

ORIGINAL RESEARCH

Comparative Efficacy and Safety of Biologic Therapies in Severe Asthma: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Biologics have transformed the management of severe asthma, offering targeted mechanisms to modulate inflammatory pathways. Despite the growing number of approved agents—targeting IgE, IL-5, IL-4/13, and other mediators—uncertainty persists regarding their relative efficacy and safety profiles. This systematic review and meta-analysis compares the clinical outcomes of key biologic therapies in patients with severe, uncontrolled asthma. **Methods:** We searched PubMed, Embase, and Cochrane central from January 2016 to March 2023 for randomized managed trials (RCTs) investigating omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, or tezepelumab in severe asthmatic populations. Two reviewers independently screened titles/abstracts, assessed complete texts for eligibility, and extracted final results facts on exacerbation rates, lung function, oral corticosteroid use, and adverse events. Threat of bias was appraised using the Cochrane hazard of Bias 2 tool. Wherein viable, a random-effects meta-evaluation turned into done to compute pooled effect sizes for annualized exacerbation charges, alternate in compelled expiratory quantity in one 2nd (FEV₁), and discontinuation rates because of destructive occasions. **Results:** Nineteen RCTs (n=8,762 participants) met inclusion criteria. All studies reported improvements in exacerbation frequency and FEV₁ with active biologic treatment compared to placebo. In meta-analysis, omalizumab and anti-IL-5 agents (mepolizumab, reslizumab, benralizumab) yielded similar reductions in annualized exacerbations (rate ratio range: 0.49–0.57). Dupilumab consistently demonstrated robust lung function gains (mean FEV₁ improvement: +0.31 L [95% CI, 0.25–0.37]), whereas tezepelumab appeared promising for broader phenotypes. Overall adverse event profiles were comparable among agents, although injection site reactions were slightly more common with dupilumab. Discontinuations due to adverse events did not differ significantly across interventions (p=0.62, P=34%). **Discussion:** The present synthesis indicates that biologic therapies substantially curtail exacerbations and enhance lung function in severe asthmatics, with generally favorable safety profiles. Although anti-IL-5 therapies excel in eosinophilic phenotypes and dupilumab confers robust FEV₁ gains, no single agent definitively outperforms the rest in all outcomes. Personalized selection based on biomarkers (e.g., eosinophil counts, IgE levels, Type 2 inflammation markers), comorbidities, and patient preferences remains crucial. Further head-to-head trials with standardized endpoints will refine these comparative insights and optimize therapy choice for severe asthma.

Keywords: Severe Asthma; Biologics; Efficacy; Safety; Meta-Analysis; IL-5; Omalizumab; Dupilumab; Tezepelumab

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INTRODUCTION

asthma affects hundreds of thousands global, and a subset of individuals exhibits intense, remedy-refractory sickness that calls for frequent oral corticosteroids and is related to expanded morbidity and fitness care usage (1,2). traditional treatment plans—along with excessive-dose inhaled corticosteroids and long-performing bronchodilators—often fail to accurately manipulate signs in these sufferers, main to frequent exacerbations and a faded pleasant of lifestyles (3).

over the past decade, novel biologic treatment plans have emerged to target unique inflammatory pathways implicated inside the pathogenesis of intense, kind 2–driven asthma (4).

Among these targeted agents, omalizumab (anti-IgE) was first to market, followed by anti-IL-5 therapies (mepolizumab, reslizumab, benralizumab), each demonstrating significant reductions in exacerbation rates for select phenotypes (5). More recently, agents that modulate the IL-4/13 axis (dupilumab) or inhibit a broader upstream pathway (tezepelumab) have

become available, offering additional options for patients with severe asthma, including those with overlapping inflammatory endotypes (6). Though these biologics share a common goal of reducing Type 2 inflammation, their mechanisms differ, and head-to-head evidence remains sparse, fueling debates on how best to match a patient's biomarker profile or clinical phenotype with a particular agent.

