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Biologic Therapies for Chronic Obstructive Pulmonary Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Despite limited breakthroughs in COPD pharmacotherapy, recent trials have shown promising results for biologics in COPD patients. However, robust evidence synthesis in this area is currently lacking.

Methods: We conducted a systematic review of MEDLINE, EMBASE, and Cochrane CENTRAL from inception to July 17, 2024, to identify randomized trials of biologic medications in patients with COPD. We performed a random effects frequentist network meta-analysis and present the results using relative risk (RR) and 95% confidence intervals (CI). We used the GRADE framework to rate the certainty of the evidence. Outcomes of interest included exacerbations, change in FEV1, change in quality of life, and serious adverse events.

Results: Dupilumab reduced exacerbations as compared to placebo (RR 0.68 [95% CI 0.59 to 0.79]) (high certainty). Benralizumab (RR 0.89 [95% CI 0.78 to 1]), itepekimab (RR 0.81 [95% CI 0.61 to 1.07]) and tezepelumab (RR 0.83 [95% CI 0.61 to 1.12]) may reduce exacerbations as compared to placebo (all low certainty). Dupilumab probably reduced exacerbations more than mepolizumab (RR 0.74 [95% CI 0.62 to 0.89]) (moderate certainty). Dupilumab may reduce exacerbations more than tezepelumab (RR 0.82 [95% CI 1.14]) (low certainty). For all patients, no treatment improved FEV1 above the pre-specified minimal clinically important difference (MCID) of 0.1 L. Dupilumab probably has no meaningful effect on FEV1 compared to placebo (MD 0.07 [95% CI 0.02 to 0.13]) (moderate certainty). However, in the subgroup of patients with blood eosinophils $\geq 300/\text{mL}$, both tezepelumab (MD 0.15 [95% CI 0.05 to 0.26]) and dupilumab (MD 0.13 [95% CI 0.06 to 0.19]) probably improved FEV1 above the MCID.

Conclusion: Dupilumab is effective at improving patient-relevant outcomes in COPD with higher eosinophil levels. Other biological therapies, including tezepelumab, have no important effect on patient-relevant outcomes.

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KEYWORDS

COPD; biologics; network meta-analysis

Background

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder that affects millions of individuals worldwide [1]. There have been limited breakthroughs in COPD pharmacotherapy in recent decades. Biologic therapies have shown to be effective in improving outcomes for patients with eosinophilic asthma [2]; however, individual trials investigating similar biologic therapies have not shown comparable efficacy in patients with COPD, with the exception of the recent BOREAS and NOTUS trials investigating dupilumab for COPD with blood eosinophils [3–6].

Dupilumab is a monoclonal antibody targeting the shared receptor component for interleukin-4 (IL-4) and interleukin-13 (IL-13), cytokines central to Type 2 inflammation [2, 6, 7]. By

inhibiting these pathways, dupilumab reduces eosinophilic inflammation, airway smooth muscle contractility, and mucus production. Mepolizumab and benralizumab target interleukin-5, a cytokine critical for eosinophil recruitment and survival, thereby reducing eosinophil counts and associated airway inflammation [3, 8–10].

Recently, there has been growing interest in the use of biologics targeting epithelial-derived cytokines (EDC) (i.e. often referred to as anti-alarmins) for the treatment of COPD after the success of recent randomized trials, suggesting benefit for patients with asthma regardless of eosinophilic phenotype [2, 11]. Anti-EDCs are a class of biological therapies that target upstream cytokines involved in inflammation and immune response. EDCs have downstream effects on Type 2 cytokines, IL-4 and IL-13, notably the

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targets of dupilumab. If there is indeed an effect on non-eosinophilic airway disease, these molecules may have a greater role in COPD, given that it is a condition more often associated with non-eosinophilic inflammation.

However, a recent phase 2 trial (COURSE) suggested potential benefits in patients with COPD and eosinophils $\geq 150/\text{mCL}$ [12]. This trial was not powered to investigate patients with COPD with blood eosinophils. Phase 3 trials are ongoing to further test the efficacy of tezepelumab in a population of COPD with eosinophils, rather than the broader population studied in COURSE. Given the recent emergence of new evidence regarding dupilumab and tezepelumab for COPD, a potential shared mechanism affecting IL-4 and IL-13, and the lack of studies comparing the effectiveness of anti-EDC therapy versus other biologic therapies for COPD, evidence synthesis and evaluation is needed to help guide the design of future research studies, clarify biomarker utility for biologicals in COPD, and eventually to guide clinicians and patients on appropriate treatment selection.

In this context, we performed a network meta-analysis of the relative efficacy and safety of different biological therapies for COPD, including anti-EDC therapy. This approach can help inform clinical decision-making and guide the development of future research in this field.

Methods

We prepared this manuscript following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analyses (PRISMA-NMA) [13, 14]. We registered a protocol on Open Science Framework on May 2, 2024: <https://osf.io/pgfnr>.

Search strategy and eligibility criteria

We worked with an experienced research librarian to develop a search strategy up to July 17, 2024. We searched Embase, Medline, Cochrane CENTRAL, and clinicaltrials.gov for parallel group randomized trials of COPD patients randomized to any biologic therapy without restrictions based on publication status, language, or date of publication. We included COPD patients of any severity, on any baseline therapies. We included the following biologics: IL-4/13 inhibitors (Dupilumab), IL-5 inhibitors (Mepolizumab, Benralizumab, and Reslizumab), and anti-EDCs (anti-IL-33, anti-IL-25, anti-TSLP). We included patients in the outpatient setting and not in exacerbation. eTable 1 presents our search strategy.

