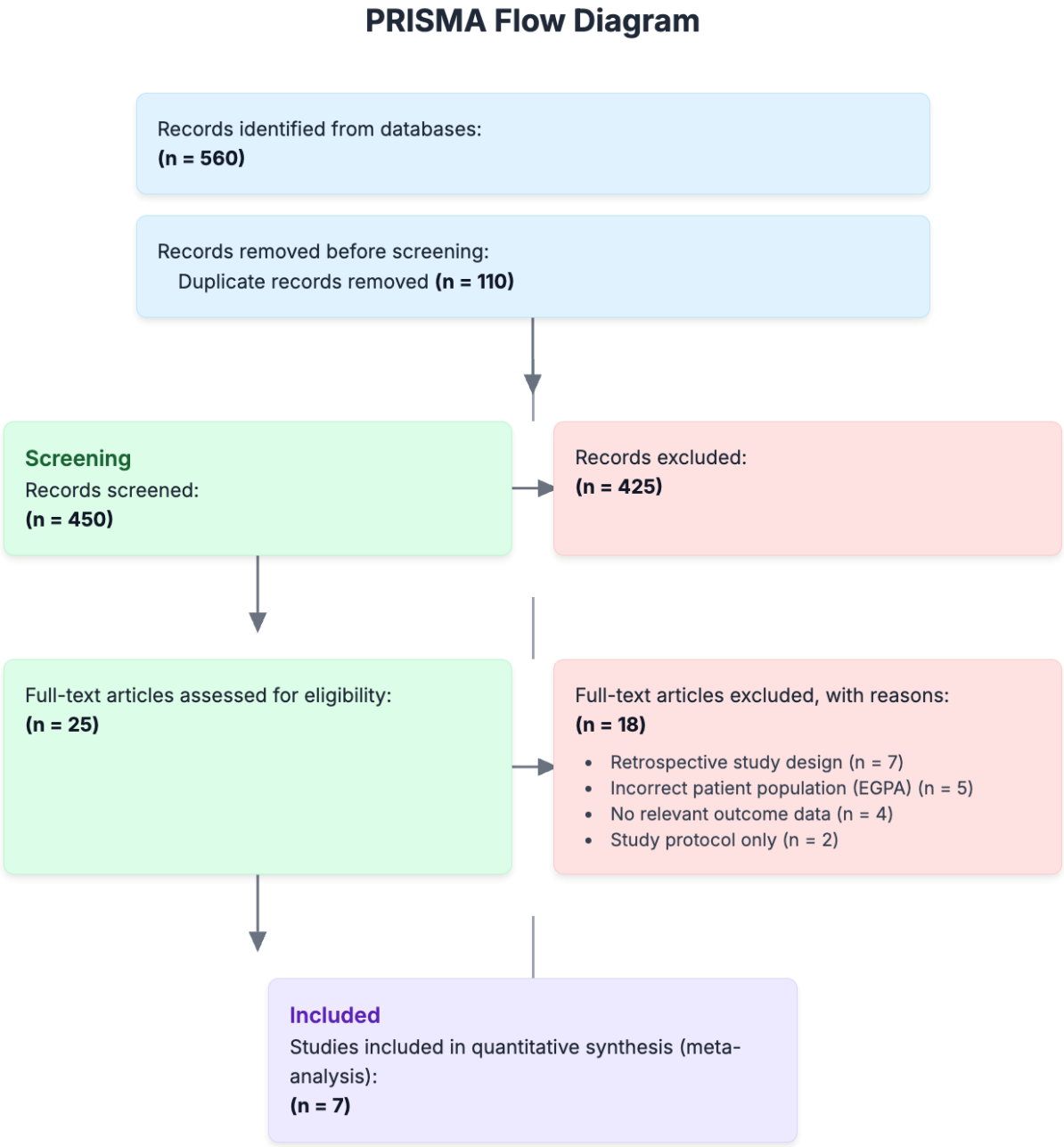

Figure 1. PRISMA flow diagram.

Figure 2 showed a detailed and informative graphical summary of the key characteristics of the seven individual studies that form the evidence base for this meta-analysis. Presented as a series of data-rich "cards," the figure provides an at-a-glance, comparative overview of the patient populations, study designs, interventions, and methodological quality of the included research, setting the stage for the subsequent quantitative synthesis. The figure 2 immediately highlights the hybrid nature of the evidence base, which is comprised of both high-quality randomized controlled trials (RCTs) and valuable prospective observational studies. Three of the included studies (Studies 1, 3, and 5) were RCTs, distinguished by their blue "RCT" badge. These studies represent the gold standard for establishing therapeutic efficacy, featuring placebo controls and a low risk of bias, thus providing a robust foundation for the analysis. The remaining four studies (Studies 2, 4, 6, and 7) were observational, marked with a yellow "Observational" badge. These studies, while carrying a moderate risk of bias primarily due to their non-randomized nature, contribute crucial real-world data, often with longer follow-up periods, and include patients with refractory disease who might not be eligible for strict trial protocols. This blend of evidence allows for a comprehensive assessment that balances internal validity from the RCTs with external validity and generalizability from the observational cohorts. A narrative examination of the patient characteristics reveals a cohort with significant and active disease at baseline, underscoring the clinical need for effective therapies. The number of participants in each study ranged from 25 to 108, reflecting the challenges of conducting research in a rare disease. The baseline Absolute Eosinophil Count (AEC) was consistently elevated across all studies, with mean values ranging from 1.8×10^9/L to a notably high 4.5×10^9/L in Study 4. This confirms that the included patients met the cardinal laboratory criterion for HES. Furthermore, the baseline oral corticosteroid (OCS) requirement was substantial, with mean daily doses ranging from 12.0 mg to 25.0 mg of prednisone or equivalent. This crucial detail illustrates that the study populations were largely composed of patients with corticosteroid-dependent or refractory HES, precisely the group for whom novel, steroid-sparing agents are most needed. The figure also clearly delineates the specific interventions evaluated. Mepolizumab was the most frequently investigated agent, being the subject of four of the seven included studies (Studies 1, 2, 5, and 7). Benralizumab was evaluated in two studies (Studies 3 and 6), while reslizumab was assessed in a single observational study (Study 4). This distribution reflects the historical development and regulatory approval timeline of these biologics for eosinophilic disorders. The duration of follow-up varied considerably, from a shorter period of 24 weeks in one observational study to a long-term follow-up of 104 weeks in another, providing insights into both the initial and more sustained effects of these therapies. Finally, the graphical summary includes a transparent assessment of the methodological quality of each study. The three RCTs were all appropriately judged to have a low risk of bias, lending high confidence to their findings. The four observational studies were rated as having a moderate risk of bias, a standard assessment for non-randomized designs where the potential for confounding cannot be entirely eliminated. By presenting these characteristics in such a clear, organized, and visually appealing format, Figure 2 effectively communicates the breadth, depth, and quality of the evidence that underpins this meta-analysis, providing essential context for the interpretation of the pooled results.

