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Comparative efficacy of mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: A Bayesian network meta-analysis

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Abstract

Background.—The comparative safety and efficacy of the biologics currently approved for asthma is unclear.

Objective.—To compare the safety and efficacy of mepolizumab, benralizumab, and dupilumab in individuals with severe eosinophilic asthma.

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Disclosures:

Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee. All other authors have no conflicts of interest to disclose.

Methods: Systematic review of peer-reviewed literature from 2000 through 2021, and Bayesian network meta-analyses of exacerbation rates, prebronchodilator FEV1, the Asthma Control Questionnaire (ACQ) and serious adverse events (SAE) in individuals with eosinophilic asthma.

Results.—Eight randomized clinical trials (n=6,461) were identified. In individuals with ≥300 eosinophils per microliter (eosin/mcl), in reducing exacerbation rates in comparison to placebo: dupilumab (risk ratio [RR] 0.32; 95% credible interval [CI], 0.23–0.45), mepolizumab (RR, 0.37; 95%CI, 0.30–0.45), and benralizumab (RR, 0.49; 95%CI, 0.43–0.55). In improving FEV1: dupilumab (mean difference in milliliters [MD] 230; [CI], 160–300), benralizumab (MD 150; 95%CI, 100–200), and mepolizumab (MD 150; 95%CI, 66–220); and in reducing ACQ: mepolizumab (MD −0.63; [CI], −0.81 to −0.45), dupilumab (MD −0.48; 95%CI, −0.83 to −0.14), and benralizumab (MD −0.32; 95%CI, 0.43 to −0.21). In individuals with eosinophil counts of 150–299 eosin/mcl, benralizumab (RR, 0.62; 95%CI, 0.52–0.73) and dupilumab (RR, 0.60; 95%CI, 0.38–0.95) were associated with lower exacerbation rates; and only benralizumab (MD 81; 95% CI, 8–150) significantly improved FEV1. These differences were minimal in comparison to clinically important thresholds. For SAE in the overall population, mepolizumab (odds ratio, 0.67; 95% CI, 0.48–0.92) and benralizumab (0.74; 95% CI, 0.59–0.93) were associated with lower odds of a SAE, while dupilumab was not different from placebo (1.0; 95% CI, 0.74–1.4).

Conclusions.—There are minimal differences in the efficacy and safety of mepolizumab, benralizumab, and dupilumab in eosinophilic asthma.

Clinical Implication.—In individuals with eosinophilic asthma, mepolizumab, benralizumab, and dupilumab are similar in their effect on exacerbations, FEV1, or ACQ.

Capsule Summary

While there are some differences in the efficacy of mepolizumab, dupilumab, and benralizumab in the treatment of eosinophilic asthma, these differences are minimal and did not meet clinically important thresholds.

Keywords

asthma; eosinophilic; mepolizumab; benralizumab; dupilumab; network meta-analysis; Bayesian; monoclonal antibody; comparative effectiveness

INTRODUCTION

Although fewer than 10% of individuals with asthma have severe disease, such individuals account for most asthma-related morbidity and mortality.[1,2] While historically inhaled corticosteroids and beta-agonists have constituted mainstays of therapy for individuals with severe asthma, since 2003, several biologic products have been available for those with severe disease. These products, which target various interleukin signaling pathways and include mepolizumab (Nucala), benralizumab (Fasenra) and dupilumab (Dupixent), have been shown in placebo-controlled trials to decrease exacerbation rates, improve lung function and improve quality of life among individuals with severe eosinophilic asthma.[3–6]

Despite their demonstrated efficacy, many questions remain regarding the comparative effectiveness of products since trials that have been performed to date have been placebo

controlled rather than having provided “head-to-head” comparisons.[7,8] We conducted a systematic review of the peer-reviewed and grey literature and a Bayesian network meta-analyses (NMA) to assess the evidence for the comparative efficacy and safety of mepolizumab, benralizumab, and dupilumab. The Bayesian NMA allows simultaneous comparisons of these treatments, rather than pair-wise comparisons, and the generation of a probability-based ranking of their safety and efficacy.

METHODS

Eligibility Criteria

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO #CRD42021232084). We included parallel placebo-controlled randomized controlled trial (RCT) of FDA-approved or bioequivalent doses. We included studies of individuals aged 12 years or older with severe asthma. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and its adaptation for NMA.[9]

Literature Search

We sought articles published from January 1, 2000, through February 17, 2021, in English language, indexed in PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We also reviewed two trial registries, ClinicalTrials.gov and the European Union Clinical Trials Register, and conference abstracts, reference lists of included articles and systematic reviews, and contacted manufacturers of the three biologics to get additional data. We used Covidence systematic review software for title, abstract screening and full-text screening. Two investigators (AA and GL) independently performed the screening, and both independently extracted data from included articles. Discrepancies were resolved through discussion. We extracted details of the trial design, interventions, comparator, outcomes of interest, baseline characteristics, and results.

Efficacy Outcomes and Safety

The primary outcome of interest was clinically significant exacerbations, and secondary outcomes included prebronchodilator forced expiratory volume in 1 second (FEV1) and asthma control questionnaire score using Asthma Control Questionnaire (ACQ) version 5 or 6. To account for clinical heterogeneity given that the eosinophil count is a modifier of the therapeutic effects of these treatments and based on prespecified strata commonly reported in the RCTs, we focused on groups with eosinophil counts of ≥300 cells per microliter (cells/mcL) and between 150–299 cells/mcL. The occurrence of serious adverse events (SAE) in the overall population was our safety outcome of interest. Treatment effect was assessed at the follow up time designated by each study given prior evidence that the length of follow up did not influence biologic efficacy.[10]

In the case of multiple records pertaining to the same trial, we collected and analyzed the data as a single study. For these trials, we initially collected data from the original full text publication and then extracted any missing relevant data from published secondary analyses

of the main trials. In the case of discrepancies, we used the most complete data set. For pooled reports, we treated each trial as a separate study in the analysis.

Risk of Bias and Certainty of Evidence Assessment

We used the Cochrane Collaboration's tool (version 2.0, RoB2) in assessing the risk of bias of each included trial.[11] RoB2 assesses bias in each outcome separately across 5 domains: randomization process, deviations from intended interventions, missingness in outcome data, measurement of the outcome and selection of reported results on a scale of low, some, and high risk of bias. Based on these, an overall bias assessment is given to each study. A study with "low" overall bias was judged to be low if all domains were at low risk of bias and "high" if 1 or more domains were at high risk of bias or multiple domains had "some concerns". We considered a study with a dropout rate or missing outcome of ≥10% to have at least "some concerns". A.A and G.L. independently assessed study bias with disagreements resolved by discussion. We employed The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating the certainty in evidence from NMA and incorporated this in the interpretation of results.[12,13] Domains included were the risk of bias, inconsistency and heterogeneity of estimates for which we compared the placebo effects in all included trials, indirectness or intransitivity, imprecision, and publication bias.

Statistical Analysis

We fitted Bayesian NMA models with generalized linear models.[14] For exacerbation rate, we estimated risk ratios between two treatments, and for continuous outcomes (FEV1 and ACQ) we estimated mean differences. We considered NMA with fixed effects assuming ignorable heterogeneity across studies, and alternatively, random effects accounting for between-study heterogeneity. We made conclusions based on results from the fixed-effect models as the relatively small number of included trials made it difficult to estimate variability of random effects, given the low tau-squared, and given that the results from both models were similar both qualitatively and quantitatively. For SAEs, the counts of events in individual trial arms were analyzed to estimate the overall odds ratios (ORs) between intervention arms and the comparator arms. In sensitivity analyses, we incorporated the risk of bias assessment by excluding studies that were rated as having at least "some bias" on the specific outcome. In further sensitivity analyses, we excluded the intervention arms with non-FDA approved doses from the meta-analyses.