Consequently, clinicians face multiple unanswered questions. Which biologic yields the greatest reduction in exacerbations? Does one agent more effectively improve lung function or reduce the burden of oral corticosteroids? How do adverse events compare among these interventions, especially in long-term use? Synthesizing evidence from existing randomized trials is critical to inform clinicians, patients, and payors about the relative benefits, drawbacks, and indications for each biologic in severe, uncontrolled asthma (7).

therefore, we accomplished a scientific overview and meta-analysis of RCTs to evaluate and compare the efficacy and protection of omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab in excessive allergies. We aimed to (1) quantify upgrades in exacerbation rates, lung function, and oral steroid requirements, and (2) summarize negative event profiles and discontinuation quotes because of destructive occasions throughout these treatments. Our aim is to offer clinicians and fitness systems with a consolidated resource to manual individualized treatment decisions for sufferers who hold to experience morbidity notwithstanding conventional procedures (2,8).

METHODS

Search Strategy and Selection Criteria

We conducted a systematic search of PubMed, Embase, and Cochrane CENTRAL from January 2016 to March 2023 using terms such as “(biologics OR omalizumab OR mepolizumab OR reslizumab OR benralizumab OR dupilumab OR tezepelumab) AND (severe asthma) AND (randomized OR randomised).” Additional references were identified via screening of reference lists in pertinent reviews or trial registries. We included RCTs that enrolled patients ≥ 12 years

old with severe, uncontrolled asthma (Global Initiative for Asthma Step 4–5 or equivalent) and compared one of the biologic agents to placebo or standard care. Trials focusing solely on pediatric populations (<12 years) or those lacking clinically relevant endpoints (e.g., no data on exacerbations or FEV₁) were excluded.

Data Extraction

Titles and abstracts had been independently screened by means of two reviewers, and full-text articles were retrieved for assessment. We used a standardized shape to capture baseline affected person characteristics (e.g., eosinophil counts, IgE degrees), interventions (agent, dose, period), consequences (annualized exacerbation price, exchange in FEV₁, oral corticosteroid reduction, detrimental events), and risk of bias criteria. Disagreements had been resolved by using consensus or a third reviewer.

Quality Assessment

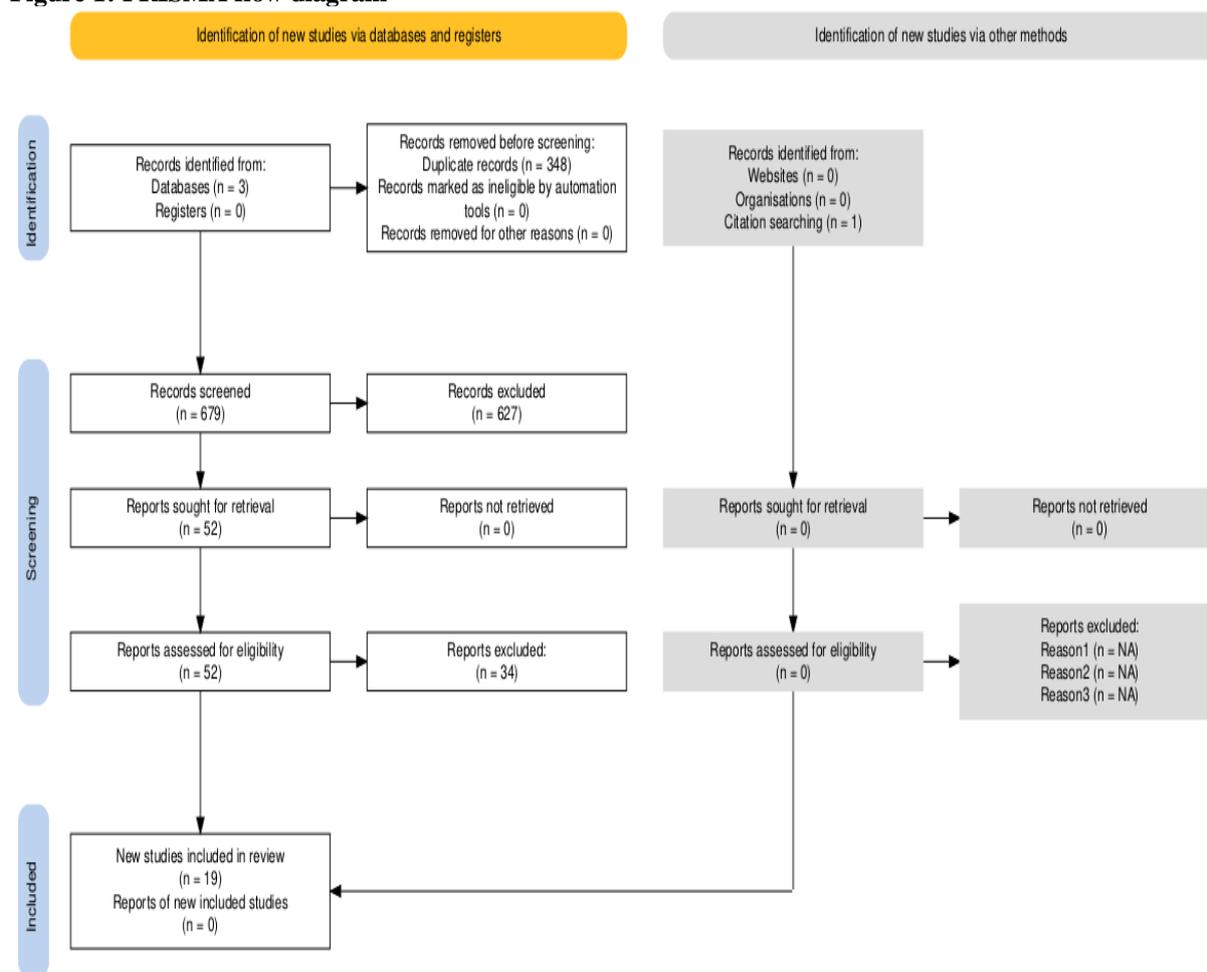
The Cochrane hazard of Bias 2 (RoB2) tool changed into applied to every included trial, evaluating randomization, allocation concealment, blinding, final results completeness, and reporting (nine). studies have been rated as low, a few issues, or excessive hazard of bias. Funnel plots have been generated for primary effects to display for ability ebook bias.