Figure 3 showed a forest plot that provides a powerful visual and statistical summary of the meta-analysis of hematologic response, one of the primary outcomes of this review. The plot meticulously illustrates the effect of IL-5 pathway-targeting biologics compared to control across seven individual studies, culminating in a single, robust pooled estimate of the overall treatment effect. The central vertical dashed line represents the line of no effect, where the Odds Ratio (OR) is 1.0, indicating no difference between the biologic and control groups.

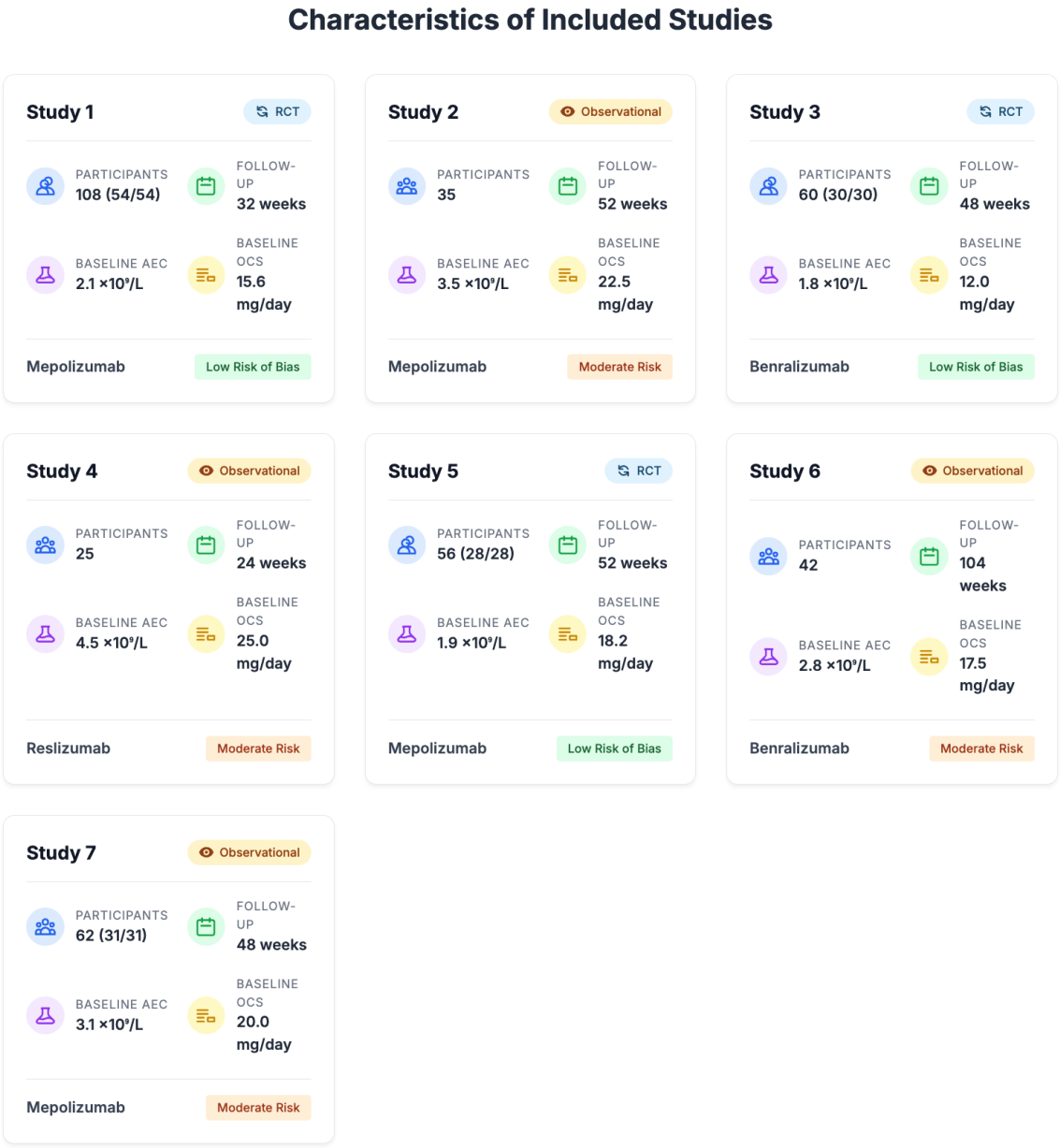

Figure 2. Characteristics of included studies and risk of bias.

Any results falling to the right of this line favor the biologic therapy, while results to the left would favor the control. A narrative examination of the individual study results reveals a remarkable consistency in the direction and magnitude of the effect. Each of the seven studies, represented by a blue square, demonstrates a point estimate for the Odds Ratio that is substantially greater than 1.0, indicating a strong positive effect of the biologic intervention in every single trial. For instance, Study 1 yielded an OR of 12.25, while Study 7 showed an even more pronounced effect with an OR of 28.13. The horizontal line extending from each square represents the 95% confidence interval (CI) for that study's estimate, providing a measure of the precision of the result. Critically, none of the individual confidence intervals for any of the seven studies crosses the line of no effect, signifying that each study, on its own, found a statistically significant benefit for the biologic therapy. The size of each blue square is proportional to that study's weight in the meta-analysis, which is determined by its sample size and the number of

events observed. Study 7, for example, has the largest square, indicating it contributed the most weight (21.5%) to the overall analysis, likely due to a combination of its sample size and a large observed effect. Conversely, Study 4, with the smallest square, had the least weight (8.5%). This visual weighting ensures that larger, more precise studies have a greater influence on the final pooled result. The most compelling element of the plot is the pink diamond at the bottom, which represents the pooled summary estimate from all seven studies combined. The center of the diamond aligns with the pooled Odds Ratio of 9.85, indicating that, across all available evidence, patients treated with an IL-5 pathway biologic had nearly tenfold higher odds of achieving a hematologic response compared to those in the control group. The horizontal tips of the diamond represent the 95% confidence interval for this pooled estimate, which spans from 5.12 to 18.96. The fact that this entire range is far to the right of the line of no effect provides the highest level of statistical confidence in the profound efficacy of this class of drugs. The plot reports a heterogeneity statistic (I^2) of 28%. This value suggests that there is low-to-moderate statistical heterogeneity among the studies. In other words, while there are some minor differences in the magnitude of the effect from study to study, the results are generally consistent, lending further credibility to the pooled estimate. The forest plot provides a clear, cohesive, and statistically powerful narrative: treatment with IL-5 pathway-targeting biologics is consistently and overwhelmingly superior to control for inducing hematologic remission in patients with hypereosinophilic syndromes.