Outcomes of interest included the annualized moderate-to-severe exacerbation rate (AER), change in FEV1 from baseline (in litres), change in disease-specific quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), and serious adverse events. We also report on changes in blood eosinophils.

Screening

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to

screen the titles and abstracts of search records and subsequently the full texts of records deemed potentially eligible at the title and abstract screening stage. Reviewers resolved conflicts through discussion and if necessary, by adjudication with a third party.

Data extraction

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to extract data from eligible studies. Reviewers resolved discrepancies by discussion and if necessary, by adjudication with a third party. We collected information on baseline characteristics (age, sex), disease severity (baseline FEV1), concurrent therapy, and blood eosinophil count.

Risk of bias assessments

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to assess the risk of bias using the revised Cochrane risk of bias tool (RoB 2) [2, 15, 16]. Reviewers resolved discrepancies by discussion and if necessary, by adjudication with a third party.

Data synthesis and analysis

We reported dichotomous outcomes as RRs and continuous outcomes as mean differences with associated 95% confidence intervals. For dichotomous outcomes, we calculated absolute effects expressed as events per 1,000 patients, using the median risk in the standard care and placebo arms.

We first performed direct pairwise meta-analysis using a random effects meta-analysis for all comparisons. Then, for all outcomes, we performed frequentist random-effects network meta-analysis using the restricted maximum likelihood (REML) estimator. We grouped drugs with similar mechanisms of action into the same node. For trials reporting on varying doses, we pooled the results of the multiple doses.

For each comparison, to test for subgroup effects, we performed pairwise meta-regressions for important comparisons, including the risk of bias and baseline FEV1. We summarized heterogeneity, for both pairwise and network estimates, using the I^2 statistic and interpreted an I^2 value of 0% to 40% as not important, 30% to 60% as moderate heterogeneity, and 50% to 90% as substantial heterogeneity and 75% to 100% may represent considerable heterogeneity [17].

We assessed for local incoherence by node-splitting. Incoherence refers to differences in estimates between direct and indirect comparisons. For example, trials that directly compare two treatments may yield different results from the indirect network estimate for the comparisons between the two treatments due to differences in disease etiology, severity, or methods for the measurement of outcomes between trials that contributed to the direct estimates and trials that contributed to the indirect estimates [10]. If we observed evidence of incoherence, we looked for sources of incoherence and split nodes and networks when necessary. We

assessed for transitivity—comparability of trials in the network – by examining the distribution of potential effect modifiers across comparisons in the network [17].

We performed all analyses using the *meta* and *netmeta* packages in R (version 4.1.2) and produced network plots using the network plot command in Stata version 18.0 [18, 19].

Subgroups

We assessed subgroups using pairwise subgroup analyses. We used the following moderators: eosinophil count (high defined as ≥ 300 cells/mcL, low as < 300 cells/mcL) and baseline FEV1 (% predicted). For trials that reported on eosinophil count subgroups at different levels, we selected the ones closest to 300 cells/mcL. We expected that patients with higher eosinophils would have a larger and more positive effect as compared to those with lower eosinophil counts, based on previous research [2, 20]. Of note, both the BOREAS and NOTUS studies required blood eosinophils ≥ 300 cells/mcL during the screening period but provided subgroup analysis based on blood eosinophils that were measured prior to randomization.

Assessment of the certainty (quality) of evidence

We evaluated the certainty of evidence using the GRADE approach for network meta-analysis [21–23]. For each outcome, we rated the certainty of each comparison as either high, moderate, low, or very low based on the risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision. We made judgments of imprecision using the minimally contextualized approach and sourced minimally important differences for outcomes from the literature or by consensus by authors [24].

For a change in FEV1, we used a change of 100 mL as minimally important. For SGRQ, we used a 4-unit change as minimally important [25, 26]. For acute exacerbations, mortality, and serious adverse events, we used the null effect as minimally important.

Results

Our search identified 5215 unique citations and 103 met the criteria for full-text review (Figure 1). Of these, 93 were excluded, most commonly because they had the wrong study design or were duplicates of other studies. Eleven trials (6392 patients) met the criteria for inclusion in the study [3–6, 12, 27–30].

Risk of bias

Most trials were rated at low or probably low risk of bias. For acute exacerbations, we found one trial at risk of bias due to bias arising from missing data. Figure 2 and eTable 2 present more details on the risk of bias assessments for all outcomes.

Network meta-analysis

Figure 3 and eFigures 1–16 present the network and pairwise forest plots for all analyses. Our network was connected *via* placebo as there were no head-to-head trials included in the analysis (eFigures 17–20).

Because we did not have direct trials to generate node split models, we were unable to assess for incoherence properly. However, based on the similarity of the trials and overall low heterogeneity, we did not have a significant concern for incoherence in the analysis. Our analysis of baseline characteristics and subgroups did not find evidence of intransitivity.

We found no to unimportant heterogeneity for acute exacerbations ($I^2 = 0\%$ [0.0%; 79.2%]), change in SGRQ ($I^2 = 6.4\%$ [0.0%; 80.5%]), and serious adverse events ($I^2 = 0\%$ [0.0%; 79.2%]) and moderate heterogeneity for change in FEV1 ($I^2 = 54.9\%$ [0.0%; 83.3%]).

Trial characteristics

Most trials predominantly enrolled male participants, ranging from a mean of 56.5% to 70.7%, with a mean age of 63.7 to 69.1 years old (Table 1). The participants were included across 48 different countries and six continents.

