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ORIGINAL RESEARCH

Multi-Criteria Decision Analysis of Biologics in Chronic Obstructive Pulmonary Disease

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Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with limited response to standard anti-inflammatory therapies. Biologics targeting specific inflammatory pathways have emerged as potential treatments, but their efficacy remains variable across distinct COPD endotypes.

Objective: To systematically evaluate the efficacy and trial quality of biologics tested in COPD patients using a multicriteria decision analysis (MCDA) approach, with attention to type 2 (T2) and non-T2 inflammatory targets.

Methods: We assessed 20 trials encompassing 12 biologics and 9294 patients with COPD. Each trial was scored (0–3 per domain, total 12 points) across four domains: exacerbation reduction, lung function improvement, biomarker stratification, and trial design quality.

Results: Dupilumab (anti-IL-4Rα) demonstrated the most robust efficacy in eosinophilic COPD, with consistent reductions in exacerbation rates and improvements in FEV_1, supported by high trial quality. Mepolizumab and benralizumab (anti-IL-5/IL-5R) showed moderate efficacy in biomarker-enriched populations. Anti-alarmins, specifically tozorakimab (anti-IL-33), itepekimab (anti-IL-33/IL-1RL1), astegolimab (anti-ST2), and tezepelumab (anti-TSLP), showed mixed results, with modest lung function gains but largely non-significant effects on exacerbation rates. Agents targeting non-T2 pathways, including infliximab (anti-TNF-α), canakinumab (anti-IL-1β), MEDI8968 (anti-IL-1R1), CNTO6785 (anti-IL-17A), and ABX-IL8 (anti-IL-8), consistently failed to demonstrate clinical efficacy, often due to small sample sizes, early-phase design, and lack of biomarker stratification.

Conclusion: Biologics targeting T2 inflammation offer therapeutic promise in eosinophilic COPD when guided by biomarkers. Conversely, current biologics directed at non-T2 and alarmin pathways yield limited or inconsistent benefits, emphasizing the need for improved phenotyping and targeted intervention strategies in non-eosinophilic COPD.

Keywords: COPD, biologics, randomized controlled trials, multicriteria decision analysis

Introduction

In recent years, there has been a growing recognition of the heterogeneity of chronic obstructive pulmonary disease (COPD). COPD is characterized by persistent airflow limitation and chronic airway inflammation, historically attributed to innate immune mechanisms and neutrophilic infiltration.[1] However, emerging evidence shows that adaptive immune responses, including those mediated by Type 2 (T2) cytokines and epithelial-derived alarmins, also contribute to disease heterogeneity,[2] particularly in the eosinophilic COPD phenotype.[3,4]

Alarmins, such as interleukin (IL)-33, thymic stromal lymphopoietin (TSLP), and IL-25, are released by airway epithelial cells in response to environmental stressors, including cigarette smoke and viral infections.[5] These cytokines act as upstream initiators of both innate and adaptive immune responses, activating group 2 innate lymphoid cells, dendritic cells, and Th2 cells. Activation of these cells leads to the secretion of T2 cytokines, including IL-4, IL-5, and IL-13, which are traditionally associated with asthma but increasingly recognized in a subset of COPD patients.[2]

IL-5 promotes eosinophil maturation and survival, contributing to eosinophilic airway inflammation observed in 20–40% of COPD patients,[6] particularly those with frequent exacerbations and corticosteroid responsiveness.[3] IL-4 and IL-13 drive goblet cell hyperplasia, mucus hypersecretion, and airway remodeling, features that overlap with asthma but

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are also present in T2-high COPD endotypes.[2] Elevated blood eosinophil counts are now used as biomarkers to guide corticosteroid therapy in COPD, highlighting the clinical relevance of T2 inflammation in disease management.[7]

In addition to T2 pathways, classical pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and IL-17 remain central to the neutrophilic, steroid-resistant inflammation typical of most COPD cases.[8] In some cases, however, patients manifest co-existing T2 and non-T2 inflammatory pathways,[9] underscoring the presence of overlapping endotypes with distinct molecular signatures.[10]

These insights indicate that cytokines and alarmins are key drivers of airway inflammation in COPD. Therefore, inhibiting specific immune pathways with monoclonal antibodies (mAbs) could be a possible treatment for the inflammatory component of COPD.[8] Several biologic agents, many already approved for treating severe asthma, have been investigated for their potential utility in treating COPD, particularly in patients with eosinophilic or T2-high inflammatory profiles.[8] This evolving therapeutic paradigm recognizes COPD as a biologically heterogeneous condition that could benefit from endotype-driven interventions. Biologics are thus being explored as adjunctive therapies to standard inhaled regimens, offering selective immune modulation and advancing the principles of precision medicine.[8]