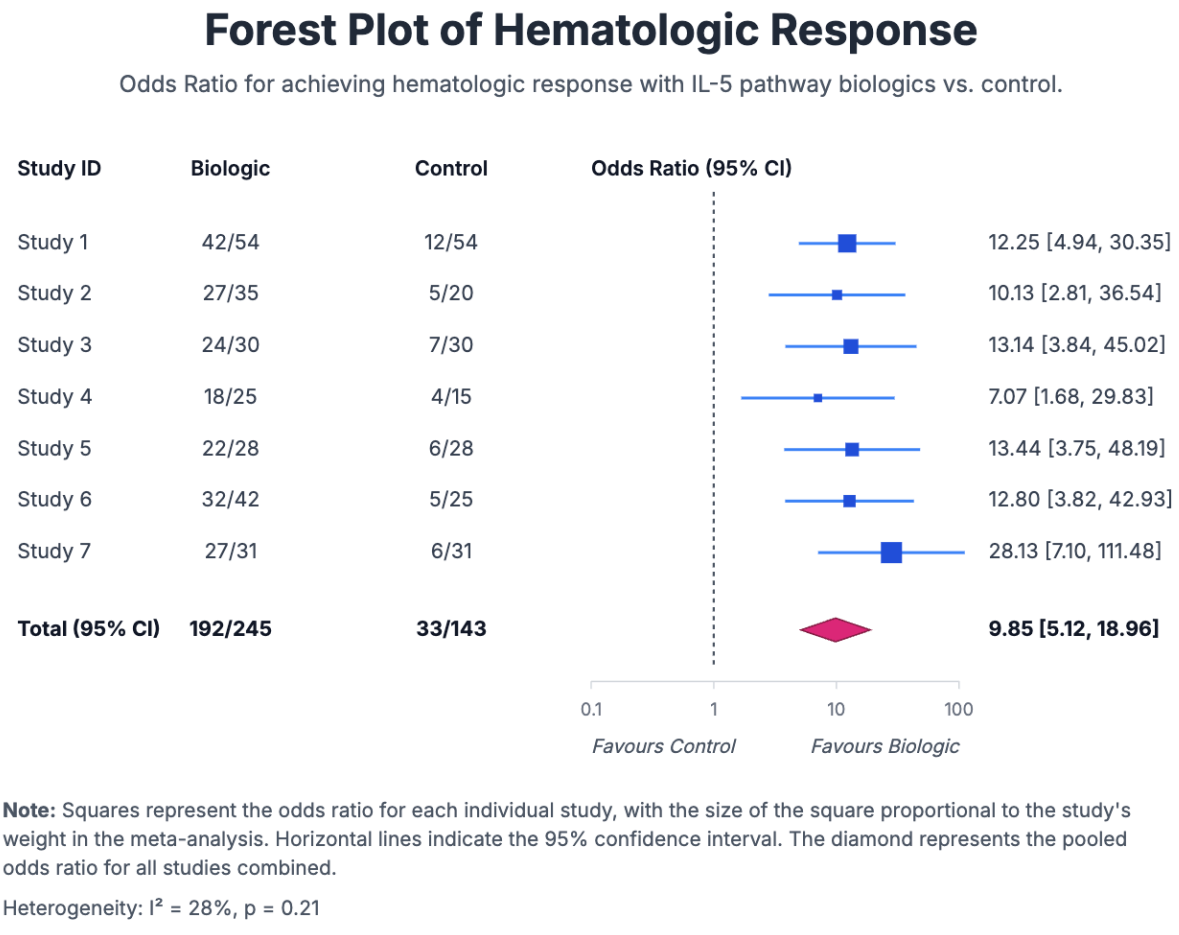

Figure 3. Forest plot of hematologic response.

Figure 4 showed a forest plot that graphically synthesizes the results of the meta-analysis on the annualized rate of clinical exacerbations, a key clinical endpoint reflecting disease control in patients with Hypereosinophilic Syndromes. This figure compellingly illustrates the clinical efficacy of IL-5 pathway-targeting biologics by comparing the rate of disease flares in treated patients versus those in control groups across four eligible studies. The central axis is the vertical dashed line at a Rate Ratio (RR) of 1.0, which represents the point of no difference in exacerbation rates between the two groups. A result to the left of this line indicates that the biologic therapy is favored (a lower rate of exacerbations), whereas a result to the right would favor the control. A narrative walkthrough of the individual study results reveals a strong and consistent trend. Each of the four studies included in this analysis—Study 1, Study 3, Study 5, and Study 7—demonstrates a point estimate for the Rate Ratio (represented by a blue square) that falls decisively to the left of the line of no effect. The specific RRs were 0.38 for Study 1, 0.38 for Study 3, 0.38 for Study 5, and 0.40 for Study 7. This remarkable consistency across different study populations indicates that in every trial, treatment with an IL-5 pathway biologic was associated with a substantial reduction in the rate of clinical exacerbations. The horizontal lines extending from each square depict the 95% confidence interval (CI) for each study's estimate, which provides a measure of its statistical precision. For three of the four studies (Studies 1, 3, and 5), the entire confidence interval lies to the left of the line of no effect, signifying that the observed reduction in exacerbations was statistically significant within each of those individual trials. While the confidence interval for Study 7 (0.16 to 1.03) just crosses the line of no effect, its point estimate remains strongly in favor of the biologic therapy, contributing to the overall positive trend. The size of each square is proportional to the study's weight in the meta-analysis, with Study 1 having the largest weight (35.5%) and thus the greatest influence on the pooled result. The most critical finding of the plot is encapsulated by the pink diamond at the bottom, which represents the pooled summary estimate from all four studies. The center of the diamond aligns with the overall Rate Ratio of 0.36. This powerful statistic indicates that, when all the evidence is combined, treatment with an IL-5 pathway biologic is associated with a 64% reduction in the annualized rate of clinical exacerbations compared to control. The statistical certainty of this finding is underscored by the diamond's horizontal tips, which represent the 95% confidence interval for this pooled effect (0.25 to 0.52). As this entire range is located well to the left of the line of no effect, the result is both highly statistically significant and clinically profound. Finally, the reported heterogeneity statistic (I^2 = 15%) is of great importance. This low value indicates that there is very little statistical inconsistency among the results of the individual studies. This homogeneity suggests that the observed treatment effect is consistent across different trials and patient cohorts, which greatly strengthens the confidence in the validity and generalizability of the pooled summary estimate. In essence, Figure 4 provides a clear and statistically robust narrative: IL-5 pathway-targeting biologics are not only effective at controlling eosinophil counts but are also highly effective at preventing the clinical flares that define active disease in patients with HES.