Participants' mean FEV1 (% predicted) ranged from 43.1% to 50.1%, and they typically had at least 2 moderate-to-severe exacerbations in the prior year to randomization. Baseline eosinophils (cells/mcL) varied significantly, with mean levels ranging from 191.1 to 504. Mean BMI was similar across included trials (range 26.55 to 27.9).

Most patients were already on stable inhaled triple therapy (long-acting beta-agonist, long-acting muscarinic antagonist, and inhaled corticosteroid) on enrollment, although one trial had only 45.54% of patients on triple therapy on enrollment. Most trials excluded patients with asthma, but two trials allowed for a previous or current diagnosis of asthma, albeit with approximately 5–6% in each trial only.

The two trials studying dupilumab only included participants with blood eosinophils ≥ 300 cells/mcL. However, both trials reported on subgroups with either maximum eosinophils lower than 500 cells/mcL (BOREAS) [6] or baseline eosinophils < 300 cells/mcL (NOTUS) [6, 27]. A 2014 trial of benralizumab included participants with sputum eosinophils $\geq 3\%$ during screening or historically [28], while the more recent trials of benralizumab were enriched for patients with blood eosinophils ≥ 220 cells/mcL [4].

For subgroup analyses, one trial reported on eosinophil subgroups with a maximum of 500 cells/mcL [6], six reported subgroups at a level of 300 cells/mcL [3, 4, 12, 27–29], and one reported subgroup at a level of 250 cells/mcL [5].

Exacerbations

Ten trials reported exacerbations, including 6,374 patients, with a mean follow-up of 52 weeks.

Dupilumab reduced exacerbations as compared to placebo (RR 0.68 [95% CI 0.59 to 0.79]) (high certainty).

Benralizumab (RR 0.89 [95% CI 0.78 to 1.00]), itepekimab (RR 0.81 [95% CI 0.61 to 1.07]) and tezepelumab

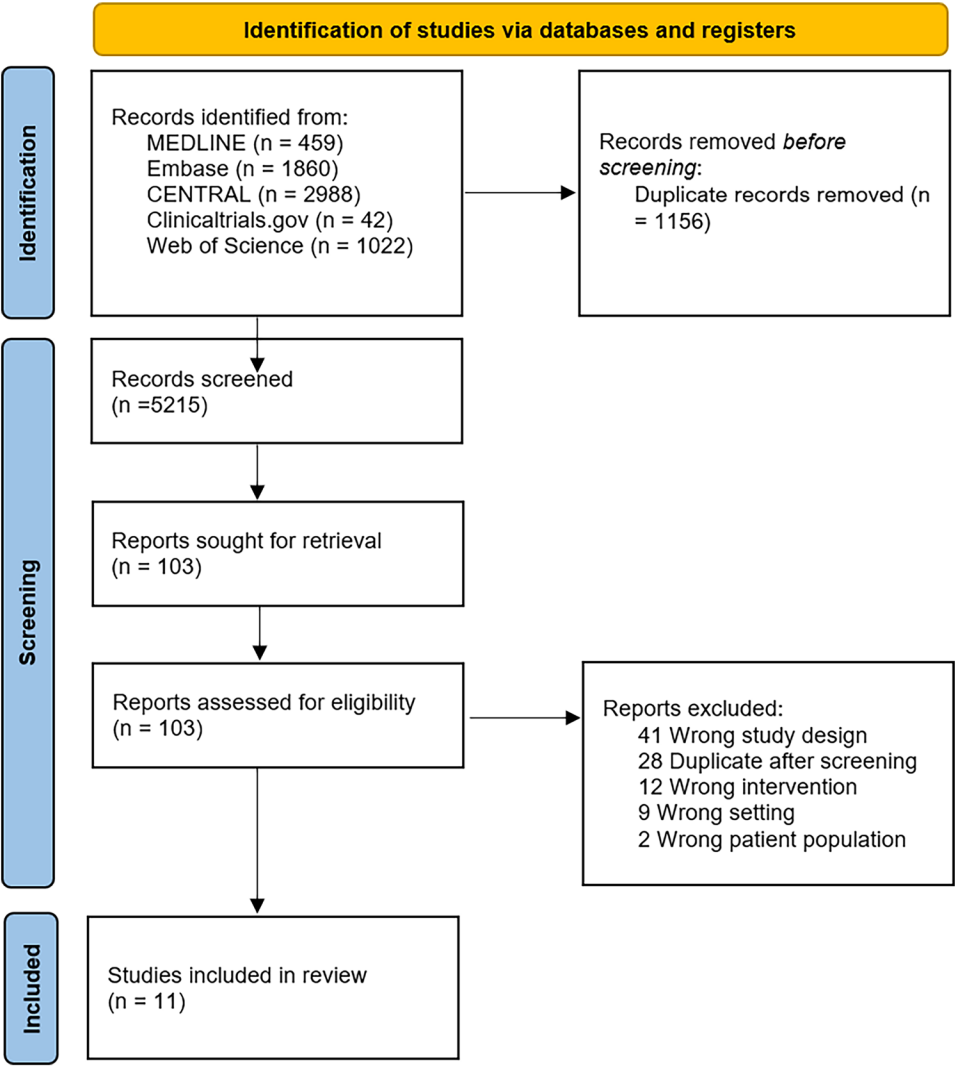


Figure 1. PRISMA diagram presenting the inclusion and exclusion process of our systematic review.