Among the biologics explored in COPD, anti-interleukin therapies have attracted particular interest (Table 1). IL-5 is a key cytokine involved in eosinophil differentiation and survival. Mepolizumab, an anti-IL-5 mAb, has demonstrated efficacy in reducing exacerbations in patients with eosinophilic asthma and has therefore been investigated in COPD with elevated blood or sputum eosinophils.[13–16] Benralizumab, an anti-IL-5Rα mAb that induces direct eosinophil apoptosis via antibody-dependent cell-mediated cytotoxicity, has also been studied extensively in COPD.[11,12] Dupilumab, targeting IL-4Rα and thereby blocking IL-4 and IL-13 signaling, addresses broader T2 inflammation and has recently shown favorable results in eosinophilic COPD subgroups.[17,18]

Beyond T2-targeted therapies, other cytokine inhibitors such as those targeting IL-33 (itepekimab, tozorakimab),[19,20] tumor suppressor protein 2 (ST2) (astegolimab),[21] TSLP (tezepelumab),[22] TNF-α (infliximab, but one study just collected malignancy and mortality data from completed clinical studies of infliximab in COPD treatment),[23,24] IL-1 family members (canakinumab, MEDI8968),[25,26] IL-8 (ABX-IL8),[27] and IL-17A (CNTO6785)[28] have been evaluated (Table 1), albeit with limited or inconsistent efficacy outcomes. Most of these trials enrolled unselected COPD populations without inflammatory phenotype stratification, which may explain their lack of significant clinical benefit.

Notably, recent regulatory decisions have reflected the potential of targeted biologics in COPD. The US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Chinese National Medical Products Administration have

Table 1 General Features of the Examined RCTs

Study (Year)	Biologic	Comparator	Duration	Primary Endpoint	Reference
Brightling et al (2014)	Benralizumab	Placebo	56 weeks	Rate of moderate/severe exacerbations	[11]
Criner et al (2019) GALATHEA	Benralizumab (30/100 mg)	Placebo	56 weeks	Annual exacerbation rate	[12]
Criner et al (2019) TERRANOVA	Benralizumab (10/30/100 mg)	Placebo	56 weeks	Annual exacerbation rate	[12]
Dasgupta et al (2017)	Mepolizumab	Placebo	6 months	Sputum eosinophils, change in FEV_1, exacerbations	[13]
Pavord et al (2017) METREX	Mepolizumab	Placebo	52 weeks	Annual exacerbation rate	[14]
Pavord et al (2017) METREO	Mepolizumab (100/300 mg)	Placebo	52 weeks	Annual exacerbation rate	[14]
Flynn et al (2025)	Mepolizumab	Placebo	52 weeks	Annual exacerbation rate	[15]
Sciurba et al (2025)	Mepolizumab	Placebo	52-104 weeks	Annualized exacerbation rate	[16]
Bhatt et al (2023)	Dupilumab	Placebo	52 weeks	Annualized exacerbation rate	[17]
Bhatt et al (2024)	Dupilumab	Placebo	52 weeks	Annualized exacerbation rate	[18]
Rabe et al (2021)	Itepekimab	Placebo	24 weeks	Annual exacerbation rate, change in FEV_1	[19]
Singh et al (2025)	Tozorakimab	Placebo	24 weeks	Change in FEV_1	[20]
Yousuf et al (2022)	Astegolimab	Placebo	48 weeks	Exacerbation rate	[21]
Singh et al (2025)	Tezepelumab	Placebo	52 weeks	Exacerbation rate	[22]
Rennard et al (2007)	Infliximab	Placebo	32 weeks	FEV_1 and health status	[23]
Rennard et al (2013)	Infliximab	Placebo	5-year follow-up	Malignancy and mortality	[24]
Novartis (2011)	Canakinumab	Placebo	48 weeks	Exacerbation rate	[25]
Calverley et al (2017)	MEDI8968	Placebo	52 weeks	Exacerbation rate	[26]
Mahler et al (2004)	ABX-IL8	Placebo	12 weeks	FEV_1 and symptoms	[27]
Eich et al (2017)	CNTO6785	Placebo	24 weeks	Change in FEV_1	[28]

approved dupilumab as an add-on treatment for COPD.[29] The FDA has also approved mepolizumab as an add-on maintenance therapy for patients with COPD with an eosinophilic phenotype,[30] and an EMA review of this indication is ongoing.[31]

The present study systematically evaluates the efficacy and quality of evidence from biologic trials in COPD through a multicriteria decision analysis (MCDA) framework. MCDA offers a transparent and structured methodology for comparing therapies across multiple domains, efficacy, biomarker appropriateness, and study quality,[32] while facilitating comparative assessments across T2 and non-T2 inflammatory endotypes.

Methods

Study Design and Objective

This study conducted a structured MCDA to compare the clinical impact of biologic therapies targeting inflammatory pathways in patients with COPD. The primary objective was to synthesize and quantify the relative value of different mAbs tested in randomized controlled trials (RCTs) for COPD using predefined clinical and methodological domains.