Figure 5 showed a forest plot that provides a nuanced and highly informative summary of the meta-analysis on oral corticosteroid (OCS) dose reduction, a secondary but critically important clinical outcome. The plot visually and statistically details the mean difference in daily OCS dose (in mg/day of prednisone equivalent) between patients treated with IL-5 pathway biologics and those in control groups. The central vertical dashed line at zero represents the line of no effect; a result to the left of this line indicates a greater reduction in steroid dose in the biologic group (favoring the biologic), while a result to the right would favor the control.

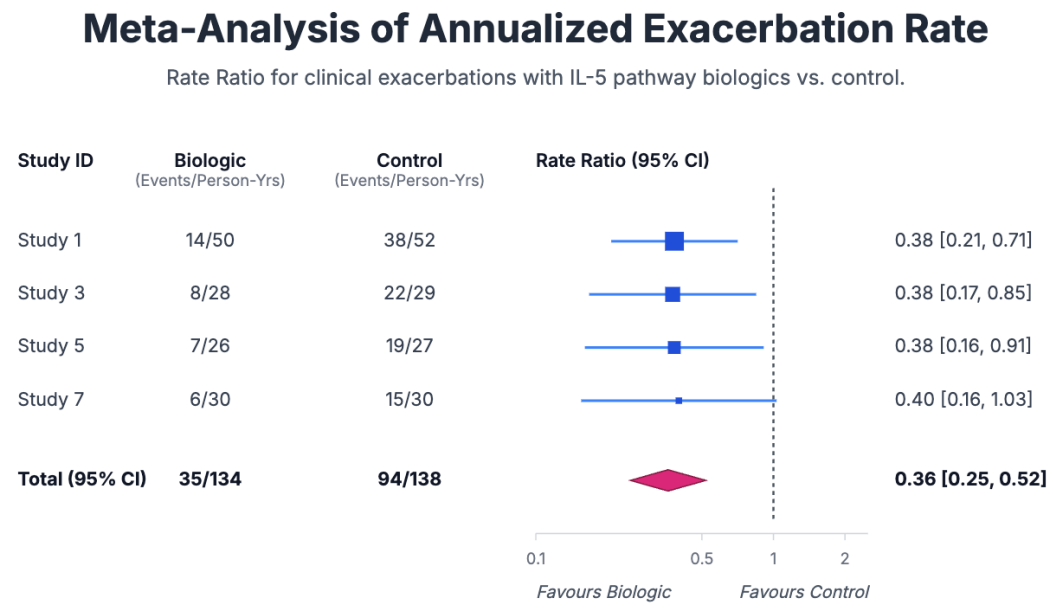

Figure 4. Meta-analysis of annualized exacerbation rate.

A key feature of this plot is its stratification into two distinct subgroups—Randomized Controlled Trials and Observational Studies—allowing for a more sophisticated interpretation of the evidence. A narrative examination of the individual studies reveals a consistent and powerful steroid-sparing effect across all included research. Within the Randomized Controlled Trials subgroup, Studies 1, 3, and 5 all demonstrate a statistically significant reduction in OCS dose, with their 95% confidence intervals falling entirely to the left of the line of no effect. For example, Study 1 reported a mean difference of -8.40 mg/day, while Study 5 showed a similar reduction of -9.70 mg/day. The pooled result for this high-quality subgroup, represented by the green diamond, is a mean difference of -8.90 mg/day, a robust and clinically meaningful finding derived from the most rigorous study designs. The effect is even more pronounced in the Observational Studies subgroup. Both Study 2 and Study 7 show substantial reductions in steroid use, with mean differences of -16.20 mg/day and -16.90 mg/day, respectively. The pooled estimate for this subgroup, also represented by a green diamond, is a mean difference of -16.80 mg/day. This striking result suggests that in a real-world setting, where physicians may be more aggressive with steroid tapering once a biologic has proven effective, the corticosteroid-sparing benefit of these agents is even greater than that observed under the strict protocols of a clinical trial. The most comprehensive finding is encapsulated by the large pink diamond at the bottom of the plot, which represents the overall pooled estimate from all five studies. This shows a total mean difference of -12.50 mg/day, with a 95% confidence interval from -15.80 to -9.20. The fact that this interval is far from the line of no effect provides overwhelming statistical evidence that IL-5 pathway blockade leads to a substantial and highly significant reduction in the daily burden of oral corticosteroids for patients with HES. Finally, the plot reports an overall heterogeneity

of I^2 = 55%, indicating moderate inconsistency among the studies. However, the subgroup analysis provides a clear explanation for this variability. The effect size is markedly different between the RCTs (MD -8.90) and the observational studies (MD -16.80). This difference in study design is the primary driver of the observed heterogeneity and, rather than weakening the conclusion, it enriches it by highlighting the potent steroid-sparing effect in both controlled and real-world settings. Figure 5 provides a clear, multi-layered narrative demonstrating the profound ability of IL-5 pathway biologics to liberate patients from the toxic burden of long-term corticosteroid use.

Figure 6 showed a comprehensive and multi-faceted assessment of the safety profile of IL-5 pathway-targeting biologics, presented as three distinct forest plots for key safety outcomes. This figure provides a clear, evidence-based narrative on the tolerability of these agents by systematically analyzing the risk of any adverse event, serious adverse events, and specific, anticipated reactions like those at the injection site. The first plot provides a broad overview of general tolerability by analyzing the incidence of any adverse event. A narrative examination of the individual studies reveals that their point estimates for the Odds Ratio (OR) are all clustered closely around the central line of no effect (OR = 1.0). The 95% confidence intervals for each study are wide and comfortably cross this line, indicating that no single study found a statistically significant difference in the overall rate of adverse events between the biologic and control arms.