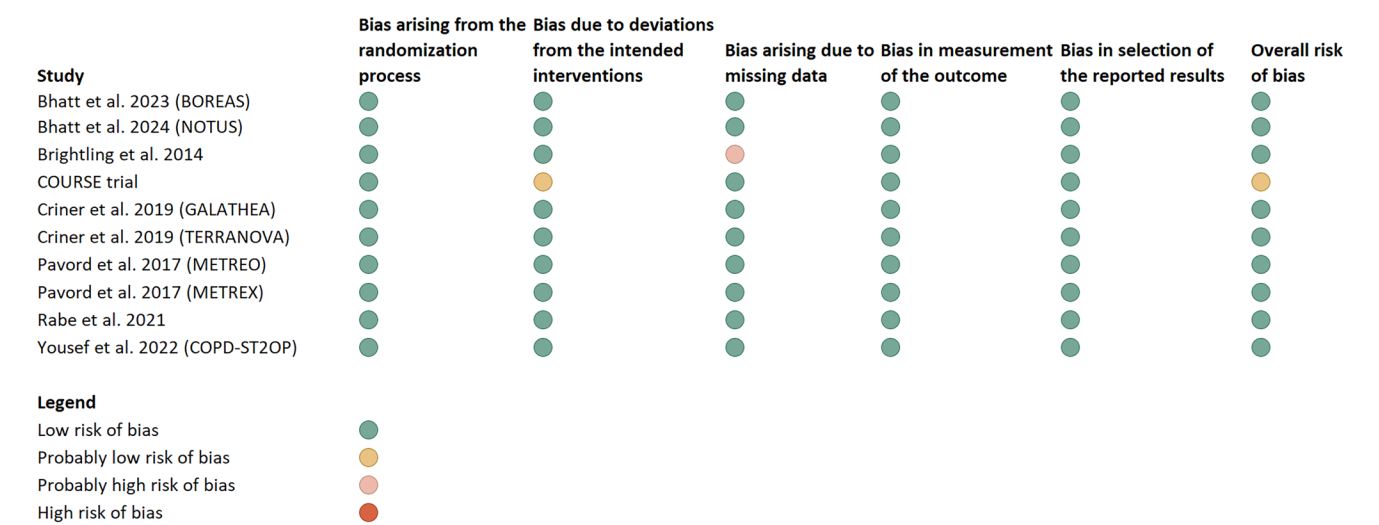


Figure 2. Risk of bias assessments for exacerbations using the revised Cochrane risk of bias tool (RoB 2).

(RR 0.83 [95% CI 0.61 to 1.12]) may reduce exacerbations as compared to placebo (all low certainty) (Table 2 and Figure 3)).

Mepolizumab may have no important effect on reducing exacerbations as compared to placebo (RR 0.92 [95% CI 0.82 to 1.03]) (low certainty).

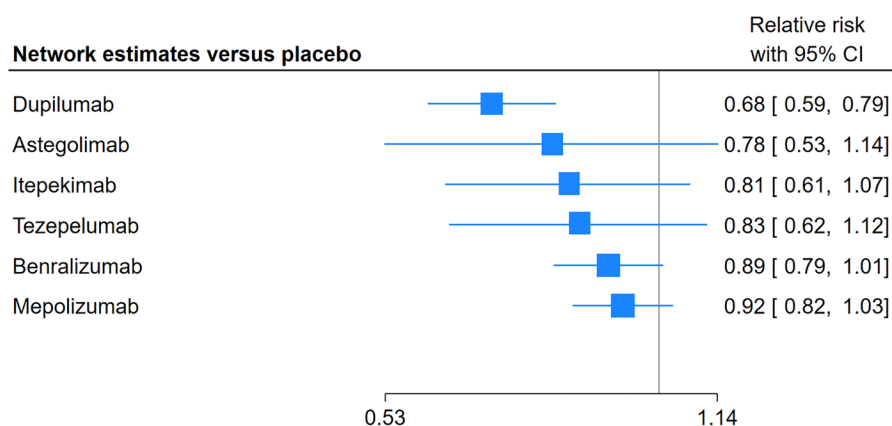


Figure 3. Network Forest plot comparing the effectiveness of existing biologics in reducing exacerbations in COPD, presented in relative risk (RR) and 95% confidence intervals (95% CI).

Table 1. Trial characteristics of the included studies.

Study	Registration	Male (%)	Age	Moderate-to-severe exacerbations in prior year (rate)	Blood eosinophil (cells/uL)	FEV1 (%)	BMI	Triple therapy (%)	Asthma diagnosis (%)	Treatment	Number	Comparison	Number
Bhatt et al. 2023 (BOREAS) ⁶	NCT03930732	66.0	65.1	2.3	401.0	NR	27.6	97.6	0.0	Dupilumab	468	Placebo	471
Pavord et al. 2017 (METREX) ³	NCT02105948	62.0	65.5	2.5	275.0	44.2	NR	94.5	0.0	Mepolizumab	233	Placebo	229
Pavord et al. 2017 (METREO) ³	NCT02105961	66.0	65.0	2.7	306.7	46	NR	96.0	0.0	Mepolizumab	448	Placebo	226
Brightling et al. 2014 ²⁸	NCT01227278	63.6	63.7	1.6	239.1	47.02	26.5	45.5	0.0	Benralizumab	51	Placebo	50
Criner et al. 2019 (GALATHEA) ⁴	NCT02138916	70.7	65.6	2.3	435.2	43.1	27.5	69.6	5.4	Benralizumab	761	Placebo	359
Criner et al. 2019 (TERRANOVA) ⁴	NCT02155660	66.3	65.2	2.3	504.5	45	26.8	58.6	6.1	Benralizumab	1157	Placebo	229
Yousef et al. 2022 (COPD-ST2OP) ²⁹	NCT03615040	63.4	69.1	3.1	191.1	46.6	26.8	78.0	NR	Astegolimab	42	Placebo	39
Rabe et al. 2021 ⁵	NCT03546907	57.0	63.8	2.2	300.0	45.6	NR	66.0	0.0	Itepekimab	172	Placebo	171
Bhatt et al. 2024 (NOTUS) ²⁷	NCT04456673	67.6	65.0	2.1	407.0	50.1	27.9	98.8	0.0	Dupilumab	470	Placebo	465
Singh et al. 2024 (COURSE) ¹²	NCT04039113	56.5	67.7	2.7	205.0	40.9	27.1	100	0.0	Tezepelumab	165	Placebo	168
Dasgupta et al. 2017 ³⁰	NCT01463644	72.2	66.0	>=1	490.0	40.8	NR	NR	NR	Mepolizumab	8	Placebo	10