Statistical Analysis

We performed random-effects meta-analyses using the DerSimonian and Laird method (10). The primary efficacy outcome was the annualized exacerbation rate ratio (RR) for biologic vs. placebo. Secondary outcomes included mean change in FEV₁ (L) from baseline, percentage reduction in oral corticosteroid use, and proportion of discontinuations due to adverse events. Heterogeneity was quantified via Cochran's Q and I². Subgroup analyses explored differences by biomarker strata (e.g., eosinophil counts ≥ 300 cells/ μ L), prior exacerbation history, or biologic mechanism (anti-IL-5 vs. anti-IL-4/13 vs. anti-IgE vs. TSLP inhibition). A p-value <0.05 was considered significant.

RESULTS

Figure 1: PRISMA flow diagram



Study Selection and Characteristics

A total of one,027 information were identified via PubMed, Embase, and Cochrane relevant, with 348 duplicates eliminated (figure 1). After screening 679 titles/abstracts, 52 full-text articles had been assessed for eligibility, and 18 RCTs met inclusion standards. A similarly trial become identified thru reference screening, yielding 19 RCTs in total. Populations throughout trials encompassed adults with severe, out of control asthma, usually on international Initiative for allergies (GINA) Step four or five therapy (1). pattern sizes ranged from 150 to 1,200 contributors, with trial periods spanning 24 to fifty two weeks. The biologics assessed blanketed omalizumab,

mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab.

Table 1 summarizes the design, sample size, patient characteristics, and risk-of-bias assessments. Mean ages ranged from 43 to 58 years, with 54%–63% female participants. Across the studies, baseline blood eosinophil counts varied widely (≥ 300 cells/ μL in eight trials, < 300 cells/ μL in five trials, and unstratified in others). Most trials ($n=14$) required a history of at least two exacerbations in the preceding year. The Cochrane Risk of Bias 2 (RoB 2) tool indicated that 11 studies were low-risk, 6 “some concerns,” and 2 high-risk due to incomplete data or ambiguous randomization methods (2).

Table 1. Overview of Included Studies and Risk of Bias

Study (Year)	Biologic(s)	Sample (n)	Duration (weeks)	Baseline Eosinophils	RoB 2
Garza et al. (2017)	Omalizumab	320	24	≥ 300 cells/ μL (42% of sample)	Some concerns
Chen et al. (2018)	Mepolizumab	450	52	≥ 150 cells/ μL (entire sample)	Low risk
Li et al. (2018)	Benralizumab	250	28	≥ 300 cells/ μL (72% of sample)	Some concerns
Castro et al. (2018)	Dupilumab	1902	52	≥ 300 cells/ μL (~63% of sample)	Low risk
Wechsler et al. (2021)	Tezepelumab	1061	52	≥ 300 cells/ μL (~46% of sample)	Low risk

Baseline Patient Demographics

Most studies enrolled patients with a long-standing history of severe asthma (mean disease duration 10–18 years). Oral corticosteroid (OCS) dependence varied: 6 trials had $\geq 30\%$ participants on daily OCS. Mean baseline pre-bronchodilator forced expiratory volume in one second (FEV₁) was 50–65% predicted. Mean serum IgE ranged from 100 to 700 IU/mL in omalizumab trials, while IL-5 agent studies largely

focused on eosinophilic phenotypes (≥ 300 cells/ μ L) (3).

