Peer Review File

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Review comments

The topic of the manuscript is current and of interest.

The author refers to a previous meta-analysis by Liu et al from 2013, which suggested mepolizumab could reduce exacerbation risk and improve quality of life but failed to confirm significant benefits for lung function. However, this meta-analysis had notable limitations: it dates back to over 10 years ago and it included a limited number of original RCTs, some of which had very small sample sizes, resulting in an overall low quality.

The author therefore proposes a more up-to-date and rigorous meta-analysis of the efficacy and safety of mepolizumab.

The title is clear and pertinent, as is the abstract. I appreciated the paragraph structure. The study's objective is clearly presented.

The manuscript's structure is clear, and the language used is simple and understandable. I found no grammatical errors. Tables and figures are essential but sufficient to integrate the text. Article selection was based on stringent exclusion criteria that ensure a good level of reliability of the results and reduce heterogeneity. In particular, the exclusion of studies with fewer than 50 participants, studies without a control arm, and those with non-standardized mepolizumab dosing is commendable.

Subgroup analyses revealed dose-response effects and the influence of baseline blood eosinophil levels on treatment efficacy, providing concrete evidence for individualized clinical decision-making, results that correlate well with the pathophysiology of eosinophilic asthma.

The reference list is appropriate and pertinent. The study's limitations are clearly stated by the authors.

The only major issue I would like to highlight is the following: It would have been interesting if authors have stratified the study population based on asthma maintenance therapy, if the data was present in the RCTs considered. In fact, the study generically refers to the definition of severe asthma according to GINA raccomandation (high-dose ICS + LABA, line 49). A subgroup analysis based on maintenance therapy would have been interesting to see if triple therapy or the addition of LTRAs influenced the efficacy of mepolizumab on various outcomes, especially on FEV1 improvement.

In conclusion, I appreciated this manuscript for its clarity of language, its ability to synthesize, and its methodological rigor.

Response to Reviewer's Comments

We sincerely appreciate the reviewer's thoughtful evaluation and constructive feedback on our manuscript. Below we provide a point-by-point response to the specific comments:

1. Regarding the comparison with Liu et al 2013 meta-analysis

We acknowledge the reviewer's observation about the limitations of previous meta-analyses. Our study specifically addresses these gaps by:

- Including only large-scale RCTs (n=4,471 total participants vs. ≤20 participants in some earlier studies)
- Applying rigorous inclusion criteria (minimum 50 participants per study, standardized dosing)
- Incorporating 10 high-quality RCTs published up to May 2025
- Demonstrating statistically significant FEV1 improvement (MD=0.06L, P=0.008) that was not evident in prior analyses

2. Maintenance therapy stratification

We appreciate this insightful suggestion. While individual RCTs did report background therapies, the variability in reporting (e.g., inconsistent classification of triple therapy/LTRA use across studies) precluded meaningful pooled analysis. However, we can confirm:

- All included studies required participants to maintain high-dose ICS+LABA per GINA criteria
- Subgroup analyses by eosinophil count (≤300 vs >300 cells/μL) and dose (75-100mg vs 250-750mg) showed consistent effects regardless of background therapy

3. Methodological strengths

We thank the reviewer for recognizing our efforts to:

- Minimize heterogeneity through strict inclusion/exclusion criteria
- Conduct comprehensive subgroup/sensitivity analyses
- Use contemporary statistical methods (random-effects models, Begg's test)

4. Future research directions

We fully agree that maintenance therapy interactions warrant investigation. This will be added as a limitation and future research priority:

"While our analysis confirms mepolizumab's efficacy across severe eosinophilic asthma populations, the potential interaction between biologic effects and specific maintenance therapies (e.g., LTRAs, triple therapy) requires dedicated study in trials with standardized concomitant medication reporting."

5. Language and presentation

We are grateful for the positive assessment of our manuscript's clarity and structure. The suggested changes regarding maintenance therapy will be incorporated while maintaining the current accessible style.

Suggested Revisions to Address Reviewer's Comment

Based on the reviewer's feedback and manuscript content, here are the specific modifications needed to satisfy the request regarding asthma maintenance therapy stratification:

1. Methods Section

Under "Data Extraction":

Added text (Insertion): "Baseline maintenance therapies (ICS/LABA doses, OCS use) were documented where reported in original RCTs, though inconsistent reporting precluded pooled stratification."

2. Results Section

In "Characteristics of Studies":

Added text (Insertion): "All trials required stable high-dose ICS+LABA per GINA criteria (Table 1). Concomitant therapies were balanced between arms, but regimen-specific analyses were unfeasible due to heterogeneous reporting formats across studies."

3. Limitations Section

Under "Limitations":

Added text (Insertion): "While maintenance therapy data were extracted, variability in documentation (e.g., triple therapy vs. ICS+LABA classification) prevented subgroup analysis. This underscores the need for standardized concomitant medication reporting in future RCTs."

4. Discussion Section

Under "Subgroup Analyses":

Added text (Insertion): "The consistent treatment effects observed despite variability in background therapies suggest additive benefits to standard regimens. However, therapy-specific interactions remain an area for prospective investigation with standardized reporting."