NR: not reported; FEV1: forced expiratory volume in 1s; BMI: body mass index.

Dupilumab probably reduced exacerbations more as compared to mepolizumab (RR 0.74 [95% CI 0.62 to 0.89]) (moderate certainty) (eTable 3). Dupilumab may reduce exacerbations more than tezepelumab (RR 0.82 [95% CI 0.59 to 1.14]) (low certainty).

We did not find a credible subgroup effect based on high versus low eosinophil counts. Although there was a larger benefit for dupilumab in the high eosinophil subgroup, this was not significantly different from the effect in the low eosinophil group ($p=0.31$). Figure 4 presents the subgroup analysis.

Change in FEV1 (L)

Ten trials, including 4,730 patients, reported on change in FEV1 (L), with a median follow-up of 52 weeks.

For all patients, no treatment improved FEV1 above the pre-specified MCID of 0.1 L (Table 2, eTable 4). Dupilumab

(MD 0.07 [95% CI 0.02 to 0.13]) and mepolizumab (MD 0.06 [95% CI 0.01 to 0.11]) probably had no significant effect on FEV1 more than placebo (moderate certainty).

Astegolimab (MD 0.04 [95% CI -0.04 to 0.12]), benralizumab (MD -0.00 [95% CI -0.05 to 0.05]), and itepekimab (MD 0.06 [95% CI -0.02 to 0.14]) may not improve FEV1 as compared to placebo (all low certainty).

Using the ICEMAN tool, we did not find a credible subgroup effect based on high versus low eosinophil counts. In the higher eosinophil group, both tezepelumab (MD 0.15 [95% CI 0.05 to 0.26]) and dupilumab (MD 0.13 [95% CI 0.06 to 0.19]) probably improved FEV1 above the MCID. Figure 5 presents the subgroup analysis.

Change in SGRQ

Nine trials, including 4,385 patients, reported on change in SGRQ with a median follow-up of 52 weeks.

Table 2. Summary of findings table for network estimates of biologic medications vs. placebo for COPD across included outcomes.

Treatment	Efficacy outcomes						Safety outcomes	
	Acute exacerbations		Change in FEV1 (L)		Change in SGRQ		Serious adverse events	
	RR (95% CI)	GRADE	MD (95% CI)	GRADE	MD (95% CI)	GRADE	RR (95% CI)	GRADE
Astegolimab	0.78 (0.53 to 1.14)	✓	0.04 (−0.04 to 0.12)	✓✓	−4.10 (−7.60 to −0.60)	✓✓	0.70 (0.38 to 1.28)	✓✓
Benralizumab	0.89 (0.78 to 1.0)	✓✓	−0.001 (−0.05 to 0.05)	✓✓	−1.56 (−3.26 to 0.13)	✓✓	0.96 (0.86 to 1.07)	✓✓✓
Dupilumab	0.68 (0.59 to 0.79)	✓✓✓✓	0.07 (0.02 to 0.13)	✓✓✓	−3.35 (−5.09 to −1.60)	✓✓✓	0.85 (0.68 to 1.06)	✓✓✓
Itepekimab	0.81 (0.61 to 1.07)	✓✓	0.06 (−0.02 to 0.14)	✓✓	–	–	0.80 (0.52 to 1.24)	✓✓
Mepolizumab	0.92 (0.82 to 1.03)	✓✓✓	0.06 (0.01 to 0.11)	✓✓✓	−0.28 (−2.08 to 1.53)	✓✓	0.87 (0.73 to 1.03)	✓✓✓
Tezepelumab	0.83 (0.61 to 1.12)	✓✓	0.05 (−0.02 to 0.13)	✓✓	−2.94 (−6.34 to 0.46)	✓✓	–	–

RR: relative risk; MD: mean difference; CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; FEV1: forced vital capacity in one second.

All included estimates are network estimates.

High certainty (very confident that true effect lies close to that of effect estimate), moderate certainty (moderately confident in effect estimate; the true effect is likely to be close to effect estimate, but there is a possibility that it is substantially different), low certainty (confidence in the effect estimate is limited; true effect may be substantially different from the effect estimate) or very low certainty: (very little confidence in the effect estimate; true effect is likely to be substantially different from the effect estimate).

✓✓✓✓=high certainty.

✓✓✓=moderate certainty.

✓✓=low certainty.

✓=very low certainty.