Bayesian models estimate treatment effects via Markov chain Monte Carlo algorithms. We used noninformative priors so that results are driven primarily by the observed trial data. Primary analyses were conducted using the *gemtc* package in R, version 4.0.2, with 4 parallel Markov chains consisting of 50,000 samples after a 20,000-sample burn-in.[14] Given that all data were from indirect treatment comparisons, i.e. no head-to-head RCTs, we were unable to assess statistical inconsistency.[15] Convergence of Markov chains was evaluated by trace plots and Gelman-Rubin diagnostic statistics.[16]

Based on the results of the NMA, we calculated each biologic's rank using the probability that a given biologic would be the best, second best, or worst for an outcome and the Surface

Under the Cumulative Ranking (SUCRA) score.[17] The SUCRA score accounts for both the magnitude of the point estimate and the uncertainty of the estimate. A higher SUCRA value indicates that a biologic has a higher probability of being more effective in improving the outcome in comparison to the other biologics.[17] Additional details of the SUCRA is shown in Section 1.1 in the Supplementary appendix. We ranked each biologic based on SUCRA with respect to each efficacy outcome. Given that clinicians may also be interested in the biologic that is likely to improve two or more outcomes, we plotted correlograms of ranks in pairs of outcomes.

Finally, we evaluated the probability that each treatment improved that outcome for varying thresholds up to a clinically important threshold. The validated minimal clinically important difference (MCID) for ACQ is a reduction of ≥0.5.[18] For exacerbation rates and FEV1, there are currently no validated MCID for FEV1 reduction in individuals with asthma.[19] However, for exacerbations, we defined the MCID as a reduction of at least 50% in annualized rate, and for FEV1, we considered the MCID to be an increase of 100 milliliters or more in FEV 1.

RESULTS

Study Selection and Network

Of 2040 unique studies that were screened, we identified 105 for full text review and 8 for inclusion in the meta-analyses (eFigure 1 and eTable1). All eight were randomized placebo-controlled trials which included 6,461 patients, 3 each compared mepolizumab[20–22] and benralizumab to placebo,[23–25] while 2 compared dupilumab[26,27] to placebo. (Table 1)

For benralizumab, we were able to extract some of the data for the ITT population by eosinophil thresholds of interest from a pooled follow-on study using the SIROCCO and CALIMA data (but CALIMA data included only patients on high dose ICS/LABA which was 1091 of the original 1306 patients).[28] For mepolizumab, data for the eosinophil subgroup of 150–299 cells/mcL were retrieved from a follow-on pooled MENSA and MUSCA study.[29] For DREAM, data for the eosinophil subgroups for exacerbation rates were available from a follow-on study.[30] However, we did not include data for FEV1 and ACQ from this study because data were presented as integrated analyses across the three doses of the intervention arms in DREAM (75 mg, 250 mg, and 750 mg, all administered intravenously) and the latter two doses are not considered bioequivalent to the FDA-approved dose of 100 mg administered subcutaneously.[21,30,31] We assessed the ACQ outcome only in the subgroup with eosinophils ≥300 cells/mcL because only a few of the studies with eosinophil count of 150–299 cells/mcL reported the ACQ outcome in this subgroup. The safety outcome, serious adverse events, was available for all studies.

Study and Patient Characteristics

The mean age of patients ranged from 48 to 53 years, and 57% to 66% of the trial populations were women (eTable 2). In studies where racial or ethnic proportions were reported, whites made up the larger proportion of patients (73–90%). A total of 49% in MENSA-mepolizumab study to 69% in QUEST-dupilumab study had allergic rhinitis at

baseline, while 10–23% reported nasal polyposis. Follow-up duration for all the included studies was 24 to 56 weeks. Risk of bias was noted for 4 trials with missing data, and 2 trials with some concerns due to un-prespecified analyses. (eTable 3) There was no strong evidence of publication bias. (eFigure 3)

Network Meta-analysis of Efficacy Outcomes

In the subgroup of patients with eosinophil counts of ≥300 cells/mcL, all three biologics were significantly better than placebo in reducing exacerbations: dupilumab (risk ratio [RR] 0.32; 95% credible interval [CI], 0.23–0.45), mepolizumab (RR, 0.37; 95%CI, 0.30–0.45), and benralizumab (RR, 0.49; 95%CI, 0.43–0.55); improving FEV1: dupilumab (mean difference in milliliters [MD] 230; [CI], 160–300), benralizumab (MD 150; 95%CI, 100–200), and mepolizumab (MD 150; 95%CI, 66–220); and reducing ACQ: mepolizumab (MD −0.63; [CI], −0.81 to −0.45), dupilumab (MD −0.48; 95%CI, −0.83 to −0.14), and benralizumab (MD −0.32; 95%CI, −0.43 to −0.21). (eFigures 2A–C) Dupilumab was significantly better than benralizumab in improving exacerbations (risk ratio [RR] 0.66, 95% credible intervals [CrI] 0.47–0.94) with mepolizumab also better than benralizumab (RR 0.75, CrI 0.60–0.95). Dupilumab and benralizumab had larger effect sizes on improving FEV1. Mepolizumab significantly improved the ACQ compared to placebo but the effects of dupilumab and benralizumab on ACQ were not significantly different. In patients with eosinophil counts of 150–299 cells/mcl, benralizumab (RR, 0.62; 95%CI, 0.52–0.73) and dupilumab (RR, 0.60; 95%CI, 0.38–0.95) were associated with lower exacerbation rates; and benralizumab (MD 81; 95% CI, 8–150) was associated with improved FEV1 in comparison to placebo. Mepolizumab's effect on FEV1 was similar to benralizumab's effect but this did not reach statistical significance (MD 82; 95% CI, −26 −190). (eFigures 2D–E). Table 2 shows the summary of results and the certainty in evidence as per GRADE criteria which ranged from very low to moderate. Details of how grading was assigned are in the table footnote. All fitted models converged well. In exploration of placebo effects, we found that in the mepolizumab studies, the mean change in FEV1 and ACQ from baseline in the placebo group ranged from 56 to 86 milliliters and −0.40 to −0.59 respectively. In the benralizumab studies, 156 to 239 milliliters and −1.05 to −1.19 respectively, and in the dupilumab studies, 120–210 milliliters and −1.14 to −1.30. Summary of results incorporating the certainty of evidence are shown in Table 2. (eTable 4)

Ranking of the efficacy of the monoclonal antibodies

Figure 1 displays the SUCRA plots for all efficacy outcomes in patients with eosinophils ≥300 cells/mcl. Dupilumab had the highest SUCRA value (i.e., most effective) for both the exacerbation rate reduction and improvement in lung function with a >95% probability of having the highest or second best overall SUCRA score in reducing exacerbation rates and improving lung function. Mepolizumab and benralizumab had a 30% and ~10% chance of being ranked best respectively while placebo had a <1% probability of being ranked best, second best or third best. For ACQ, mepolizumab ranked best and was significantly better than benralizumab in improving ACQ. Figure 2 shows the SUCRA plots for patients with eosinophils of 150–299 cells/mcl. In these patients, benralizumab had the highest SUCRA value in reducing exacerbation rates. Both benralizumab and mepolizumab ranked higher than dupilumab in improving lung function and had similar SUCRA values.