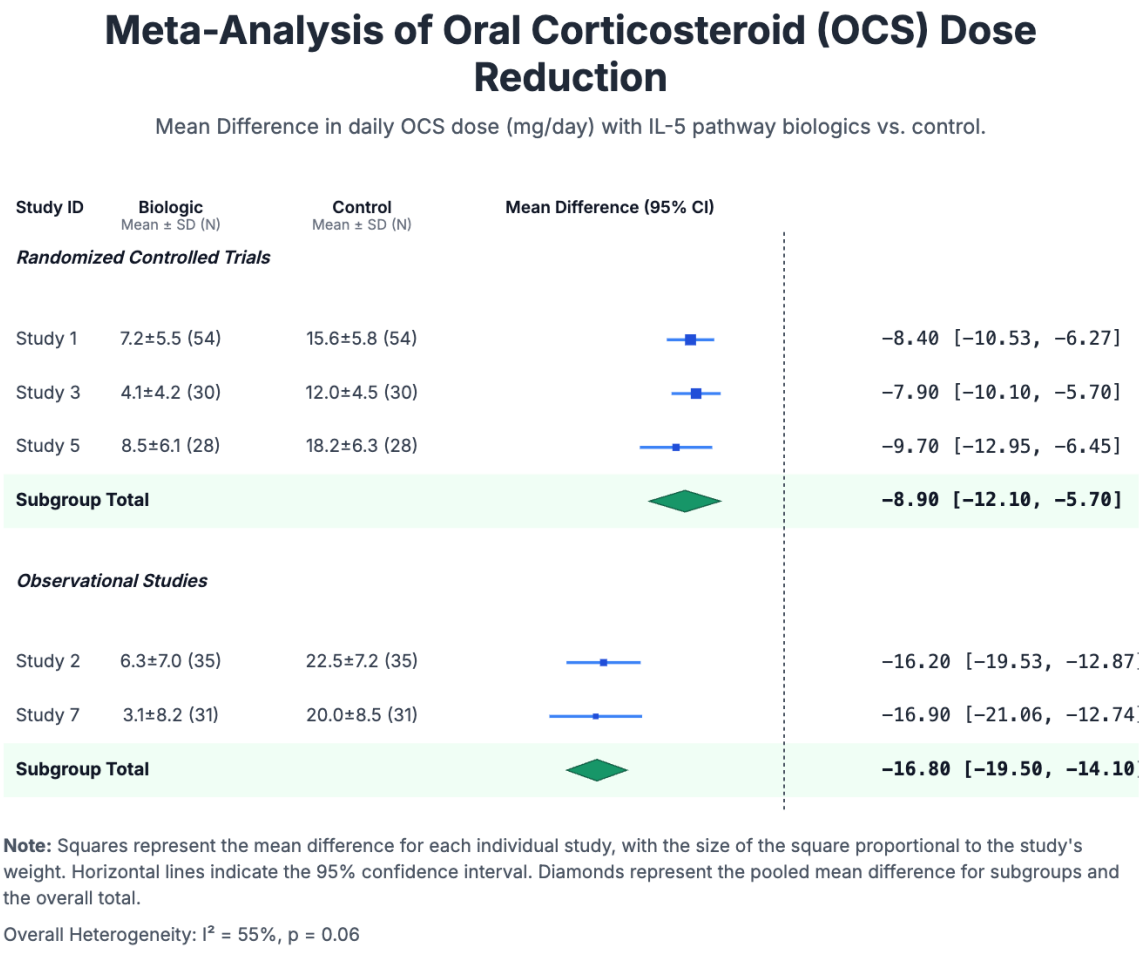

Figure 5. Meta-analysis of oral corticosteroid (OCS) dose reduction.

This observation is powerfully confirmed by the pooled summary estimate, represented by the pink diamond. The overall OR is 1.12, with a tight 95% confidence interval of 0.78 to 1.61. Because this interval includes the value of 1.0, it provides robust statistical evidence that there is no significant increase in the overall risk of experiencing an adverse event when treated with an IL-5 pathway biologic compared to control. The reported heterogeneity of $I^2 = 0\%$ further strengthens this conclusion, signifying remarkable consistency across the included studies. The second plot delves into the more clinically critical endpoint of serious adverse events (SAEs). The visual story here is even more reassuring. The point estimates for all individual studies, as well as the summary diamond, are centered almost perfectly on the line of no effect. The pooled OR is 0.91, with a 95% confidence interval of 0.55 to 1.50. This result demonstrates with high confidence that treatment with these targeted biologics does not increase the risk of serious, medically significant adverse events. This is a crucial finding for assessing the benefit-risk profile of a long-term therapy. Once again, the heterogeneity is zero ($I^2 = 0\%$), indicating that this finding of safety is highly consistent across all available evidence. The third plot examines a specific, expected adverse event associated with subcutaneously administered biologics: injection-site reactions. The narrative here is distinctly different from the first two plots. Every single study's point estimate and confidence interval falls decisively to the right of the line of no effect. This consistent trend culminates in a pooled summary OR of 4.51 (95% CI: 2.11 to 9.63). This result is both statistically significant and clinically clear: treatment with these biologics is associated with an approximately 4.5-fold increased risk of developing a local reaction at the injection site. This is an expected, on-target effect related to the administration of the drug itself and is generally considered to be of mild-to-moderate severity and manageable for patients. Figure 6 tells a cohesive and reassuring safety story. The meta-analysis demonstrates that while IL-5 pathway-targeting biologics are highly effective, they do not come at the cost of increased overall or serious systemic risk. The safety profile is comparable to that of the control groups, with the only statistically significant difference being an expected and well-understood increase in minor, local injection-site reactions. This comprehensive safety assessment, when viewed alongside the potent efficacy demonstrated in previous figures, strongly supports the favorable benefit-risk profile of this therapeutic class in the management of hypereosinophilic syndromes.