Dupilumab probably improved quality of life as measured by change in SGRQ compared to placebo (MD −3.35 [95% −5.09 to −1.60]) (moderate certainty), albeit not quite meeting the MCID (Table 2). Astegolimab may improve SGRQ as compared to placebo (MD −4.10 [95% CI −7.60 to −0.60]) (low certainty).

No other treatments improved SGRQ compared to placebo. No biologics improved SGRQ compared to other biologics (eTable 5).

Serious adverse events

Nine trials reported on serious adverse events, including 7603 patients, with a median follow-up of 52 weeks.

Dupilumab (RR 0.85 [95% CI 0.68 to 1.06]), benralizumab (RR 0.96 [95% CI 0.86 to 1.07]), and mepolizumab (RR 0.87 [95% CI 0.73 to 1.03]) probably do not increase the risk of serious adverse events as compared to placebo (all moderate certainty) (Table 2). Astegolimab may not increase the risk of serious adverse events as compared to placebo (RR 0.70 [95% CI 0.38 to 1.28]) (low certainty). The risk of serious adverse events did not differ significantly between biologics (eTable 6).

Table 2 presents the summary of findings table.

Change in blood eosinophilia

Eight trials reported on change in blood eosinophilia, including 6057 patients, with a median follow-up of 52 weeks. Both benralizumab (MD −301 cells/mcL [95% CI −330 to −300]) and mepolizumab (MD −230 cells/mcL [95% CI −310 to −150]) reduced blood eosinophilia as compared to placebo. In comparison, dupilumab barely reduced blood eosinophilia (MD −10 cells/mcL [95% −20 to −10]). eFigure 21 presents the network forest plot.

No other biomarkers were available for network meta-analysis.

Discussion

Main findings

Our study found that dupilumab reduced moderate-to-severe exacerbations in COPD with elevated blood eosinophils, with no subgroup effect based on peripheral eosinophil count at randomization, with moderate certainty evidence. No other monoclonal antibody, including tezepelumab, was effective in reducing exacerbations. While dupilumab showed a greater reduction in exacerbations among participants with eosinophil counts ≥ 300 cells/mcL at randomization, the difference between this group and those with lower eosinophil counts was not statistically significant. The significance of eosinophil-based subgroup analysis for dupilumab is questionable given that all participants required eosinophils ≥ 300 cells/mcL at screening. This could explain the lack of difference in outcomes based on blood eosinophils for this biologic.

No treatment, including dupilumab and tezepelumab, significantly improved FEV1 (L) compared to placebo above the pre-specified MCID. However, in patients with eosinophil counts ≥ 300 /mcL at randomization, both dupilumab and tezepelumab showed improvement in FEV1 (L) compared to placebo, with no statistically significant subgroup difference between networks. The subgroup was borderline significant, but when assessing the credibility of the subgroup with the ICEMAN tool, we found low credibility overall given the current evidence.

Dupilumab also may improve quality of life as measured by changes in SGRQ, although this improvement was just below the pre-specified MCID. Interestingly, astegolimab appeared to improve respiratory-related quality of life but did not reduce acute exacerbations or improve FEV1 (L). There