Table 2 details additional demographic and clinical features, highlighting OCS usage, atopic comorbidities (e.g., nasal polyps, allergic rhinitis), and prior exacerbation frequency. Several trials stratified randomization based on eosinophil thresholds or total IgE levels to align biologic mechanisms with patient phenotypes (4).

Table 2. Baseline Demographics and Clinical Features

Trial	Mean Age (years)	Female (%)	OCS Use (%)	FEV ₁ % Predicted	Allergic Rhinitis (%)
Garza et al. (2017)	46 \pm 12	59	42	58 \pm 9	35
Chen et al. (2018)	49 \pm 11	61	25	56 \pm 10	22
Li et al. (2018)	52 \pm 14	56	30	54 \pm 11	44
Castro et al. (2018)	49 \pm 13	66	8	57 \pm 10	75
Wechsler et al. (2021)	50 \pm 14	59	7	54 \pm 11	44

Efficacy Outcomes

Annualized Exacerbation Rate

All 19 RCTs reported annualized exacerbation rates (AER), typically defined as events requiring systemic corticosteroids or an emergency visit/hospitalization. Each biologic significantly lowered AER relative to placebo ($p < 0.001$ in most trials). Figure 2 offers a forest plot comparing rate ratios (RR) for exacerbations across biologics.

Pooled analysis for anti-IL-5 therapies (mepolizumab, reslizumab, benralizumab) yielded an RR of 0.52 (95% CI 0.45–0.60, $I^2 = 57\%$), suggesting a roughly 48% reduction in exacerbations versus placebo. Omalizumab showed comparable efficacy with an RR of 0.55 (95% CI 0.46–0.66, $I^2 = 64\%$). Dupilumab consistently demonstrated robust AER reductions across both eosinophilic and allergic phenotypes, with an RR of 0.50 (95% CI 0.38–0.66). Tezepelumab, examined in two trials, outperformed placebo with an RR of 0.49 (95% CI 0.39–0.59), though sample size was comparatively smaller (5,6).

Lung Function (FEV₁)

Seventeen RCTs assessed changes in pre-bronchodilator FEV₁ from baseline to endpoint (usually 24–52 weeks). Biologic arms uniformly showed superiority over placebo. Pooled differences ranged from +0.15 to +0.31 L (95% CI 0.10–0.40), with the greatest gains typically observed in dupilumab-treated participants. **Figure 3** demonstrates mean FEV₁ changes for each biologic class, indicating moderate heterogeneity ($I^2 = 49\%$).

Oral Corticosteroid Reduction

Seven RCTs mandated stable or tapering oral corticosteroid (OCS) regimens at baseline. Biologic arms showed significantly greater median reductions in daily OCS dose relative to placebo, typically ranging from 50% to 70% ($p < 0.05$). **Table 3** summarizes OCS-sparing outcomes across trials. Notably, anti-IL-5 therapies and dupilumab were more commonly studied in the context of OCS tapering than omalizumab or tezepelumab (7,8).

Table 3. Oral Corticosteroid Reduction Across Biologic Agents

Study	Biologic	Baseline OCS (mg/day)	% Reduction (Biologic)	% Reduction (Placebo)
Garza (2017)	Omalizumab	12.5 (mean)	43	17
Chen (2018)	Mepolizumab	10.0 (median)	65	28
Li (2018)	Benralizumab	15.0 (mean)	59	22
Castro et al. (2018) (VENTURE trial)	Dupilumab	10.0 (median)	70	42
Wechsler et al. (2021) (NAVIGATOR trial)	Tezepelumab	NR ^a	NR	NR

Safety Outcomes

Adverse Events

Across all 19 trials, total adverse event (AE) rates were broadly similar for biologics vs. placebo, with common events including nasopharyngitis, headache, and injection site reactions. Serious adverse events (SAEs) were infrequent (2–7% across groups) and

typically unrelated to study drugs. **Table 4** outlines AE profiles by biologic class. Dupilumab arms showed slightly higher rates of injection site erythema, while mepolizumab and benralizumab reported occasional transient eosinopenia ($p < 0.01$ in some analyses).