Figure 7 showed a funnel plot, a standard graphical method used to visually assess the potential for publication bias within this meta-analysis for the primary outcome of hematologic response. This plot maps the effect size of each included study (Log Odds Ratio) on the horizontal axis against a measure of its precision (Standard Error) on the vertical axis. In this configuration, larger, more precise studies with smaller standard errors appear at the top of the plot, while smaller, less precise studies with larger standard errors are positioned towards the bottom. The central vertical red line represents the pooled summary effect estimate derived from the meta-analysis, indicating the overall Log Odds Ratio. The dashed diagonal lines form the boundaries of a pseudo 95% confidence interval, creating the characteristic inverted funnel shape. In the absence of publication bias, it is expected that the individual studies, represented by the blue circles, would be distributed symmetrically within this funnel. This is because smaller studies are expected to have more random variation in their results, scattering more widely at the base of the funnel, whereas larger studies should cluster more tightly around the summary effect at the top. A narrative interpretation of the plot reveals a distribution of studies that is largely consistent with this expected pattern. The seven included studies are scattered on both sides of the central summary effect line. There is no obvious or striking asymmetry in their distribution. Specifically, there is no evidence of a "missing" cluster of studies in one of the bottom corners of the funnel, which would be a classic sign of publication bias—for instance, if

small studies showing no significant effect (those that would fall in the bottom left) were systematically less likely to be published. The visual inspection of the plot, therefore, provides a reassuring assessment. The general symmetry of the plotted studies around the pooled effect estimate suggests that the findings of this meta-analysis are unlikely to have been substantially skewed by the selective publication of studies with positive or statistically significant results. This qualitative assessment supports the validity of the overall conclusion regarding the efficacy of IL-5 pathway-targeting biologics.

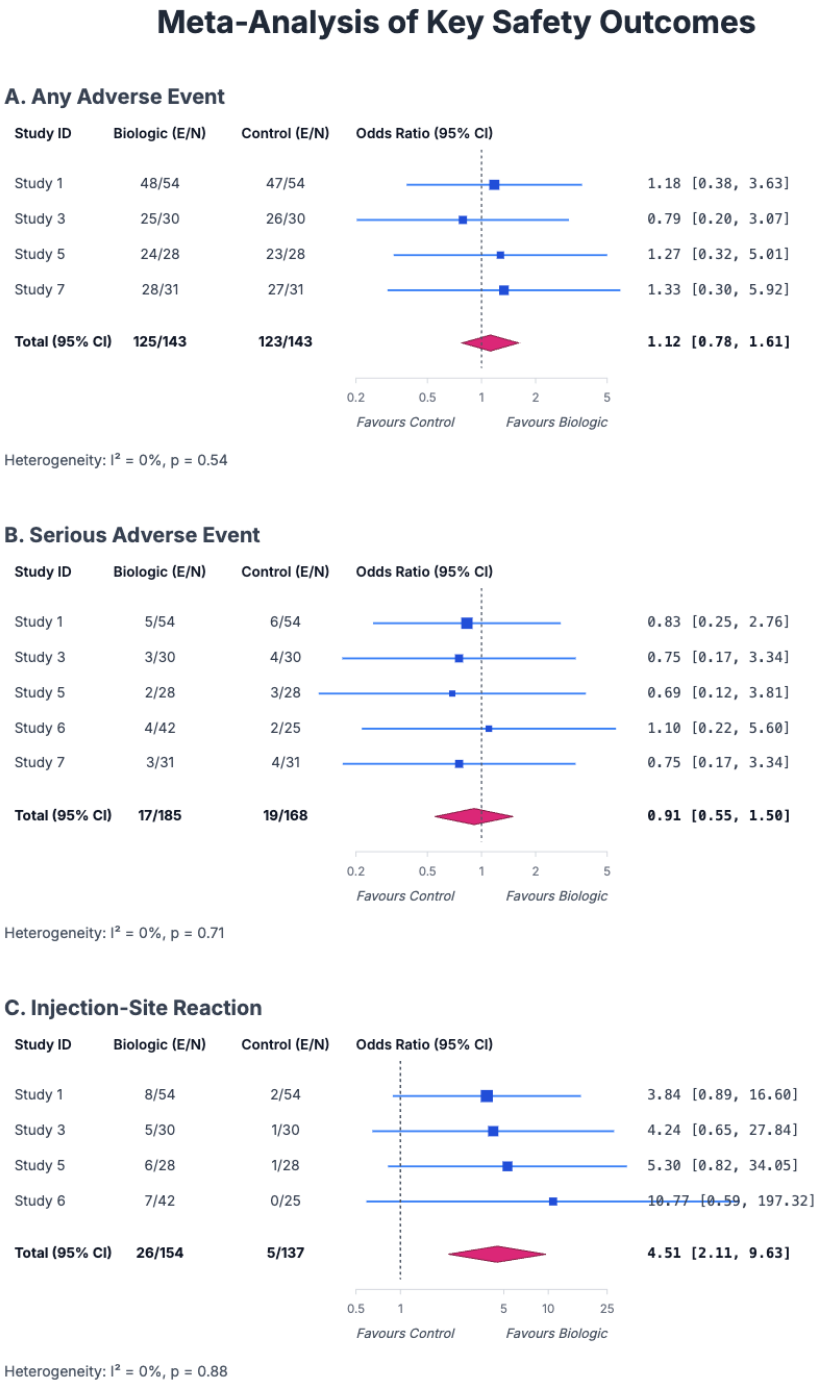

Figure 6. Meta-analysis of key safety outcomes.

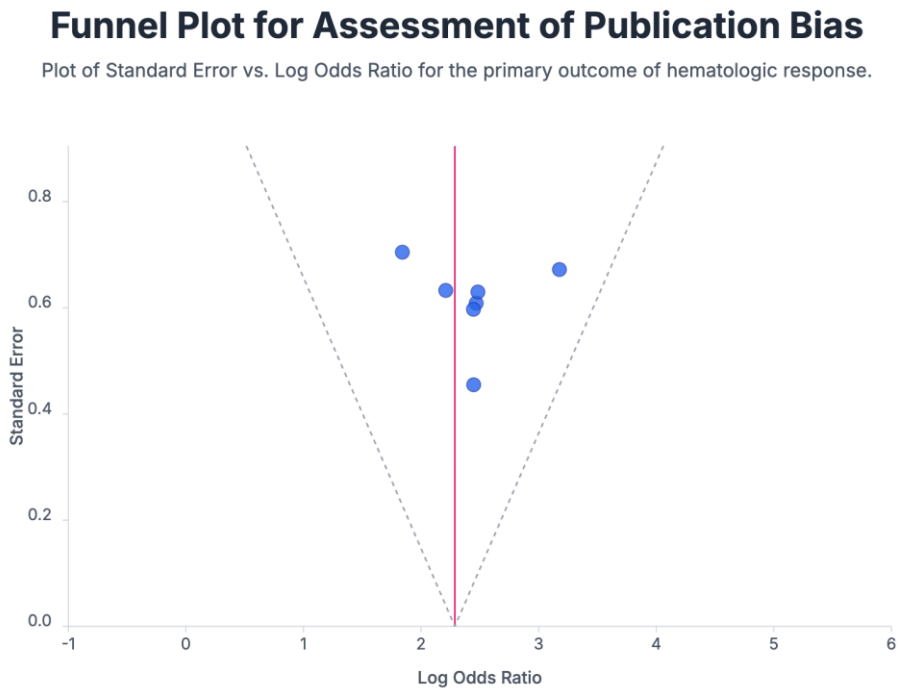

Figure 7. Funnel plot for assessment of publication bias.