Relative efficacy by varying thresholds up to MCID

In patients with eosinophil counts of ≥300 cells/mcL, all three biologics had a probability of 1 in improving the exacerbation rate by 20% or more (rate ratio: ≤0.80) in comparison to placebo. (eTable 5). This decreased to 0.999, 0.996, and 0.659 for mepolizumab, dupilumab, and benralizumab respectively for a reduction of ≥50% (rate ratio of 0.50) in comparison to placebo. The probability of dupilumab leading to a reduction of 50% or more in comparison to benralizumab was 5.3%. In patients with eosinophil counts of 150–299 cells/mcL, dupilumab had the highest probability of leading to a reduction of ≥50% in exacerbation rate: 0.216 in comparison to placebo, 0.024 in comparison to mepolizumab, and 0.004 in comparison to benralizumab. (eTable 5).

In patients with eosinophil counts of ≥300 cells/mcL, all three biologics had a probability of 1 in improving FEV1 by ≥ 50 milliliters above the placebo effect (eTable 6). Dupilumab also had a probability of 1 in improving FEV1 by at least 100 milliliters when compared to placebo. However, none of the three biologics had an increase of ≥100 milliliters in FEV1 when compared to the other two therapies. In patients with eosinophil counts of-299 cells/mcL, mepolizumab had a probability of 0.852 in improving FEV1 by ≥ 50 milliliters above the placebo effect, benralizumab 0.617, and dupilumab 0.001. In this subgroup, none of the biologics had an increase of ≥100 milliliters in FEV1 when compared to placebo or the other two therapies (eTable 6).

For ACQ in patients with eosinophil counts of ≥300 cells/mcL, all the biologics had a probability of ~0.50 in improving ACQ compared to placebo and compared to the other biologics (eTable 7).

Network Meta-analysis of Safety Outcomes

In the overall population, in order of safety, mepolizumab (odds ratio 0.67; 95% CI, 0.48–0.92) and benralizumab (0.74; 95% CI, 0.59–0.93) were associated with lower odds of a SAE while dupilumab was not different from placebo (1.0; 95% CI, 0.74–1.4) (eFigure 4). Mepolizumab had significantly lower odds of SAE than dupilumab (0.65; 95% CI, 0.41–1.00).

Comparing efficacy and/or safety on pairs of outcomes

Given that patients and clinicians may be interested in the treatment with the higher probability of improving outcomes across multiple domains, we evaluated the optimal biologic for each pair of outcomes. For improvements in both exacerbation rate and FEV1, dupilumab and benralizumab had the largest benefits in those with ≥300 and 150–299 eosinophils/mcl respectively (Figure 3A). To improve both FEV1 and ACQ in those with ≥300 eosinophils/mcl, dupilumab had the highest SUCRA values, and both dupilumab and mepolizumab had higher SUCRA values than benralizumab in improving both exacerbations and ACQ. (Figure 3B)

Considering both efficacy and safety, mepolizumab and benralizumab had the largest benefits in improving exacerbations and having lower odds of a SAE in individuals with ≥300 and ≥150–299 eosinophils/mcl respectively. (Figure 3C and D) For improvement in

both lung function and the odds of not having a SAE, both benralizumab and mepolizumab had similar overall SUCRA values, and higher than dupilumab. Pneumonia, which occurred in 0.3% of patients in both the dupilumab and placebo arm, was the most common serious adverse event reported in LIBERTY ASTHMA QUEST[26] but it is not clear what these SAEs were in the phase 2B trial.[27]

Sensitivity Analyses:

In sensitivity analyses in individuals with ≥300 eosinophils/mcl, we excluded studies that were rated as having at least “some bias”. The median rank for each monoclonal antibody as regards exacerbation rate and prebronchodilator FEV1 were consistent with the main analyses. However, as regards ACQ, benralizumab and mepolizumab swapped ranks and were ranked first and second respectively. Placebo remained the least favorable treatment for all outcomes. We did not conduct sensitivity analyses in the subgroup with ≥150 eosinophils/mcl only due to limited sample size. In further sensitivity analyses, we excluded the DREAM trial which had evaluated a dose and route of administration of mepolizumab which is not FDAaround effect sizes f -related outcomes were wider but rankings and conclusions remained unchanged.

DISCUSSION

We have conducted a Bayesian network meta-analysis and indirect treatment comparison of mepolizumab, benralizumab, and dupilumab for the treatment of severe eosinophilic asthma. Our meta-analysis was informed by a systematic search of eligible RCTs which met pre-specified criteria. We synthesized the information from these studies which were generally with low risk of bias and provided a ranking of these monoclonal antibodies as related to exacerbation rate reduction, improvement in prebronchodilator FEV1, decrease in the ACQ, and incidence of serious adverse events. Eight eligible placebo-controlled trials were identified leading to a sparse network with no direct head-to-head trials.

All the biologics examined were associated with significant improvement of exacerbation rates compared to placebo although the relative ranking of the treatments varied based on eosinophil thresholds. When assessing these differences using prespecified clinically important thresholds, we note minimal differences between the biologics with a ≤5% probability that any of these biologics would lead to halving of the exacerbation rate when compared with another biologic. We also found that, the differences in the safety and efficacy of these biologics were relatively small though dupilumab and mepolizumab ranked higher than benralizumab in exacerbation rate reduction, and mepolizumab higher than benralizumab in ACQ reduction in individuals with eosinophil count ≥300 cells/mcl. The difference in ACQ between the therapies however did not meet the MCID of 0.5. None of the comparison between biologics had a mean difference in FEV1 of ≥100 milliliters compared to each other. In individuals with eosinophil counts of 150–299 cells/mcl, while benralizumab had a higher SUCRA value in reducing exacerbations and improving FEV1, it was not significantly different from dupilumab and mepolizumab. In this subgroup, all the biologics had a probability of 0 for improving FEV1 by ≥100 milliliters compared to placebo, or of improving FEV1 by ≥30 milliliters when compared to another biologic.

Mepolizumab had significantly lower odds than dupilumab in SAEs. Considering SAEs and exacerbation rates together and SAEs and FEV1 together, mepolizumab and benralizumab had a higher SUCRA value than dupilumab in both groups although overall differences were minimal. Importantly, we noted differences in the placebo effects of the mepolizumab trials compared to the dupilumab and benralizumab trials which had large placebo effects on lung function and ACQ. Based on this, we rated the certainty of evidence from this NMA, particularly in comparisons to mepolizumab, as moderate at best with many comparisons rated as 'low' or 'very low' certainty.

There is ample evidence supporting a dose-response relationship between blood eosinophil count and efficacy of mepolizumab, benralizumab, and dupilumab, with individuals with higher eosinophil counts experiencing greater benefits when compared to placebo. These support our findings of a greater effect in individuals with eosinophil counts of ≥300 cells/mcl compared to individuals with eosinophil counts of 150–299 cells/mcl.

Our analysis provides several additional insights into the comparative effectiveness of these biologics. First, a Bayesian NMA overcomes some of the limitations of pairwise meta-analyses conducted within a frequentist framework and allows for probability-based ranking of treatment benefits. We were able to confirm that these monoclonal antibodies are generally effective in improving exacerbation rates but with no or modest improvements in lung function and asthma control questionnaire, consistent with prior studies that used pairwise comparisons and/or frequentist methodology.[32–34] Second, by focusing on the subgroups of individuals based on eosinophil counts, we limited clinical heterogeneity which is a challenge in the absence of individual patient-level data, but also provide results which have clinical relevance as providers seek to optimize the care of their patients with eosinophilic asthma. Third, by comparing the efficacy of these biologics in the context of their safety, we provide valuable information for clinicians and patients as they navigate the delicate balance between the safety and efficacy of these biologics.