Data Sources and Selection

A systematic inclusion of biologic COPD trials published or indexed to May 2025 was performed, utilizing the PubMed, Scopus, Web of Science, and Google Scholar databases and ClinicalTrials.gov (for unpublished or industry-sponsored trials).

Inclusion criteria were Phase 2 or 3 RCTs that assessed biologic agents targeting ILs or other inflammatory pathways in patients with moderate to very severe COPD and were focused on at least one of the following endpoints: exacerbation rate, forced expiratory volume in one second (FEV_1), quality of life, or biomarker-stratified subgroup outcomes. Non-RCTs, abstracts without full-text data, and studies exclusively focusing on asthma or without COPD-specific data were excluded.

The following mAbs were evaluated: anti-IL4/13: dupilumab; anti-IL5: mepolizumab; anti-IL5R: benralizumab; anti-IL-33/ST2: itepekimab, tozorakimab, astegolimab; anti-TSLP: tezepelumab; anti-IL-1: canakinumab, MEDI8968 (which inhibits IL-1 receptor 1 [IL-1R1]); anti-TNF-α: infliximab; anti-IL-17/IL-8: CNTO 6785; anti-IL8 (ABX-IL8).

Each mAb was scored based on four predefined domains relevant to COPD biologic efficacy, using a 0–3 scale (higher is better): efficacy, lung function, biomarker selection strategy, and evidence quality, including the risk of bias[33] (Table 2). No differential weighting was applied to the domains, as there is currently no established empirical or consensus-based rationale for prioritizing one over another in COPD biologic assessment; equal weighting avoids introducing subjective bias and allows transparent, domain-by-domain interpretation, in line with other exploratory MCDA applications in respiratory medicine.[34]

For the lung function domain, FEV_1 cut-offs were defined a priori based on COPD trial conventions and ATS/ERS minimal clinically important difference (MCID) recommendations:[35] <50 mL improvement was considered negligible; 50–99 mL as marginal; ≥100 mL as moderate (meeting MCID); and ≥150 mL with consistent results across timepoints as strong.

Evidence quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating randomization process, deviations from intended interventions, missing data, outcome measurement, and selective reporting.[33] Overall domain scores incorporated RoB 2 judgments together with trial size, multicenter status, and reproducibility across populations.[33]

Two reviewers performed the scoring independently. Discrepancies were resolved through discussion and, if necessary, by a third reviewer. Although formal inter-rater agreement statistics were not calculated, agreement exceeded 90% across domains after initial scoring. Final scores were averaged when more than one trial per agent was available.

Ethical Statement

The data used in this study are from previously published clinical trials, in which the participants were presented anonymously. Therefore, approval from an ethics committee was not required for this analysis.

Results

Overview of Trials

The MCDA evaluation included 12 biologics across 20 trials, covering 9294 patients with COPD (Table 3). The therapeutic targets spanned a broad spectrum of cytokines implicated in both T2 and non-T2 inflammatory pathways.

Table 2 MCDA Scoring Criteria and Definitions for Biologic Therapies in COPD

Criterion	Description	Score = 0 (None)	Score = 1 (Marginal)	Score = 2 (Moderate)	Score = 3 (Strong)
Efficacy	Reduction in moderate/severe exacerbations vs placebo	No reduction (RR ≈1.0)	Small effect (<10% reduction or RR 0.95–0.99)	Clinically relevant (10–25% reduction; statistically significant)	Robust >25% reduction; statistically significant and consistent
Lung Function (FEV_1)	Improvement in trough FEV_1 vs placebo	<50 mL	50–99 mL increase	≥100 mL increase (moderately improved lung function)	≥150 mL and consistent across studies/timepoints
Biomarker Selection	Degree of enrichment for T2 inflammation (eg, eosinophils)	No biomarker-based enrollment or stratification	Biomarker examined post hoc or exploratory	Partial enrichment; subgroups defined but not prespecified	Strong enrichment (eg, eos ≥300/μL as inclusion criterion)
Evidence Quality	Methodological rigor: size, risk of bias, consistency	High risk of bias, small N, single center or exploratory design	Some concerns: modest sample, unclear bias, inconsistent findings	Adequate power, multicenter RCT, low-moderate bias, generally consistent	Large Phase 3 RCTs, low risk of bias, reproducible across populations