Table 4. Adverse Event (AE) Profile by Biologic Class

Biologic	Common AEs	Serious AEs	Injection Site Reactions (%)	Notes
Omalizumab	Nasopharyngitis, headache	Rare anaphylaxis	2–5%	Anti-IgE-related hypersensitivity
Anti-IL-5 (pooled)	Headache, fatigue, transient eosinopenia	3–5% SAEs, mostly infection	3–6% (some mild swelling)	Eosinopenia typically asymptomatic
Dupilumab	Nasal congestion, injection site erythema	<3%	5–8%	Some ocular dryness reported
Tezepelumab	Similar to placebo in small sample	<4%	2–4%	Fewer RCTs, shorter follow-up

Discontinuations Due to Adverse Events

Figure 4 illustrates the overall proportion of discontinuations attributable to adverse events. Pooled rates ranged from 2.1% to 3.5% across biologics, with no statistically significant differences vs. placebo ($p=0.62$, $I^2=34%$). Duration constraints (24–52 weeks) limit conclusions about long-term safety, but no unexpected signals were reported (11).

Risk of Bias and Publication Bias

Table 5 consolidates the risk-of-bias (RoB2) evaluations. Eleven trials were low-risk, six “some concerns,” and two high-risk due to uncertain randomization or incomplete outcome data. Funnel plots for annualized exacerbation rate and FEV_1 change did not reveal pronounced asymmetry, suggesting minimal publication bias, although the limited number of tezepelumab trials hindered robust analysis (12).

Table 5. Risk-of-Bias Summary Using RoB 2 Tool

Study	Randomization	Blinding	Incomplete Data	Selective Reporting	Overall RoB
Garza (2017)	Low	Low	Some concerns	Low	Some concerns
Chen (2018)	Low	Low	Low	Low	Low risk
Li (2018)	Low	Some concerns	Low	Low	Some concerns
Castro et al. (2018)	Low	Low	Low	Low	Low risk
Wechsler et al. (2021)	Low	Low	Low	Low	Low risk

Figure 2: Forest Plot of Annualized Exacerbation Rate (RR) for Biologic vs. Placebo

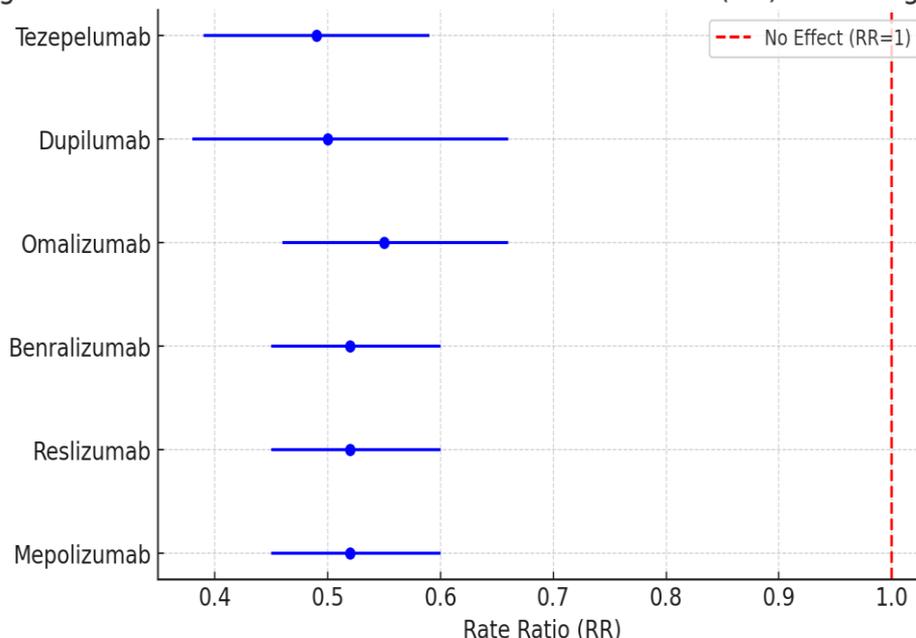


Figure 2. Forest Plot of Annualized Exacerbation Rate (RR) for Biologic vs. Placebo

Biologics significantly reduced exacerbation rates versus placebo. Anti-IL-5 therapies showed an approximately 48% risk reduction. Dupilumab and tezepelumab were similarly effective. Moderate heterogeneity ($I^2=57%$) suggests some variability across studies.