Some prior meta-analyses and a matched adjusted indirect treatment comparison had shown similar efficacy between mepolizumab and benralizumab,[5,34–36] with one indirect treatment analyses finding that mepolizumab performed better than benralizumab in improving exacerbation rates and asthma control questionnaire across all eosinophil subgroups.[10] That study, however, created subgroups based on eosinophil count that were inclusive in comparing the treatments (≥150 cells/mcl, ≥300 cells/mcl, ≥400 cells/mcl) and not distinct subgroups as we have done here. Consistent with prior reports, we found that in individuals with eosinophil count of ≥300 cells per mcl, dupilumab ranked best in improving lung function and exacerbation rates,[36,37] while mepolizumab ranked the best in improving asthma control as measured by the ACQ.[10,37] However, we show that dupilumab may not be the preferred treatment when SAEs are considered. Importantly, all differences were small and did not meet prespecified MCIDs.

Additionally, we found that benralizumab was particularly effective in individuals with eosinophil count of 150–299 cells/mcL, although the differences between biologics were not statistically significant. Benralizumab's better efficacy in this group of individuals may be related to the IL5 receptor blockade, which usually leads to near complete depletion

of eosinophils.[32] These results may be helpful to clinicians as they optimize patient care. The ultimate choice of biologic for each patient would however depend on multiple factors including cost considerations and timing of administration. For instance, dupilumab, which was approved for self-administration at initial approval, may have been preferred to a biologic requiring administration in the hospital or by a healthcare provider, although mepolizumab and benralizumab have now been approved for home administration.[38] Some patients may also prefer the bimonthly dosing of benralizumab to the monthly dosing of mepolizumab or the biweekly dosing of dupilumab.

Our results should be interpreted with caution given that these analyses have limitations, some of which are relevant to drug development and regulation in the United States and worldwide. First, indirect comparisons cannot replace randomized trials that compared these three drugs directly. We have utilized aggregated data to answer questions. Thus, these findings may not apply to individual patients and the differences observed may not be clinically important. Although, we have embedded this NMA within a systematic review to ensure that the meta-analyses are comprehensive and avoid selection bias, these analyses were limited by reported data. We stratified by eosinophil subgroups to create a relatively homogeneous group, however, there may be other effect modifiers which differ between the studies and may have influenced these results. Specifically, individuals included in the dupilumab studies had fewer exacerbations at baseline than the mepolizumab and benralizumab studies. However, prior studies, including the DREAM trial for mepolizumab and CALIMA for benralizumab, had shown that patients with higher baseline exacerbation rates had the greatest effects of these biologics. Thus, the effect estimate for dupilumab may be higher in subgroups with baseline exacerbation rates which mirror that of the other biologics. The different placebo effects noted here also suggest that the populations enrolled in these studies may be different in other ways not measured, such as in baseline medication adherence. However, the relative estimates been compared incorporates both the placebo and intervention effects. Secondly, all studies included are placebo-controlled, i.e., no direct comparisons. Thus, we were unable to assess statistical inconsistency between direct and indirect comparisons. This however highlights the importance of this study in providing some evidence on the comparative efficacy and safety of these treatments. It is also important to note that the studies included in a meta-analysis will ultimately influence the results and the differences between this study and others may be due to random differences or differences in the studies included. Revisions to the current regulations relevant to drug development may serve to improve comparative effectiveness of biologics. These could include the required use of active comparators, when a valid comparator is available, and/or the use of similar inclusion criteria and study designs such that *post hoc* comparisons such as these are less likely to be biased. However, these solutions would need multiple stakeholders buy-in and commitment. Finally, these findings, which are from randomized placebo-controlled trials, may not be representative of real-world populations. Nonetheless, in the absence of head-to-head trials, these results may help suggest the pharmacologic agent likely to have the largest benefit based on the eosinophil count and specific outcome of interest. It also raises further questions for research. For instance, there are questions about the right outcomes to focus on, or why asthma control and lung function are only minimally impacted by these biologics compared to exacerbation rates.

Conclusion

In this NMA with low to moderate certainty of evidence, mepolizumab, dupilumab, and benralizumab were similar in safety and efficacy in patients with severe eosinophilic asthma. The differences in exacerbation rates, FEV1 and ACQ did not meet clinically important thresholds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations/Acronyms:

ACQ	Asthma Control Questionnaire
ANDHI	Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab
AQLQ	Asthma Quality of Life Questionnaire
CALIMA	Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma
CGI-C	Clinical Global Impression of Change
CI	Credible Interval
DREAM	Mepolizumab for severe eosinophilic asthma
FEV1	Forced Expiratory Volume in 1 second
FVC	forced vital capacity
LIBERTY ASTHMA QUEST	Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma
mcL	microliter
MD	mean difference

MENSA	Mepolizumab treatment in patients with severe eosinophilic asthma
MUSCA	Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma
NMA	network meta-analysis
OCS	oral corticosteroid
PGI-C	Patient Global Impression of Change
PHASE 2B	Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial
PSIA	Predominant Symptom and Impairment Assessment
SAE	Serious Adverse Events
SGRQ	St George's Respiratory Questionnaire
SIROCCO	Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β 2-agonists
SNOT-22	Sino-nasal Outcome Test
SUCRA	Surface Under the Cumulative Ranking (SUCRA) score