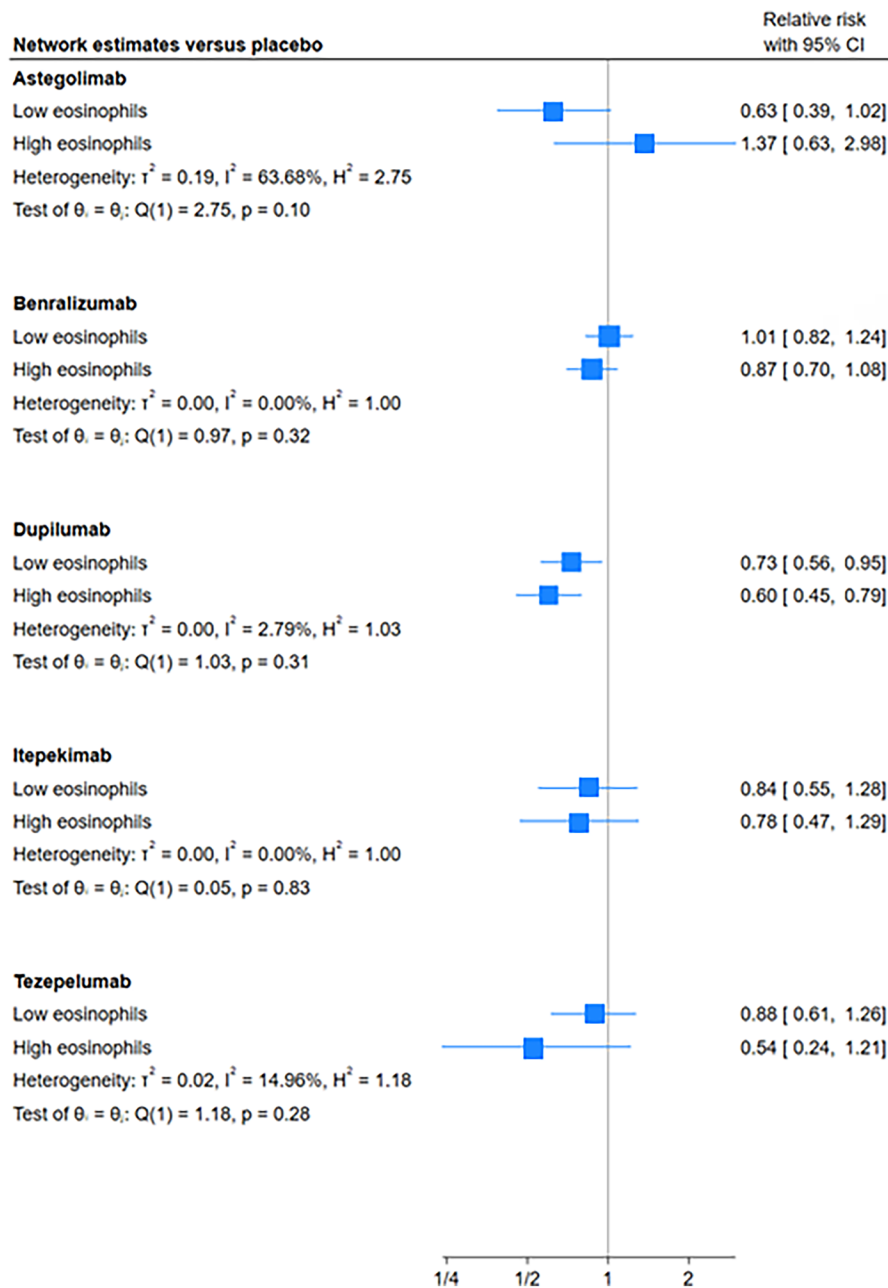


Figure 4. Network subgroup comparison of exacerbation network estimate in patients with high eosinophils versus low (i.e. ≥ 300 cells/mL vs. < 300 cells/mL).

was a statistically significant subgroup effect when assessing the networks of low and higher eosinophil groups. However, the credibility of this subgroup was very low. No treatment was associated with an increased risk of adverse effects.

In relation to previous findings

Post-hoc analyses of both the METRO and METREX studies showed that mepolizumab reduced exacerbations in patients with COPD and high blood eosinophils, irrespective of the dose administered [9]. Previous systematic reviews have suggested benefit for IL-5 inhibitors for patients with COPD with blood eosinophils [8, 10]. However, the certainty of the evidence was limited and based on subgroup analyses, without credibility assessments and with reliance on dose analysis. Furthermore, the inclusion of participants with

undiagnosed asthma complicates the interpretation of the effectiveness of anti Type 2 biologicals. Therefore, biologicals have not yet been approved for COPD and current guidelines have not made recommendations supporting their use.

Compared to previous analyses, we did not find compelling evidence that IL-5 inhibitors were effective at reducing exacerbations, improving lung function, or improving quality of life. Only dupilumab demonstrated consistent benefit across patient-important outcomes, and this occurred in a population of COPD patients enriched for the eosinophilic phenotype. In terms of anti-EDC, data are limited to Phase 2 studies. In this context, Asteogolimab, which blocks the target for IL-33, shows promise for low blood eosinophil groups, while Tezepelumab, which blocks thymic stromal lymphopoietin, shows promise for high blood eosinophil groups.