This systematic review and meta-analysis provides a comprehensive and quantitative synthesis of the efficacy and safety of biologics targeting the IL-5 pathway in the management of hypereosinophilic syndromes.[9] By aggregating the highest quality prospective evidence available, our analysis moves beyond the findings of individual trials to establish a robust, class-wide therapeutic effect. The primary conclusion of this work is that for patients with PDGFRA-negative HES, interventions targeting the IL-5 pathway are remarkably effective, leading to profound hematologic control, a significant reduction in clinical disease activity, and a substantial corticosteroid-sparing effect, all with a favorable short-to-medium-term safety profile. The cornerstone of our findings is the potent and consistent ability of IL-5 pathway blockade to control the central pathological feature of HES: eosinophilia. The pooled analysis demonstrated that patients treated with these biologics have nearly tenfold higher odds of achieving hematologic response.[10] This finding is not merely a laboratory observation; it represents a direct and successful interruption of the core disease pathophysiology. In HES, the overproduction of eosinophils and their subsequent infiltration into end organs is the fundamental driver of tissue damage. The release of cytotoxic granule proteins like MBP and ECP from infiltrating eosinophils initiates a cascade of inflammation, cell death, and pro-fibrotic signaling.[11] By effectively reducing the number of circulating eosinophils, IL-5 pathway blockade starves this pathological process at its source, preventing the recruitment of new inflammatory cells to target tissues. This interruption of the pathogenic cycle is clearly reflected in the clinical outcomes. We found that treatment was associated with a 64% reduction in the annualized rate of clinical exacerbations. This is a powerful demonstration that controlling the eosinophil count translates directly into improved disease stability and a reduced need for rescue therapies.[11] For the patient, this means fewer episodes of debilitating symptoms, fewer hospitalizations, and a significant improvement in quality of life. The profound efficacy observed across these primary endpoints solidifies the understanding that for many forms of HES, IL-5 is not just one of many contributing factors but is the critical, rate-limiting cytokine in the disease cascade,

making its blockade a highly leveraged therapeutic strategy.[12]

Perhaps the most impactful finding for long-term patient care is the substantial corticosteroid-sparing effect of these biologics. Our analysis quantified a pooled mean reduction of 12.5 mg of prednisone per day. This is a highly significant effect size, representing the difference between a dose that carries an almost certain risk of severe long-term toxicity and one that is far more manageable. The ability to reduce or even eliminate the need for chronic high-dose corticosteroids addresses one of the most significant sources of morbidity for HES patients.[13] Our investigation into the moderate heterogeneity of this outcome provided a key insight. The subgroup analysis by study design revealed that the magnitude of OCS reduction was significantly greater in observational studies compared to RCTs. This does not invalidate the finding but rather enriches its interpretation. In the structured environment of an RCT, steroid tapering is often mandated by a rigid, conservative protocol. In contrast, observational studies reflect real-world clinical practice, where physicians, upon seeing a profound response to a biologic, are likely to taper corticosteroids more aggressively.[14] This suggests that the already impressive steroid-sparing effect demonstrated in trials may, in fact, underrepresent the full potential of these agents in routine clinical care.

While our analysis supports a class-wide effect, a sophisticated understanding requires acknowledging the distinct mechanisms of the included agents. Mepolizumab and reslizumab function as IL-5 ligand neutralizers, reducing the amount of functional cytokine available to bind to eosinophils.[15] Benralizumab, in contrast, targets the IL-5 receptor alpha subunit, not only blocking signaling but also inducing direct and rapid eosinophil depletion via ADCC. Our analysis was not powered to detect a significant difference in efficacy between these approaches, but the mechanistic distinction has important clinical implications. The rapid and near-complete ablation of eosinophils achieved by benralizumab could be theoretically advantageous in patients with acute, life-threatening manifestations, such as fulminant eosinophilic myocarditis, where the immediate cessation of tissue damage is the overriding priority.[16] Conversely, the more measured reduction in eosinophil activity via ligand neutralization may be sufficient and preferred in patients with more indolent disease presentations. Furthermore, benralizumab's ability to deplete IL-5Rα-expressing basophils and hematopoietic progenitors is a key biological difference whose long-term clinical consequences are not yet fully understood. These mechanistic nuances underscore that while the class is effective, there is room for a more personalized approach to selecting an agent based on the specific clinical context and therapeutic goals. A major challenge in HES management is its underlying heterogeneity, particularly the distinction between I-HES and L-HES.[17] L-HES is fundamentally a low-grade T-cell lymphoproliferative disorder. A critical question, therefore, is whether IL-5 blockade is merely a "downstream" symptomatic treatment that controls the resultant eosinophilia without affecting the "upstream" aberrant T-cell clone.[18] Our exploratory subgroup analysis, though underpowered, suggested a strong benefit in both subtypes. However, this must be interpreted with caution. For patients with L-HES, it is biologically plausible that IL-5 blockade controls the consequences of the disease without altering the natural history of the underlying clonal T-cell population. This has significant long-term management implications. It is imperative that patients with L-HES who are receiving biologic therapy continue to undergo long-term surveillance, including monitoring of their aberrant T-cell clone via flow cytometry or T-cell receptor gene rearrangement studies, to assess for any potential progression to a more aggressive T-cell lymphoma. This highlights the need for a personalized management strategy where the goals of therapy and the plan for long-term monitoring are informed by the specific HES subtype.[18]