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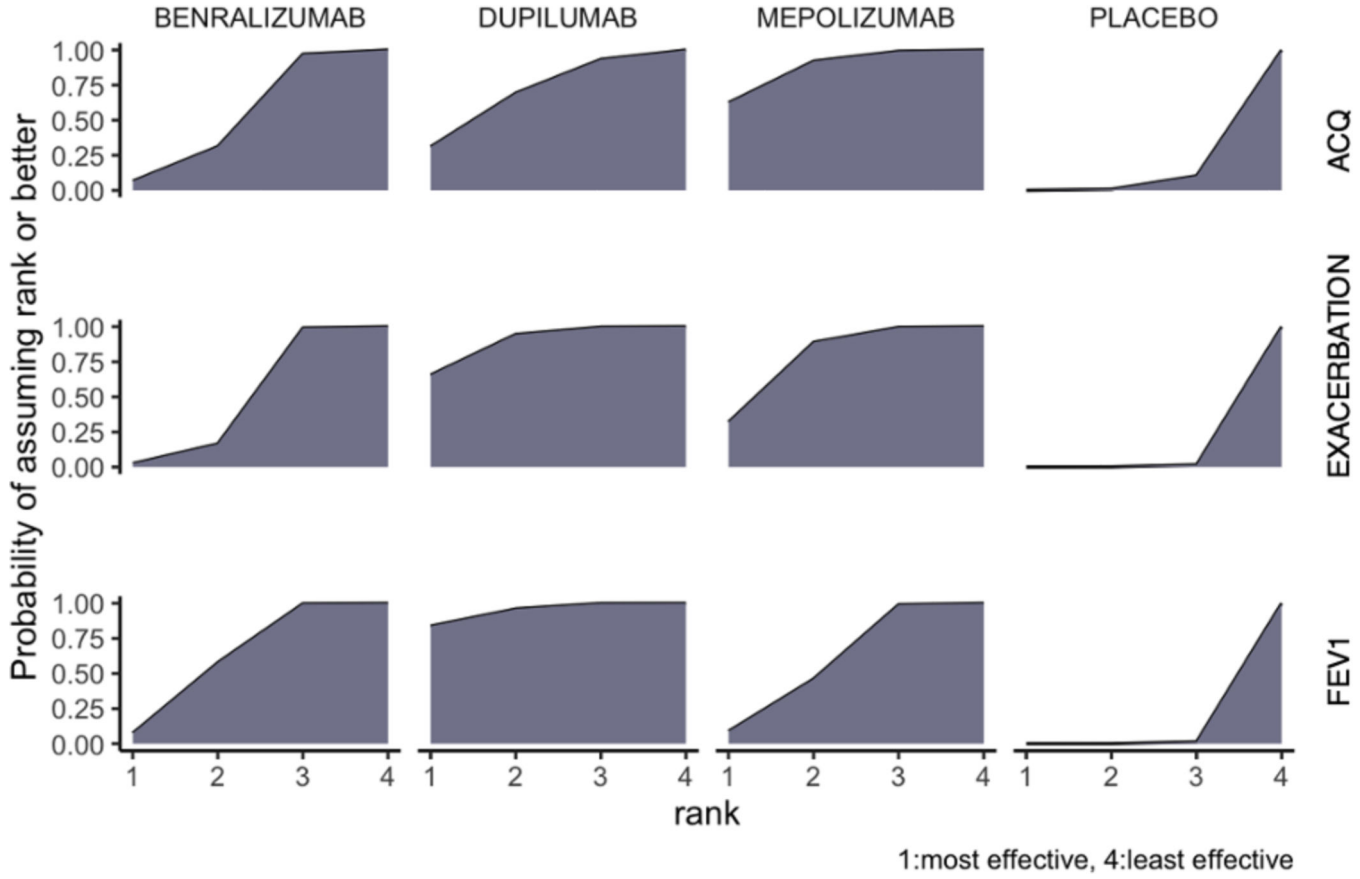


FIGURE 1:

Surface under the cumulative ranking (SUCRA) curve with regard to the efficacy outcomes, Asthma Control Questionnaire (ACQ), exacerbation, and prebronchodilator forced expiratory volume, in 1 second (FEV1) in individuals with eosinophil count of ≥300 cells per microliter. Each plot displays the cumulative ranking probabilities of each treatment being the best (#1), second-best (#2), third-best (#3), or the worst (#4) for each outcome. The best overall treatment would be the treatment with its area under curve closest to the entire area of the graph shaped a rectangle. For example, mepolizumab was the best treatment for improving ACQ, while dupilumab was the best in reducing exacerbations and improving FEV1 in these patients.