Table 3 Baseline Characteristics for All the RCTs Included in the MCDA Analysis

Study (Year)	Biologic/Comparator	N	Mean Age (years)	% Male	Mean BMI (kg/m^2)	% Current Smokers	Baseline FEV_1 (%)	Annual Exacerbations (Mean)	Reference
Brightling et al (2014)	Benralizumab/Placebo	51/ 50	62.9/ 64.9	69/ 58	26.6/ 26.5	33/ 42	44.3/ 49.9	1.6 / 1.6	[11]
Criner et al (2019) GALATHEA	Benralizumab (30 mg/100 mg)/Placebo	382/ 379/ 359	65.8/ 65.5/ 65.6	71/ 69/ 72	27.4/ 27.8/ 27.5	36.6/34.0/32.0	39.7/ 40.5/ 41.1	2.31/ 2.33/ 2.35	[12]
Criner et al (2019) TERRANOVA	Benralizumab (10 mg/30 mg/100 mg)/ Placebo	377/ 394/ 386/ 388	65.1/ 65.9/ 64.9/ 65.0	67/ 68/ 65/ 65	26.8/ 27.1/ 26.8/ 26.5	28.6/ 27.4/ 28.0/ 30.4	42.7/ 40.5/ 40.9/ 41.2	2.25/ 2.22/ 2.30/ 2.34	[12]
Dasgupta et al (2017)	Mepolizumab/Placebo	8/ 10	Not reported	Not reported	Not reported	Not reported	55.0/ 29.5	Not reported	[13]
Pavord et al (2017) METREX	Mepolizumab/Placebo	417/ 419	66/ 65	62/ 63	26.9/ 27.0	25/ 28	44.9/ 43.7	2.5/ 2.5	[14]
Pavord et al (2017) METREO	Mepolizumab (100 mg/ 300 mg)/Placebo	223/ 225/ 226	65/ 65/ 66	59/ 70/ 69	27.1/ 26.4/ 25.4	25/ 32/ 28	47/ 45/ 46	2.7/ 2.7/ 2.6	[14]
Flynn et al (2025)	Mepolizumab/Placebo	119/ 119	69.5/ 68.7	49/ 50	27.4/ 27.6	20.2/ 23.5	51.0/ 50.8	4.9/ 5.7	[15]
Sciurba et al (2025)	Mepolizumab/Placebo	403/ 401	66.4/ 66.0	68/ 69	27.4/ 27.1	28/ 28	48.1/ 48.2	2.3/ 2.2	[16]
Bhatt et al (2023)	Dupilumab/Placebo	468/ 471	65.0/ 65.2	64/ 68	27.5/ 27.6	28.6 / 31.4	50.6/ 50.6	2.2/ 2.3	[17]
Bhatt et al (2024)	Dupilumab/Placebo	470/ 465	65.2/ 64.9	68/ 67	28.1/ 27.8	30.2/ 28.8	49.5/ 50.7	2.2/ 2.1	[18]
Rabe et al (2021)	Itepekimab/Placebo	172/ 171	63.7/ 64.0	58/ 56	Not reported	43/ 48	45.7/ 45.6	2.2/ 2.2	[19]
Singh et al (2025)	Tozorakimab/Placebo	67/ 68	64.5/ 64.3	61/ 60	Not reported	35.8/ 47.1	44.0/ 45.2	≥1/ ≥1	[20]
Yousuf et al (2022)	Astegolimab/Placebo	42/ 39	67.6/ 70.8	60/ 67	27.5/ 26.1	24/ 15	48.2/ 44.9	3.1/ 3.1	[21]
Singh et al (2025)	Tezepelumab/Placebo	281/ 142	64/ 65	70/ 71	36.4/ 26.7	49/ 50	44.8/ 45.3	1.8/ 1.9	[22]
Rennard et al (2007)	Infliximab (3 mg/kg/5 mg/kg)/Placebo	78/ 79/ 77	65.0/ 65.0/ 65.4	61/ 56/ 60	26.6/ 268/ 28.3	46/ 44/ 43	43.6/ 41.4/45.2	Not reported	[23]
Rennard et al (2013)	Infliximab (3 mg/kg/5 mg/kg)/Placebo	31/ 29/ 33	68.0/ 65.0/ 67.0	66/ 54/ 51	Not reported	19/ 24/ 33	Not reported	Not reported	[24]
Novartis (2011)	Canakinumab/Placebo	74/ 73	63.9/ 63.6	62/ 58	Not reported	Not reported	Not reported	Not reported	[25]
Calverley et al (2017)	MEDI8968/Placebo	160/ 164	62.8/ 63.0	69/ 67	25.7/ 25.8	Not reported	39.7/ 38.6	≥2/ ≥2	[26]
Mahler et al (2004)	ABX-IL8/Placebo	59/ 60	65/ 65	62/ 47	Not reported	39/ 40	42/ 42	Not reported	[27]
Eich et al (2017)	CNTO6785/Placebo	92/ 93	62.0/ 63.4	66/ 69	26.4/ 26.6	49.5/ 42.6	51.9/ 50.1	≥2/ ≥2	[28]