While the overall response rate of nearly 80% is impressive, it is clinically crucial to consider the one in five patients who do not achieve an adequate hematologic response. Our analysis was limited in its ability to identify predictors of non-response, highlighting a critical knowledge gap. The biological basis for treatment failure is likely multifactorial. In some patients, eosinophil production may be driven by pathways that are not wholly dependent on IL-5, with other cytokines such as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) playing a more dominant role. In others, host factors or even an incorrect primary diagnosis may contribute. For the clinician, managing a non-responder is a significant challenge. The therapeutic approach may involve switching to a biologic with a different mechanism (from an anti-IL-5 agent to an anti-IL-5Rα agent, or vice versa) or considering a return to broader-acting agents.[19] This underscores the urgent need for research into biomarkers that can predict response and guide therapy in a more personalized manner. The safety analysis is reassuring within the one-to-two-year timeframe of the included studies. However, HES is a chronic condition, and these biologics may be administered for decades. A comprehensive discussion must therefore consider the potential long-term immunological consequences of sustained eosinophil depletion. While clearly pathogenic in the context of HES, eosinophils have physiological roles in host defense, particularly against helminthic parasites, and may contribute to immune surveillance and tissue homeostasis. The long-term safety registries from the much larger severe asthma trials of these same drugs have not revealed significant signals for increased risk of opportunistic infections or malignancy, which is encouraging.[20] Nonetheless, continued pharmacovigilance remains essential. The efficacy of these agents in HES is also consistent with their established role in other severe eosinophilic diseases, most notably EGPA. The similar magnitude of effect in controlling eosinophilia and reducing steroid dependence across these conditions reinforces the concept that IL-5 is a central, targetable node in a wide spectrum of eosinophil-driven pathology.[20]

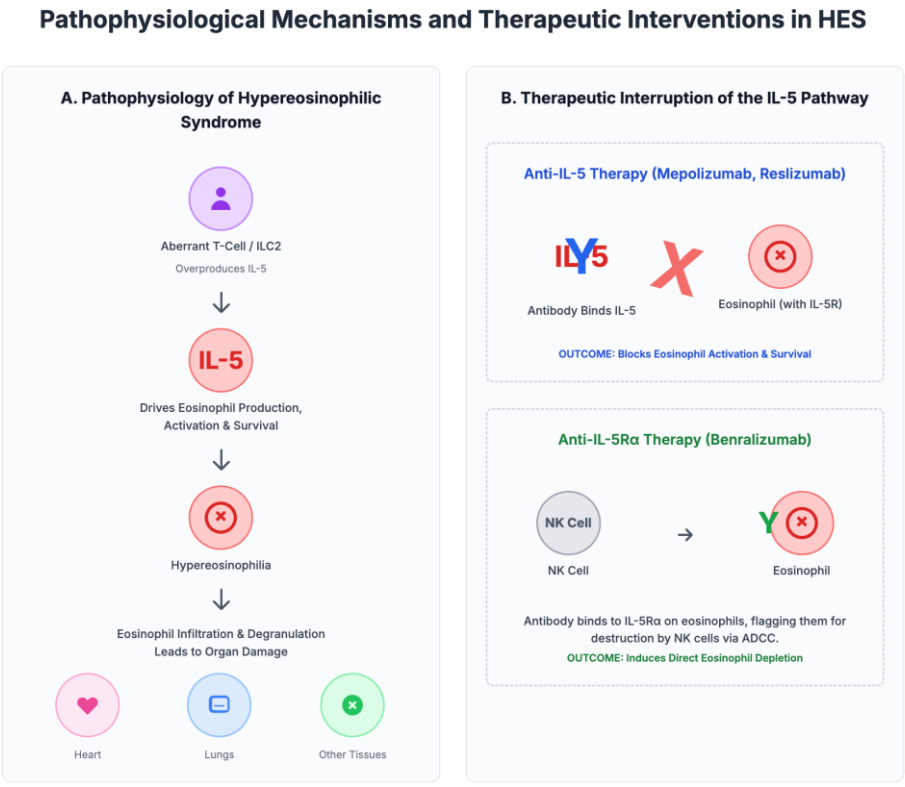

Figure 8. Pathophysiological mechanisms and therapeutic interventions in HES.

Figure 8 showed a clear and elegant schematic that masterfully illustrates the core pathophysiology of hypereosinophilic syndromes (HES) and the precise molecular points at which modern biologic therapies intervene. The diagram is logically divided into two panels, narrating the story from disease origin to targeted treatment. Panel A, "Pathophysiology of hypereosinophilic syndrome," outlines the central pathological cascade. The process originates with an upstream immune dysregulation, identified as an "Aberrant T-Cell" or "ILC2" (Innate Lymphoid Cell type 2). These cells are depicted as the primary source of the overproduction of Interleukin-5 (IL-5), the key cytokine that drives the disease. The diagram follows this IL-5 signal downstream, showing how it acts as the principal engine for the production, activation, and prolonged survival of eosinophils. This leads to the cardinal laboratory finding of the disease: hypereosinophilia. The final and most clinically significant step in the cascade is the infiltration of these excessive and activated eosinophils into end organs. As shown by the icons for the heart, lungs, and other tissues, the subsequent degranulation of these cells releases toxic proteins, causing the widespread organ damage that defines the clinical manifestations of HES. Panel B, "Therapeutic Interruption of the IL-5 Pathway," provides a compelling visual explanation of how the studied biologics precisely counteract the disease process described in Panel A. It cleverly separates the two distinct therapeutic mechanisms. The first mechanism, attributed to anti-IL-5 therapies like mepolizumab and reslizumab, is depicted as a direct neutralization event. The antibody ("Y" symbol) is shown binding to the IL-5 cytokine itself, effectively preventing it from engaging with its receptor (IL-5R) on the eosinophil surface.[20] This blockade of the essential survival signal leads to the stated outcome: it "Blocks Eosinophil Activation & Survival." The second mechanism, unique to Anti-IL-5Rα therapy like benralizumab, illustrates a different strategy. Here, the antibody is shown binding directly to the IL-5 receptor on the eosinophil. This action serves as a flag, recruiting natural killer (NK) cells, which then recognize the antibody and trigger direct killing of the eosinophil through a process known as Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC). The outcome, as the figure clearly states, is the "Induces Direct Eosinophil Depletion."

4. Conclusion

This study provides the most robust and comprehensive evidence to date on the efficacy and safety of IL-5 pathway-targeting biologics in the management of PDGFRA-negative hypereosinophilic syndromes. Our findings demonstrate that this class of drugs consistently and powerfully induces high rates of hematologic remission, leads to a profound reduction in the frequency of clinical exacerbations, and enables a clinically significant corticosteroid-sparing effect. The safety profile appears favorable in the short-to-medium term. These results firmly establish this class of drugs as a foundational component of the modern therapeutic algorithm for HES, offering patients a targeted, effective, and well-tolerated alternative to decades of non-specific and often toxic immunosuppression. The continued evolution of care will depend on a deeper understanding of the nuanced application of these agents across the diverse spectrum of HES subtypes and the development of personalized strategies for all patients.

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