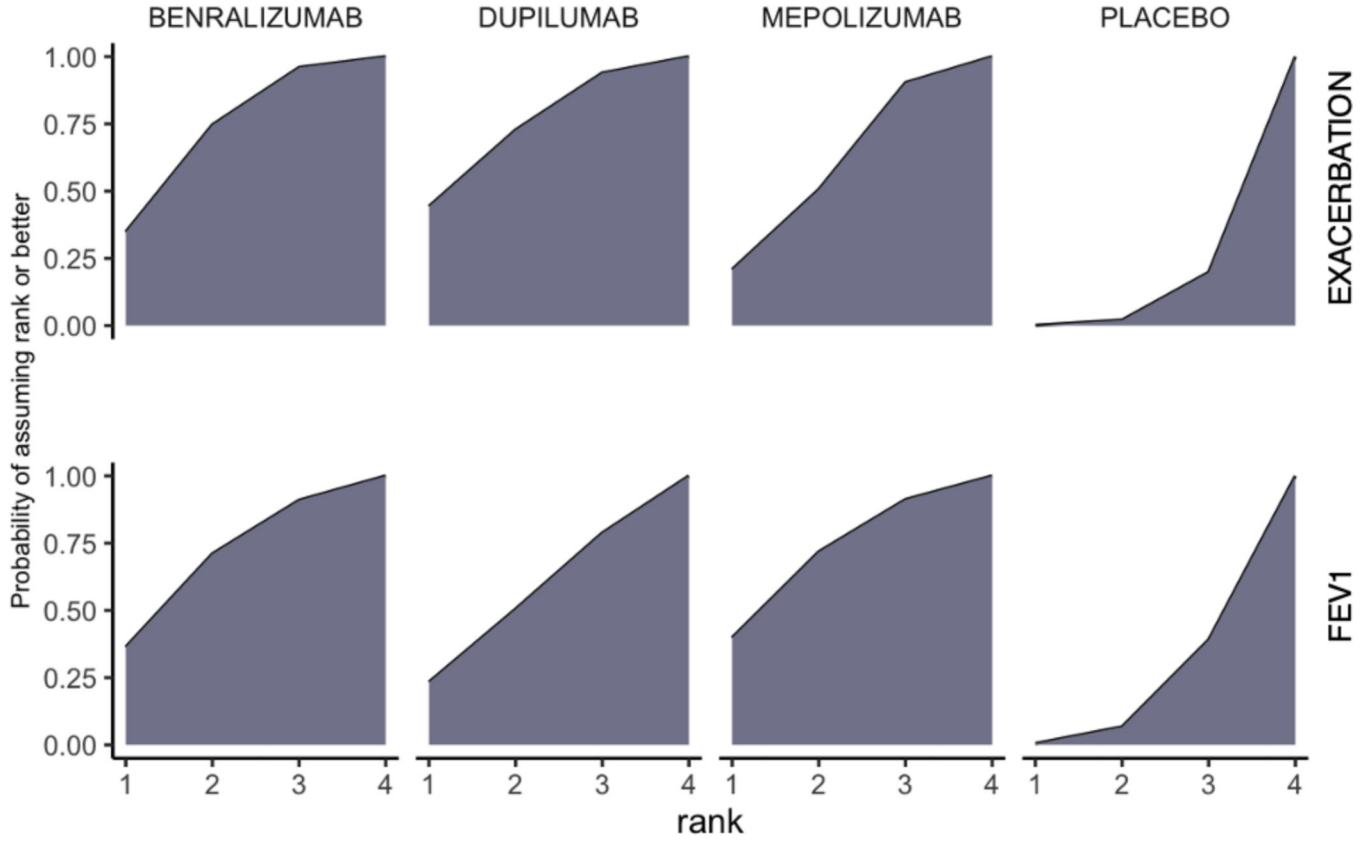
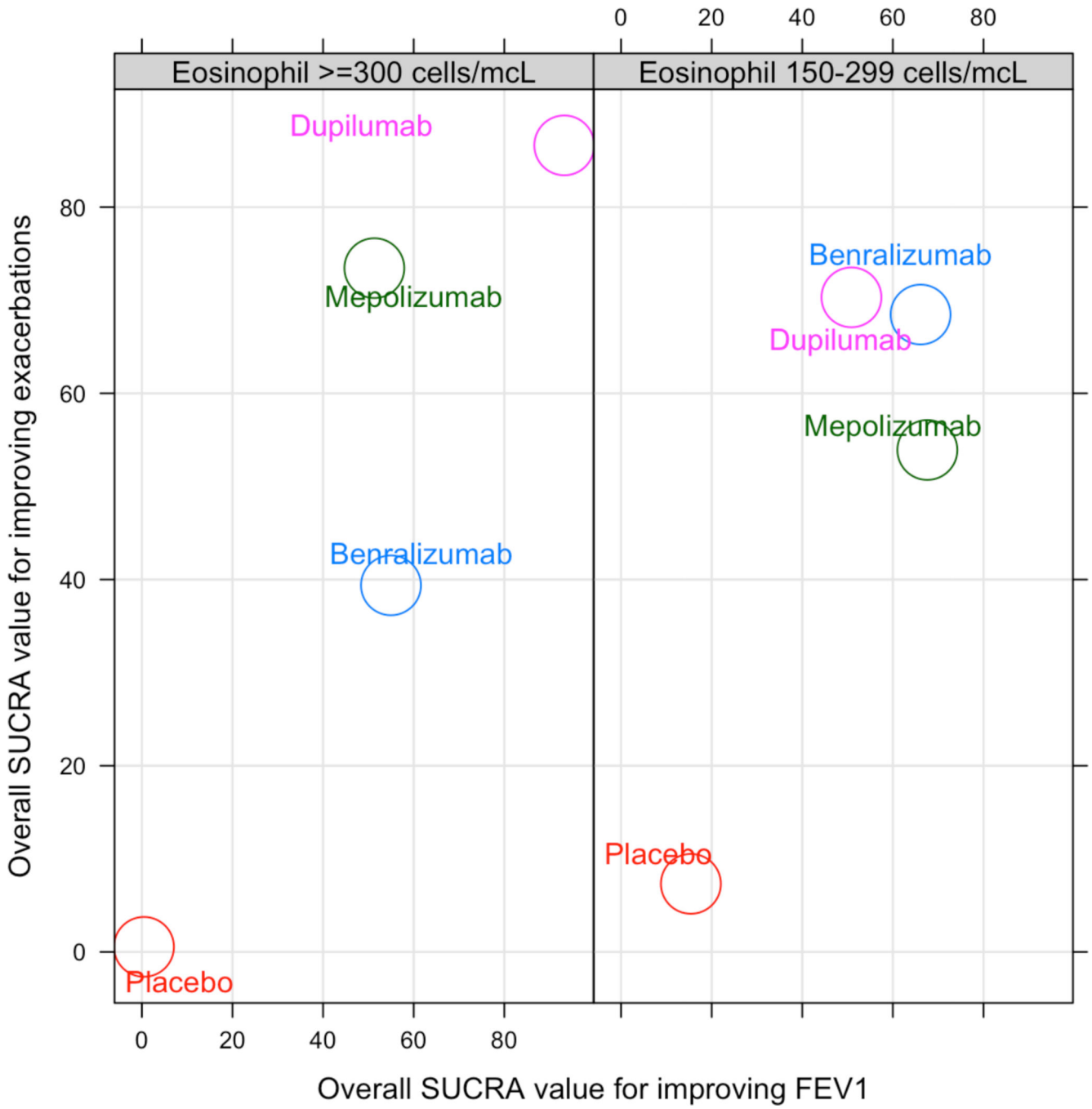
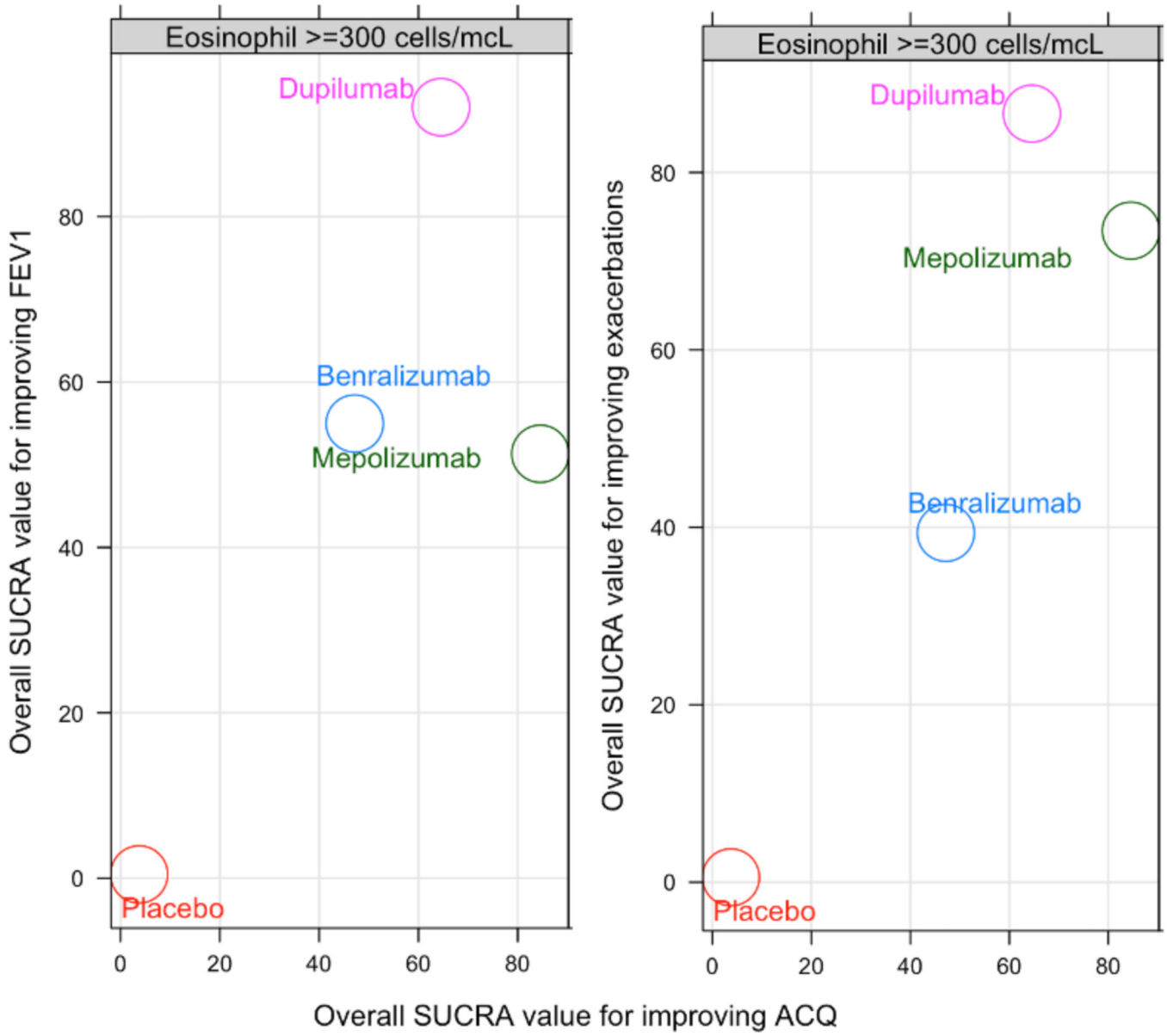
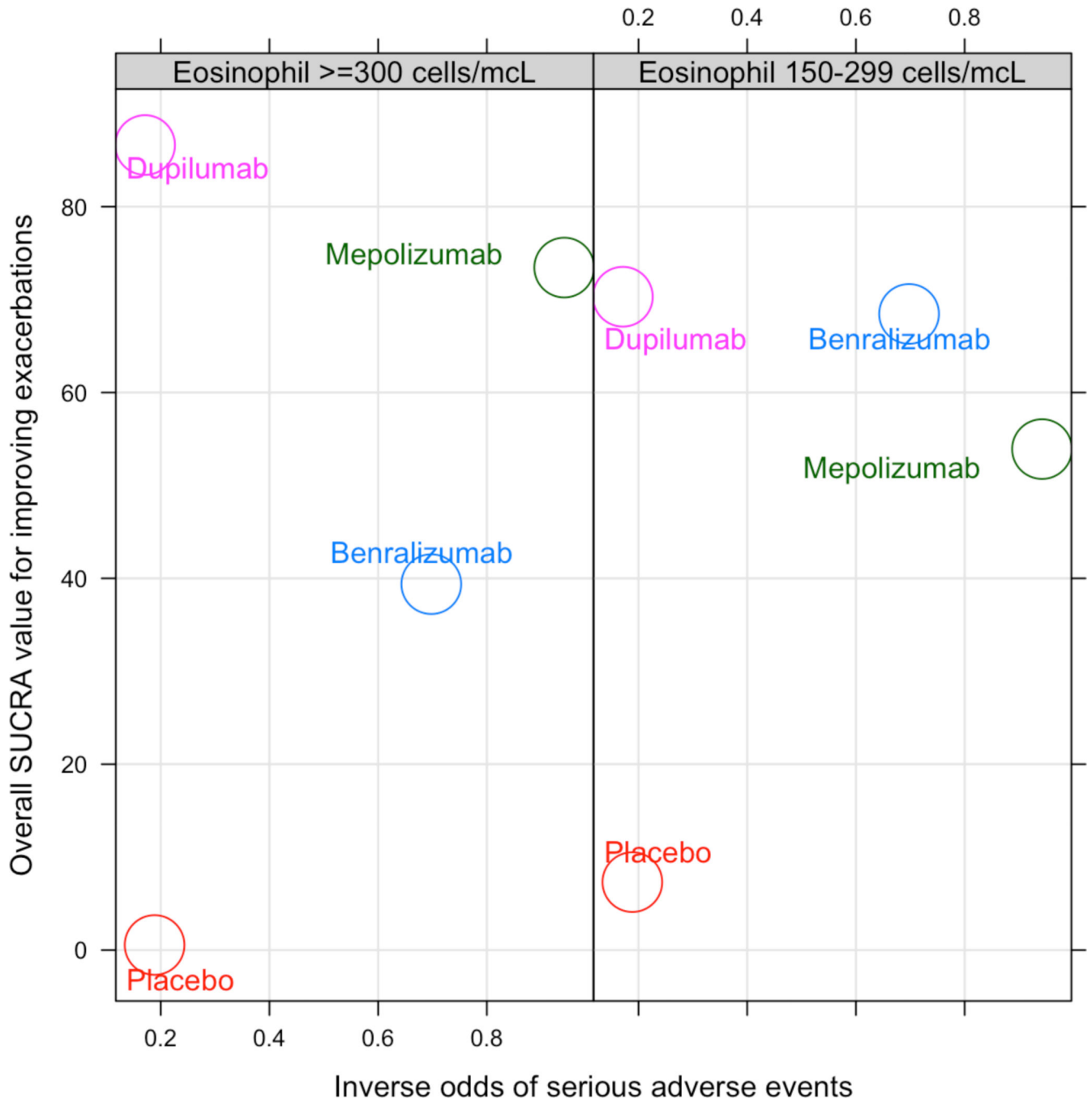