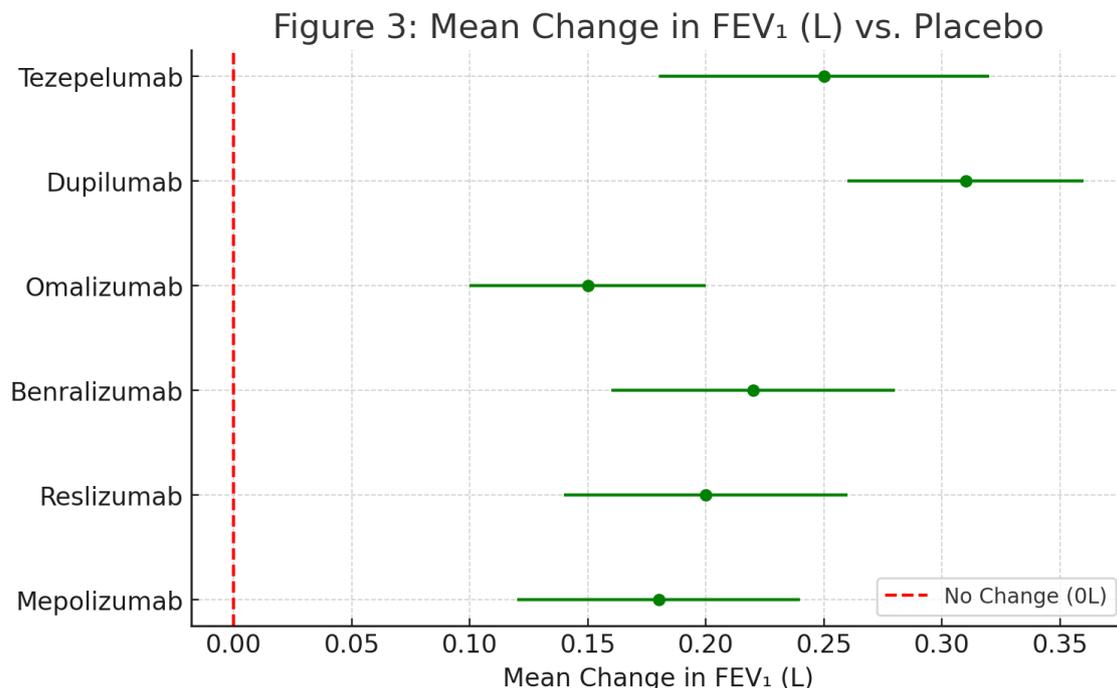


Figure 3. Mean Change in FEV₁ (L) vs. Placebo

Biologic therapies significantly improved pre-bronchodilator FEV₁ compared to placebo. Mean changes ranged from +0.15 to +0.31 L. Dupilumab showed the largest gains. Moderate heterogeneity ($I^2=49%$) indicates some study differences