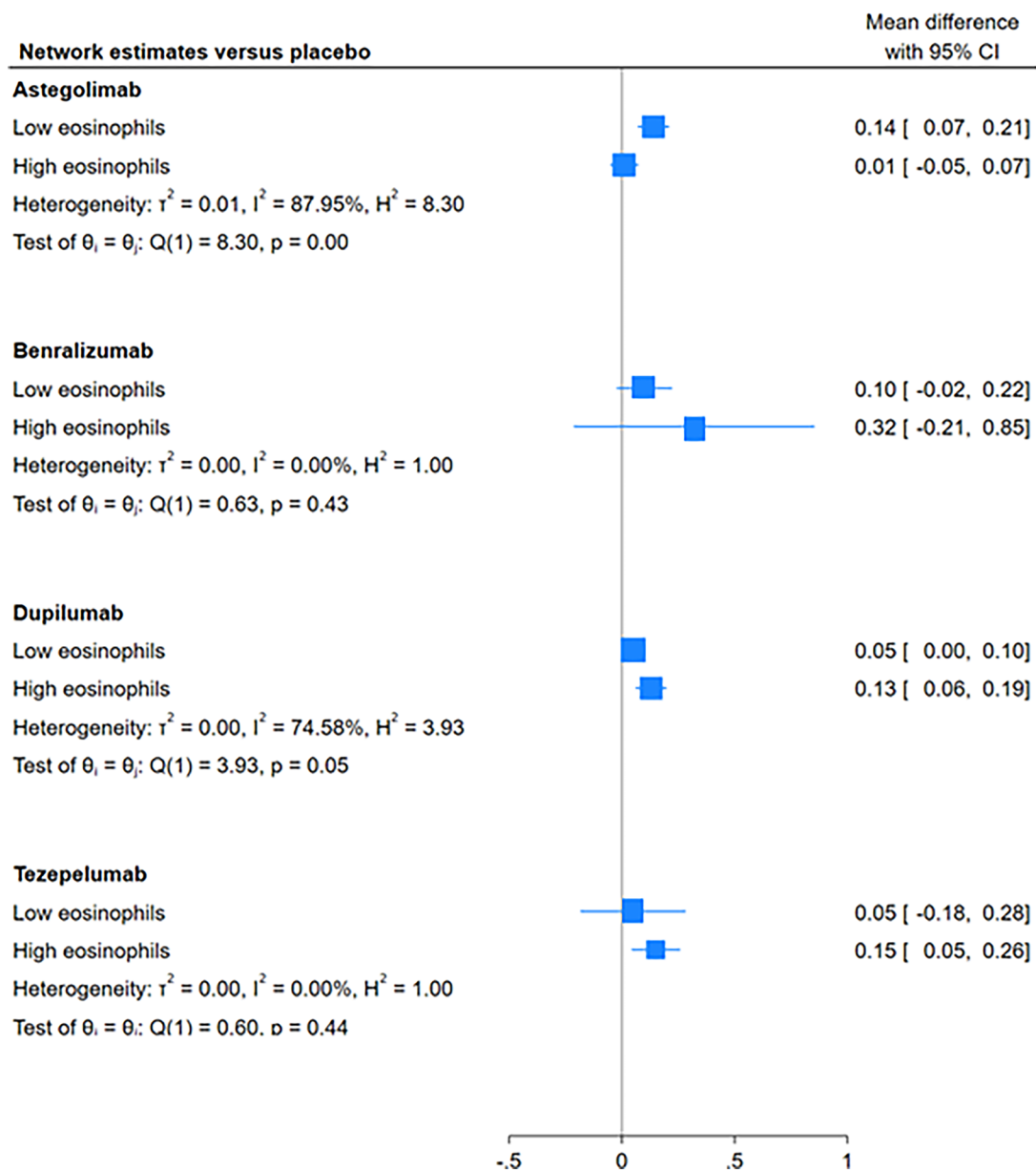


Figure 5. Network subgroup comparison of change in FEV1 (L) network estimate in patients with high eosinophils versus low (i.e. ≥ 300 cells/uL vs. < 300 cells/mcL).

Amongst the biologicals, network meta-analysis provides support only for Dupilumab. This may be related to enrichment for the eosinophilic phenotype in the corresponding trials, but also potentially differences in mechanism of action. Unlike biologicals targeting IL-5, Dupilumab is considered to have multiple mechanisms via the blockade of IL-4 and IL-13, including reducing mucus production, airway smooth muscle contractility, IgE class switching, as well as airway eosinophilia. Interestingly, there are similar results for eosinophilic asthma, where previous network meta-analyses shown a relatively larger effect of dupilumab as compared to IL-5 inhibitors [2].

Strengths and limitations

Our review has notable strengths. First, we present the most recently updated systematic review and meta-analysis of biologics for COPD to date, reducing the risk of missing data.

Second, we used the most updated methods for network meta-analyses, including GRADE guidance.

However, we note several limitations as well. First, we performed analyses assuming that arms with different doses could be pooled, thus disregarding a potential dose response relationship. Previous studies do provide reassurance that the effectiveness of some IL-5 inhibitors on COPD did not vary by dose [9].

Second, our analysis only included the phase 2 tezepelumab trial and thus could only offer low certainty assessments based on sparse data compared to existing biologic treatments. Therefore, our review will need to be updated as emerging evidence is available [12]. Furthermore, our analysis only includes very few studies for each biologic which makes the overall evidence scarce. The combined analysis in a network meta-analysis does improve the overall certainty in the network estimates but more studies would improve the overall confidence in our analysis.

Third, although given the overall homogenous patient population and study design, the risk of violation of coherence is low, without node split models (which require existing head-to-head trials), we are unable to assess for incoherence statistically with existing data. Similarly, all the head-to-head estimates are purely based on indirect estimates. Although unlikely, head-to-head trials of biologics for COPD (i.e. Dupilumab versus Tezepelumab) for eosinophilic COPD would be beneficial.

Fourth, an important limitation of our review is the limited inclusion and analysis of patient-reported outcome measures (PROMs) in the biologic's trials for COPD. PROMs, such as health-related quality of life and symptom burden assessments, provide critical insights into the patient-perceived impact of therapies, complementing clinical and physiological outcomes. PROMs have been shown to correlate with clinical outcomes and hold prognostic value, yet many trials inadequately report or prioritize these measures [31]. Future studies should aim to incorporate PROMs more systematically to capture the subjective benefits of biologic therapies and evaluate their impact on treatment adherence and satisfaction.

Lastly, we attempted to perform subgroup analysis based on blood eosinophils. We encountered several trials using aggregate data. First, not all trials reported on the 300 cells/mcL threshold we pre-specified. BOREAS and NOTUS included patients with blood eosinophils ≥ 300 cells/mcL during the screening period, and thus the subgroup analysis was performed based on blood eosinophil levels prior to randomization. This method is limited, insofar as we used a post-randomization variable for analysis and, this may just reflect the normal variation of blood eosinophilia, making the subgroup effect less reliable. This is an important limitation, as the most important indicator of success of these treatments are blood eosinophilia and proper analysis would require a more accurate assessment of eosinophilia, such as using sputum eosinophils. Furthermore, the recent COURSE trial was not powered to provide subgroup differences and therefore, our analysis requires updating after the phase 3 is completed.

Future directions

The current 2024 GOLD consensus document discuss with cautious optimism the role of biologics in treating patients with COPD [32]. However, no recommendations were made at the most recent update, and no international guidelines have currently made any recommendations for the use of any biologics for COPD. Our analysis supports the use of certain biologics for COPD. However, the mechanism by which Dupilumab works specifically in COPD is not completely clear. Future work should include mechanistic studies to identify biomarkers which will predict response to each specific biological. This type of work would ultimately provide the necessary data for future guidelines to provide clinicians and patients with clear guidance on whom is appropriate and in which stage of treatment biologics should be considered.

Conclusions

Dupilumab is effective at improving patient-relevant outcomes in patients with eosinophilic COPD. Other biological therapies, including anti-EDC, have no important effect on patient-relevant outcomes, but may have a role based on blood eosinophil levels. Future guidelines will need to address and make recommendations around the use of biologics in COPD.

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Data availability statement

All requests can be made to the corresponding author.

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