Baseline characteristics of enrolled populations demonstrated substantial heterogeneity across studies, particularly in demographics, disease severity, and exacerbation burden. Mean participant age ranged from approximately 62 to 69.5 years. More recent trials, such as those by Flynn et al,[15] included older cohorts, which may reflect a population with more advanced disease or a greater burden of comorbidities. Most studies enrolled predominantly male participants (typically >60%), although Flynn et al[15] reported a more balanced sex distribution, indicating progress toward equitable gender representation in recent COPD trials. Body mass index (BMI) was generally in the overweight range (25–28 kg/m^2), although notable deviations were observed in the tezepelumab study by Singh et al,[22] where a substantially higher mean BMI was reported in the intervention arm. This may reflect selection bias or an imbalance in randomization. The proportion of current smokers varied widely between trials (15–50%), a factor that may have influenced treatment response given the known immunomodulatory effects of active tobacco use on airway inflammation.[36] Baseline lung function, expressed as percent predicted FEV_1, was consistently reduced across trials, generally ranging between 40% and 50%. This is consistent with the inclusion of patients with moderate-to-severe COPD. However, slightly lower FEV_1 values were observed in the GALATHEA and TERRANOVA studies,[12] suggesting enrollment of more functionally impaired cohorts. Baseline exacerbation rates also varied significantly, with most trials reporting 2–3 events per year. However, Flynn et al[15] included patients with a markedly higher exacerbation burden (mean up to 5.7 events/year) consistent with a frequent-exacerbator phenotype. Notably, several earlier or smaller trials did not report key baseline variables such as BMI or exacerbation frequency, thereby limiting the comparability of findings across studies and underscoring the need for standardized reporting practices.

MCDA Scores Across Biologics

The trial-level MCDA scoring (0–3 scale per domain) revealed a clear hierarchy of biologic performance in COPD, with distinct patterns emerging across efficacy, lung function, biomarker strategy, and trial quality domains (Table 4 and Figure 1).

Dupilumab achieved the highest overall performance, with a mean total score of 10/12 across its two large-scale, high-quality Phase 3 trials (BOREAS[17] and NOTUS).[18] Both studies demonstrated robust and statistically significant reductions in moderate-to-severe exacerbations, 30% and 34%, respectively ($p < 0.001$), accompanied by clinically relevant lung function gains (mean FEV_1 increase of 82–83 mL). Each trial incorporated strict eosinophilic enrichment criteria (blood eosinophil count [BEC] ≥ 300/μL) and adhered to rigorous methodological standards, justifying maximal scoring in the biomarker and evidence quality domains.

Mepolizumab also showed consistent efficacy across multiple trials, although with more heterogeneity. The small-scale study by Dasgupta et al,[13] which employed unclear eosinophil thresholds and demonstrated only non-significant trends in exacerbation reduction without meaningful FEV_1 improvement, received a total score of 2. In contrast, the METREX and METREO trials[14] were pivotal in establishing the agent's potential efficacy in COPD patients with elevated eosinophil counts. METREX reported a statistically significant ~18% reduction in exacerbations among patients with BEC ≥ 150/μL, yielding a score of 7, while METREO, which stratified by both ≥150 and ≥300/μL thresholds, achieved a ~20% reduction without statistical significance but nonetheless merited a score of 6 due to methodological rigor and biomarker specificity. The more recent studies by Flynn et al[15] and Sciurba et al[16] provided stronger evidence of efficacy. Both trials demonstrated statistically significant reductions in exacerbation rates (19% and 21%, respectively, $p<0.01$) and had well-defined inclusion criteria for BEC (≥150 or ≥300/μL). These studies strengthened the overall evidence base for mepolizumab, earning scores of 6 and 8, respectively, reflecting their methodological strength and biomarker-driven design. Overall, mepolizumab performed well in trials, resulting in a mean total score of 5.8.

Three trials assessed benralizumab.[11,12] None of the trials achieved statistical significance in reducing exacerbation rates (4–30% reductions). FEV_1 improvements were consistently minimal (less than 50 mL), and biomarker usage ranged from early sputum eosinophil stratification to post hoc subgroup analyses. All three studies received a total score of 5, with a mean of 5.0, reflecting moderate but unconvincing efficacy.

Tozorakimab[20] did not significantly reduce exacerbations but demonstrated the largest FEV_1 improvement observed among all agents (124 mL). Eosinophilic inclusion criteria (BEC ≥300/μL) were used, and the trial was well-conducted, yielding a total score of 6.