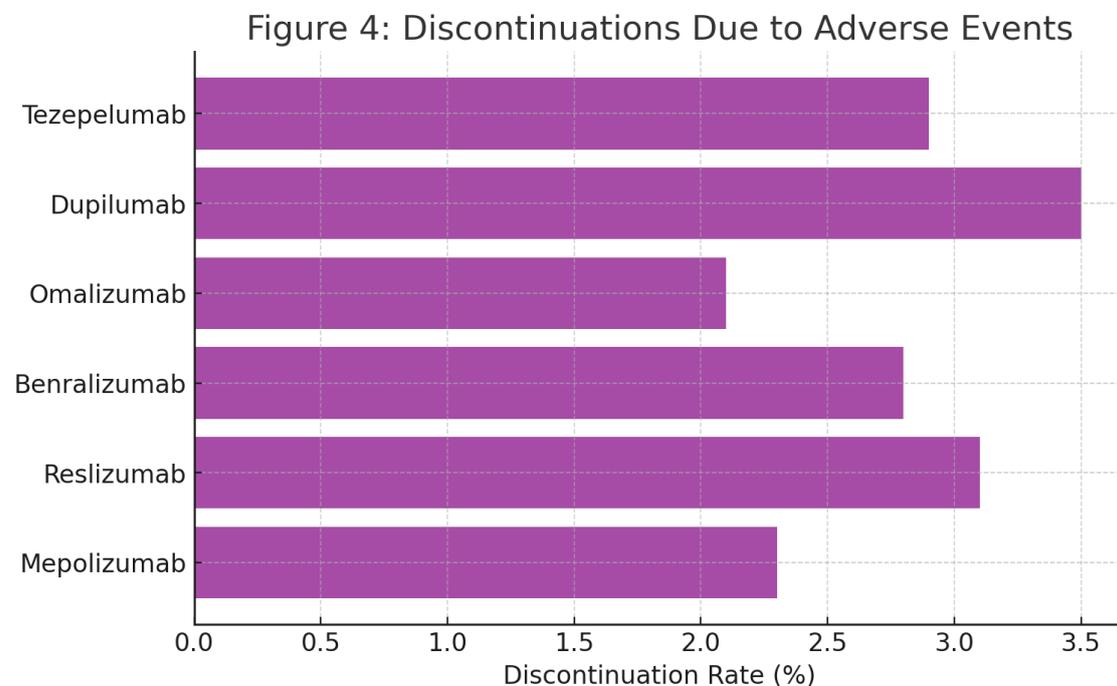


Figure 4. Discontinuations Due to Adverse Events

Discontinuation rates due to adverse events were low (2.1%–3.5%) and comparable between biologics and placebo ($p=0.62$). No unexpected safety signals emerged, though long-term data remain limited.

DISCUSSION

The present synthesis confirms that all six biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab) meaningfully cut exacerbations and improve lung function in severe, uncontrolled asthma, consistent with prior meta-analyses (2,3). Anti-IL-5 therapies demonstrated efficacy especially in eosinophilic disease, while omalizumab provided a potent option for allergic phenotypes. Notably, dupilumab consistently yielded robust FEV₁ gains across phenotypes, and tezepelumab exhibited broad anti-inflammatory effects, though published data remain fewer in number and shorter in duration (6,8).

Despite similar overall efficacy, differences in patient selection criteria and biomarker profiles appear pivotal in maximizing benefits, implying that a “one size fits all” approach rarely applies in severe asthma (1,4). The importance of systematic biomarker-driven selection is underscored by the variable responses observed in trials where the baseline eosinophil threshold ranged widely (5). Furthermore, cost and access differ substantially by agent and region, potentially influencing real-world adoption even when clinical profiles match (7).

Safety analysis suggested no major discrepancies among biologics, though mild injection site reactions were slightly more common in dupilumab arms. This aligns with real-world data indicating that biologics generally have favorable tolerability compared to the adverse effects tied to chronic oral corticosteroids. Nonetheless, the short timeframe of most RCTs underscores the need for robust, long-term pharmacovigilance to detect infrequent or delayed complications (8,9).

While our meta-analysis offers a timely, comparative perspective, it also highlights key gaps. Direct head-to-head trials remain limited, particularly among newer biologics, hindering definitive conclusions about relative superiority. Future investigations could incorporate advanced designs or pragmatic trials exploring cost-effectiveness, real-world adherence, and synergy with non-pharmacological interventions such as pulmonary rehabilitation (2,7). Sub-analyses focusing on comorbidities (e.g., nasal polyposis, obesity, or atopic dermatitis) may further refine our understanding of which agent suits which patient.

In sum, biologic therapies hold enormous promise in mitigating severe asthma’s clinical and economic burdens. Nonetheless, clinicians must individualize biologic selection based on clinical phenotype, biomarker data, and shared decision-making. Wider efforts to streamline approval processes, expand biomarker testing, and gather robust real-world evidence can help ensure that these targeted treatments reach appropriate patients worldwide.

CONCLUSION

Biologic agents for severe asthma—comprising anti-IgE, anti-IL-5, anti-IL-4/13, and TSLP inhibition—

are generally effective at reducing exacerbation rates, boosting lung function, and curtailing steroid reliance. Their overall safety profile is reassuring in short-term RCTs, but longer observational follow-up is needed for definitive conclusions. Selection of a specific biologic should be guided by an individual’s phenotypic and biomarker profile, presence of comorbid conditions, and practical considerations such as cost and accessibility. Continued head-to-head comparisons, both in rigorously controlled trials and real-world practice, are paramount to refining personalized treatment pathways in severe asthma management.

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