FIGURE 2:

Surface under the cumulative ranking (SUCRA) curve with regard to the efficacy outcomes, exacerbation and prebronchodilator forced expiratory volume in 1 second (FEV1), in individuals with eosinophil count of 150–299 cells per microliter. Each plot displays the cumulative ranking probabilities of each treatment being the best (#1), second-best (#2), third-best (#3), or the worst (#4) for each outcome. The best overall treatment would be the treatment with its area under curve closest to the entire area of the graph shaped a rectangle. For example, benralizumab and dupilumab ranked higher than mepolizumab which ranked higher than placebo in reducing exacerbations and improving FEV1 in these patients.







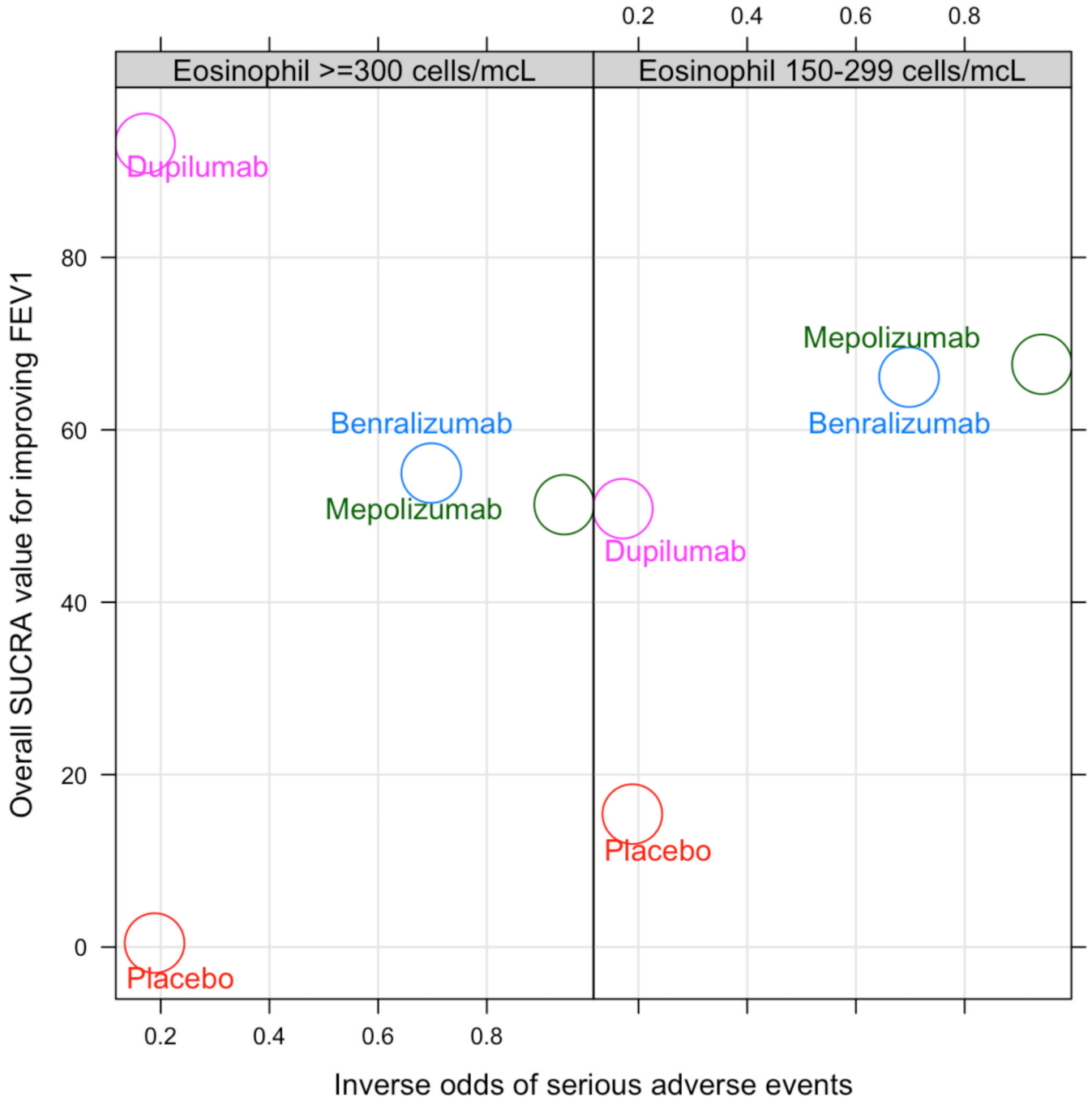


Figure 3:

Scatter plots of the overall SUCRA score (ranking probability) of improving pairs of outcomes. **(A.)** Exacerbation rate reduction vs prebronchodilator forced expiratory volume in 1 second (FEV1) improvement in individuals with eosinophil count ≥ 300 and 150–299 cells/mcl; **(B.)** (*Left panel)* FEV1 improvement vs Asthma Control questionnaire (ACQ) improvement and *(Right panel)* Exacerbation rate reductions vs ACQ improvement in individuals with eosinophil count ≥300 cells/mcl; **(C.)** Overall SUCRA score for improving exacerbations vs. inverse odds of serious adverse events (SAE) in individuals

with eosinophil count ≥300 and 150–299 cells/mcl; **(D.)** Overall SUCRA score for FEV1 vs inverse odds of SAE in individuals with eosinophil count ≥300 and 150–299 cells/mcl.