Table 4 Key Outcomes Across the 20 Examined Trials and Scores Based on Average Domain Performance Across Respective Trials (Scale: 0–3)

Biologic	Study [Reference]	Efficacy (vs Placebo)	FEV_1 Change (vs Placebo)	Biomarker Selection	Evidence Quality	Total Score
Benralizumab	Brightling et al (2014)[11]	1 (~30% reduction in eos subgroup [non-significant])	0 (<50 mL increase)	3 (Sputum eos ≥3% stratification)	1 (Small, early phase)	5
Benralizumab	GALATHEA (Criner et al, 2019)[12]	1 (~5% reduction [non-significant])	0 (<50 mL increase)	1 (Post hoc eos subgroup)	3 (Large phase 3 RCT)	5
Benralizumab	TERRANOVA (Criner et al, 2019)[12]	1 (~4% reduction [non-significant])	0 (<50 mL increase)	1 (Post hoc eos subgroup)	3 (Large phase 3 RCT)	5
Mepolizumab	Dasgupta et al, (2017)[13]	1 (Trend only, non-significant)	0 (<50 mL increase)	1 (Unclear eos definition)	0 (Very small N)	2
Mepolizumab	METREX (Pavord et al, 2017)[14]	2 (~18% reduction in eos subgroup)	0 (<50 mL increase)	2 (Eos ≥150/μL enrichment)	3 (Phase 3)	7
Mepolizumab	METREO (Pavord et al, 2017)[14]	1 (~20% reduction[non-significant])	0 (<50 mL increase)	3 (Eos ≥150/300/μL)	2 (Phase 3 moderate size)	6
Mepolizumab	Flynn et al (2025)[15]	2 (19% reduction, p<0.01)	0 (Not assessed)	2 (Eos ≥150/μL with stratification)	2 (Good RCT)	6
Mepolizumab	Sciurba et al (2025)[16]	2 (21% reduction, p<0.01)	0 (−9 mL)	3 (Eos ≥300/μL included)	3 (Large RCT)	8
Dupilumab	Bhatt et al (2023)[17]	3 (30% reduction, p<0.001)	1 (83 mL increase)	3 (Eos ≥300/μL included)	3 (Large low-risk RCT)	10
Dupilumab	Bhatt et al (2024)[18]	3 (34% reduction, p<0.001)	1 (82 mL increase)	3 (Eos ≥300/μL included)	3 (Large low-risk RCT)	10
Itepekimab	Rabe et al (2021)[19]	1 (19% reduction [non-significant])	1 (60mL increase)	0 (Unselected)	2 (Modest size, good design)	4
Tozorakimab	Singh et al (2025)[20]	0 (Non-significant change)	2 (124 mL increase)	3 (Eos ≥300/μL included)	2 (Phase 2, well conducted)	6
Astegolimab	Yousuf et al (2022)[21]	1 (~20% reduction[non-significant])	1 (40 mL increase)	0 (Unselected)	1 (Small trial)	3
Tezepelumab	Singh et al (2025)[22]	1 (17% reduction [non-significant])	0 (−6 mL)	1 (Post hoc eos subgroup)	2 (Phase 2 moderate size)	4
Infliximab	Rennard et al (2007)[23]	1 (12% reduction [non-significant])	0 (No effect)	0 (None)	2 (Phase 2 moderate size)	3
Infliximab	Rennard et al (2013)[24]	0 (Not assessed)	0 (Not assessed)	0 (None)	1 (Long-term follow-up study)	1
Canakinumab	Novartis (2011)[25]	0 (Not assessed)	0 (−11 mL)	0 (None)	1 (Small, early phase)	1
MEDI8968	Calverley et al (2017)[26]	1 (8% reduction[non-significant])	0 (5 mL increase)	0 (None)	2 (Well-conducted RCT)	3
ABX-IL8	Mahler et al (2004)[27]	0 (No efficacy)	0 (Not reported)	0 (None)	1 (Very small)	1
CNTO6785	Eich et al (2017)[28]	0 (No efficacy)	0 (Small decrease)	0 (None)	1 (Phase 2, small size)	1

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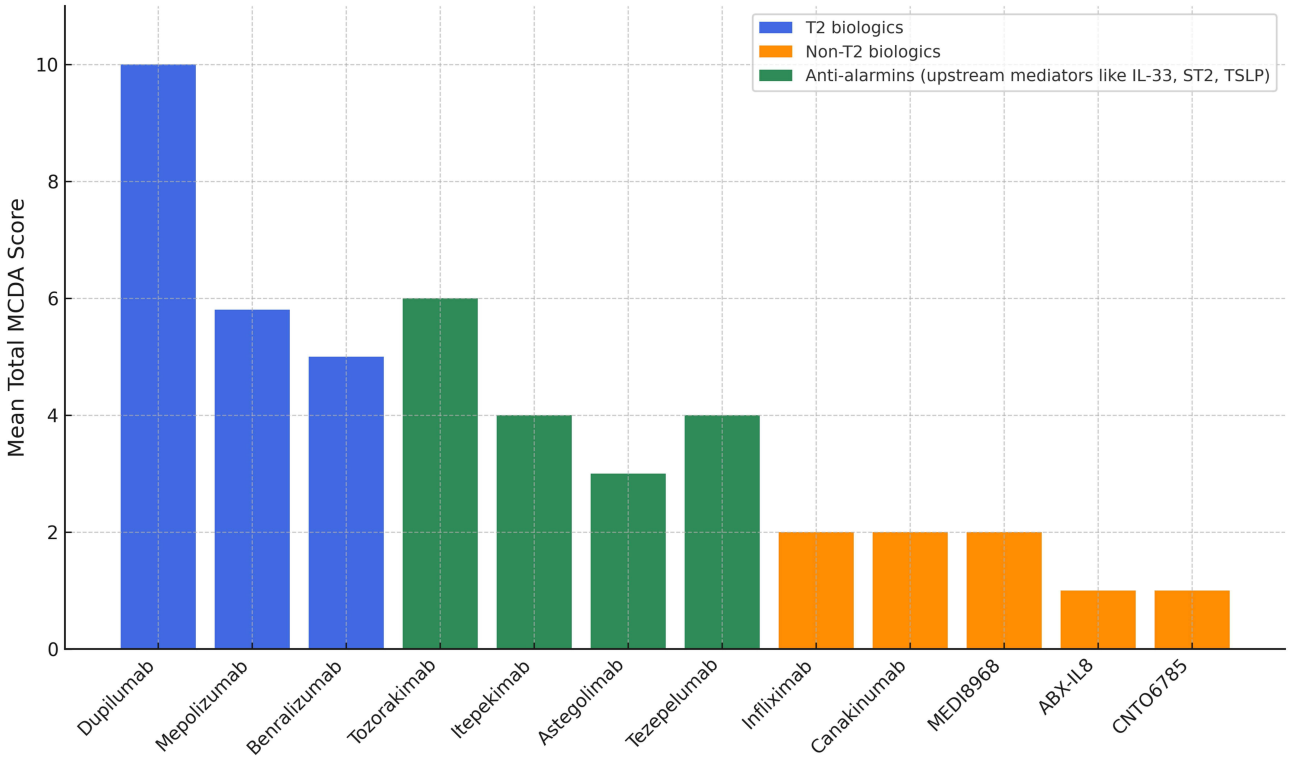

Figure 1 Mean total MCDA score for each biologic, derived from a composite assessment of efficacy, FEV_1 improvement, biomarker utilization, and evidence quality. Blue bars represent T2-targeted biologics, Orange bars represent non-T2 biologics, and green bars indicate anti-alarmins (upstream mediators such as IL-33, ST2, and TSLP).

Itepekimab[19] showed a nonsignificant 19% reduction in exacerbations and a modest increase in FEV_1 (60 mL), but it lacked biomarker-based stratification. The study received a total score of 4, reflecting moderate design quality and uncertain efficacy.

Astegolimab[21] and tezepelumab[22] each demonstrated modest, non-significant reductions in exacerbations (~17–20%), with negligible (or negative) lung function changes. Neither agent used biomarker enrichment, and small-to-moderate sample sizes limited statistical power. They received total scores of 3 and 4, respectively.

Infliximab, assessed in two trials,[23,24] showed inconsistent effects: one reported a non-significant 12% exacerbation reduction, while the other lacked a primary efficacy analysis. Neither employed biomarker stratification, and the mean total score was 2.0.

Canakinumab,[25] MEDI8968,[26] ABX-IL8,[27] and CNTO6785[28] failed to demonstrate significant efficacy or improvement in FEV_1. All lacked biomarker enrichment, and most were small, early-phase studies. Scores ranged from 1 to 3, indicating limited clinical relevance and low evidence quality.

Discussion

The present analysis underscores the evolving role of mAbs in the treatment of COPD. The study emphasizes the importance of inflammatory endotyping, biomarker-guided stratification, and patient selection. However, the composite MCDA scores, which were created by integrating efficacy (exacerbation reduction and lung function), biomarker-based stratification, and trial quality, revealed a distinct performance gradient among biologic therapies. Indeed, subjects who were targeted for T2 inflammation demonstrated the most consistent clinical benefits, particularly for patients with eosinophilic COPD. Nevertheless, it must be noted that the marked variation observed in the baseline characteristics of populations in the examined studies, which include age, sex distribution, smoking status, exacerbation burden, and lung function, might have affected the response to treatment. This underscores the critical need for standardized phenotyping and reporting procedures.