Table 1.

Characteristics of Included Trials

Trial	Intervention[a]	Size of study population	Efficacy outcomes of interest	Baseline blood eosinophil requirement	Study follow up period, weeks
MENSA	Mepolizumab	576	Exacerbation rate, prebronchodilator FEV1, SGRQ score, ACQ-5 score	≥ 150 cells per mcL at screening or ≥300 cells per mcL in previous year	32
MUSCA	Mepolizumab	556	SGRQ score, prebronchodilator FEV1, ACQ-5 score	≥ 150 cells per mcL at screening or ≥300 cells per mcL in previous year	24
DREAM	Mepolizumab	616	Exacerbation rate, prebronchodilator FEV1, ACQ-6 score, AQLQ score	≥300 cells per mcL screening or in the previous year	52
LIBERTY ASTHMA QUEST	Dupilumab	1902	Exacerbation rate, prebronchodilator FEV1	No required minimum	52
PHASE 2B	Dupilumab	776	Exacerbation rate, prebronchodilator FEV1, ACQ-5 score, AQLQ score	No required minimum	24
SIROCCO	Benralizumab	1204	Exacerbation rate, prebronchodilator FEV1, ACQ-6 score, AQLQ score	No required minimum	48
CALIMA	Benralizumab	1306	Exacerbation rate, prebronchodilator FEV1, ACQ-6 score, AQLQ score	No required minimum	56
ANDHI	Benralizumab	656	Exacerbation rate, prebronchodilator FEV1, SGRQ score, ACQ-6 score, CGI-C, PGI-C, SNOT-22, PSIA	≥ 300 cells per mcL at screening or ≥150 cells per mcL with ≥1 of the following: maintenance OCS use, nasal polyposis, ≥3 exacerbations in the previous year, FVC	24

Abbreviations: ACQ, Asthma Control Questionnaire; ANDHI, Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab; AQLQ, Asthma Quality of Life Questionnaire; CALIMA, Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma; CGI-C, Clinical Global Impression of Change; DREAM, Mepolizumab for severe eosinophilic asthma; FEV1, Forced Expiratory Volume in 1 second; FVC, forced vital capacity; LIBERTY ASTHMA QUEST, Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma; mcL, microliter; MENSA, Mepolizumab treatment in patients with severe eosinophilic asthma; MUSCA, Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma; OCS, oral corticosteroid; PGI-C, Patient Global Impression of Change; PHASE 2B, Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial; PSIA, Predominant Symptom and Impairment Assessment; SGRQ, St George's Respiratory Questionnaire; SIROCCO, Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β 2-agonists; SNOT-22, Sino-nasal Outcome Test

[a]All studies were placebo-controlled

Table 2:

Summary of results of efficacy outcomes showing GRADE criteria for certainty of evidence

Individuals with eosinophil count ≥300 cells per microliter

Exacerbation rate ratio	[T]**DUPILUMAB**	**BENRALIZUMAB**	**MEPOLIZUMAB**
DUPILUMAB	1.00		
BENRALIZUMAB	***1.52 (1.06, 2.13)	1.00	
MEPOLIZUMAB	**1.10 (0.74, 1.70)	***0.75 (0.60, 0.95)	1.00
Mean difference in FEV1 in milliliters			
DUPILUMAB	1.00		
BENRALIZUMAB	**−76 (−160, 9.9)	1.00	
MEPOLIZUMAB	*−85 (−190, 19)	*−8.5 (−100, 83)	1.00
Mean difference in ACQ			
DUPILUMAB	1.00		
BENRALIZUMAB	**0.16 (−0.2, 0.53)	1.00	
MEPOLIZUMAB	*−0.14 (−0.53, 0.24)	*−0.31 (−0.52, 0.10)	1.00

Individuals with eosinophil count 150–299 cells per microliter

Exacerbation rate ratio	**DUPILUMAB**	**BENRALIZUMAB**	**MEPOLIZUMAB**
DUPILUMAB	1.00		
BENRALIZUMAB	***1.03 (0.63, 1.69)	1.00	
MEPOLIZUMAB	**1.20 (0.61, 2.20)	***1.10 (0.70, 1.80)	1.00
Mean difference in FEV1			
DUPILUMAB	1.00		
BENRALIZUMAB	**27 (−97, 150)	1.00	
MEPOLIZUMAB	*28 (−180, 120)	*−1.3 (−130, 130)	1.00

**** High certainty:

*** moderate:

** low:

* very low:

ACQ, Asthma Control Questionnaire; FEV1, Forced Expiratory Volume in 1 second

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating the quality of evidence used. This incorporates the risk of bias, inconsistency and heterogeneity of estimates, indirectness or intransitivity, imprecision of estimates, and publication bias.

[T] The monoclonal antibody in the column is the reference category

Evidence supporting the GRADE criteria for certainty evidence

Starting point: All comparisons were rated as “high” at the start given the inclusion of only randomized placebo-controlled trials.

Downgrading:

1. **Risk of bias**: Most of the included studies had an overall assessment of 'low' risk of bias. Studies with 'some' risk of bias were mostly due to 'missing outcome data' which we defined as ≥10% dropout rate or due to the 'selection of results. (eTable 3)

a. Studies for which selection of results was a concern were downgraded by 1. Thus,

a (i) Mepolizumab comparisons (MUSCA) of exacerbation rates were downgraded

a (ii) Mepolizumab comparisons (MENSA) of ACQ were downgraded

o Missing outcome data was not considered a reason for downgrade due to the relatively balanced dropout rate between study arms

2. **Inconsistency/intransitivity/heterogeneity of estimate**s: **All comparisons were downgraded by** 1 due to potential bias introduced by indirect comparison using aggregate data and the varying distributions of effect modifiers.

2 (i) Comparisons to mepolizumab for FEV1 and ACQ were downgraded by an additional point (i.e., 2 in total for this domain) due to the larger differences in placebo effect compared to the benralizumab and dupilumab trials.

3. **Imprecision of estimate**s: comparisons were downgraded for small effect estimates and wide confidence intervals. We also incorporated whether differences in the continuous outcomes met a presumed minimal clinical important difference (100 mls for FEV1 and 0.5 for ACQ).

3 (i) **All FEV1 comparisons and ACQ were downgraded by a point** given the wide confidence intervals and the relatively small effect sizes

4. **Publication bia**s: no significant evidence supporting publication bias was found based on publication of clinical trial protocols, spread of results, and funnel plots.