Within our MCDA framework, dupilumab achieved the highest total scores, driven by substantial reductions in exacerbations and improvements in lung function in two robust, well-powered, and eosinophil-enriched phase 3 trials

(BOREAS[17] and NOTUS).[18] These findings reinforce the strong therapeutic potential of dupilumab in patients with frequent exacerbations and elevated BECs (≥300/μL) and provide compelling evidence for the application of precision medicine in COPD. In T2-high COPD, upstream IL-4/IL-13 blockade with dupilumab targets the epithelial- and mucus-centered mechanisms[37] that drive exacerbations and airflow limitation, leading to reproducible benefits in phase 3 trials.[38]

By contrast, anti-IL-5 therapies, which act primarily through eosinophil depletion,[39] have shown smaller and less consistent effects, likely because IL-13–mediated epithelial and mucus pathology remains unaddressed. Among anti-IL-5 agents, mepolizumab demonstrated variable efficacy, with the most favorable outcomes observed in biomarker-selected populations. The METREX and METREO trials[14] showed a modest yet clinically significant reduction in exacerbations among eosinophilic subgroups. More recent, large-scale studies[15,16] have strengthened the evidence base by confirming consistent benefits in patients with high exacerbation rates and elevated BECs. Variability in mepolizumab's performance likely reflects differences in study design, BEC thresholds, and patient demographics, emphasizing the need for enhanced enrichment methods to optimize its therapeutic capabilities. Despite this variability, the consistent targeting of IL-5 by mepolizumab and its favorable safety profile remain clinically relevant, particularly as emerging evidence clarifies the optimal selection criteria. Indeed, in the Flynn et al[15] and Sciurba et al[16] trials, which employed eosinophilic stratification (BEC ≥150 or ≥300/μL), the MCDA scores were 6 and 8, respectively, resulting in a mean score of 7.0 across the two trials. This finding positions mepolizumab as a viable and beneficial option in biomarker-selected COPD subgroups, albeit with a narrower efficacy spectrum compared to dupilumab. Given that both agents target eosinophilic inflammation, a head-to-head comparative trial would be necessary to determine whether the broader T2 pathway inhibition by dupilumab offers superior clinical benefits over IL-5 blockade alone.

By contrast, benralizumab, which induces eosinophil depletion via IL-5Rα blockade, produced inconclusive findings. Across three trials,[11,12] reductions in exacerbations did not reach statistical significance, and improvements in FEV_1 were modest. This inconsistency may be attributed to varied definitions of biomarkers and heterogeneous trial populations. Without clearer stratification, questions arise about its clinical positioning. While the biological rationale for benralizumab in eosinophilic COPD remains compelling, future studies employing more stringent selection criteria will be necessary to clarify its clinical role.

Biologics that target non-T2 pathways, such as tozorakimab,[20] itepekimab,[19] astegolimab,[21] and tezepelumab,[22] showed limited or inconsistent efficacy. Notably, tozorakimab produced the greatest improvement in FEV_1 of any agent assessed, although this improvement was not accompanied by a reduction in exacerbations. The lack of biomarker-guided inclusion criteria in most of these studies may have obscured potential subgroup benefits, representing a key design limitation. While upstream inflammatory blockade offers theoretical appeal through broader immunomodulation, its clinical impact in COPD may be constrained by the marked heterogeneity and incomplete characterization of inflammatory endotypes.[40] Progress in this domain will require integration of refined diagnostic tools and more precise phenotyping strategies.

Agents targeting non-T2 inflammation, such as infliximab,[23] canakinumab,[25] MEDI8968,[26] anti-IL-8,[27] and anti-IL-17A[28] mAbs, have demonstrated suboptimal performance. Conducted predominantly in unselected populations without biomarker stratification, these studies failed to demonstrate meaningful improvements in exacerbations or lung function. Collectively, these findings suggest that, despite mechanistic plausibility, broad immunosuppressive strategies may lack the specificity and efficacy required for the heterogeneous COPD population. This reinforces the urgent need to define COPD phenotypes more precisely, elucidate the underlying pathobiological mechanisms,[41,42] and ensure appropriate outcome selection before undertaking large-scale trials in unselected populations.

Despite the rigorous methodology employed, which aligns with best practices for MCDA in healthcare decision-making as outlined by the International Society for Pharmacoeconomics and Outcomes Research MCDA Task Force,[43] several limitations warrant consideration. These include reliance on summary-level data, inconsistencies in outcome reporting (eg, missing reports on exacerbation reduction and/or FEV_1 changes in certain trials), small sample sizes in certain trials, and potential publication bias. The heterogeneity across trials, particularly regarding definitions of exacerbation, eosinophil thresholds, study durations, and inclusion criteria, remains a major obstacle to the establishment of uniform, directly comparable evidence.

Conclusion

Biologics that target eosinophilic inflammation, particularly dupilumab and mepolizumab, are considered promising disease-modifying strategies for a well-defined subset of COPD patients. Conversely, the limited efficacy of non-T2 agents underscores the necessity for enhanced mechanistic alignment and precision trial design.

Future studies should prioritize biomarker-enriched populations, standardized outcome measures, and long-term endpoints to clarify the role of mAbs in COPD management and expand treatment options in this heterogeneous disease. Inclusion of cost-effectiveness, long-term safety, and patient preferences would provide a more comprehensive assessment.

Disclosure

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