

Correspondence

Reply

To the Editor:

Bourdin and Molinari¹ suggest that methodological issues may have impacted the robustness and replicability of results described in our article² that evaluated the relative efficacy of mepolizumab, benralizumab, and reslizumab through an indirect treatment comparison using the Bucher method.³ Specifically, the authors propose that matching-adjusted indirect comparison (MAIC),⁴ which was recently used in a study by Bourdin et al,⁵ is more appropriate for accounting for differences in effect modifiers between studies. However, the choice of method depends on the research question of interest and the data available. Table 1 provides a detailed comparison of the 2 studies.

First, the 2 analyses addressed different research questions: our analysis focused on evaluating licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe uncontrolled eosinophilic asthma characterized by common blood eosinophil thresholds.² In contrast, Bourdin et al compared licensed and nonlicensed doses of mepolizumab against the licensed benralizumab dose in a broader, less severe population of patients, including patients within benralizumab studies who were not eosinophilic and within mepolizumab studies who were controlled (asthma control questionnaire [ACQ] score < 1.5).⁵ Such a comparison is arguably inappropriate because it includes a considerable proportion of patients who are ineligible for both treatments.

Second, the study by Bourdin et al is itself, using their words, “fraught with methodology issues” that impact its validity. The authors rightly mention in their letter that the ACQ score is an effect modifier that should be accounted for; however, this was omitted entirely in their MAIC analysis. Consequently, given the large difference in baseline ACQ score between mepolizumab

and benralizumab studies, this omission would ultimately yield results more in favor of benralizumab because patients with an ACQ score of less than 1.5, who were not enrolled into benralizumab studies, have been shown to derive less benefit from mepolizumab than patients with a higher ACQ score. The fact that our analysis excluded such patients from the comparison of the 2 treatments is in our opinion a major advantage of this study.

Finally, the conduct of the MAIC by Bourdin et al is unclear. Despite meeting PICOS (Population, Intervention, Comparator, Outcome, Studies) criteria, the MUSCA study (NCT02281318) was not included in their primary analysis (Table 1). This is contrary to their letter stating that “all eligible trials must be included.” It is also unclear how inclusion of effect modifiers in the MAIC was determined and how these characteristics were matched. For example, weight has not been identified as an effect modifier in mepolizumab⁶ nor in benralizumab⁷ studies. In addition, it is unclear why blood eosinophil count was matched as less than 300, greater than or equal to 300 cells/μL rather than using some other threshold.

These differences help explain the discrepancies in results between the 2 analyses, which Bourdin and Molinari in their letter may have wrongly attributed to methodological issues. We therefore believe that in this circumstance, considering these differences, any claim on appropriateness is unfounded and that our analysis was appropriate and addressed a relevant scientific question for decision makers.

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TABLE 1. Comparison of PICOS criteria between Busse et al² and Bourdin et al⁵

Criteria	Busse et al ²	Bourdin et al ⁵
Population	Severe uncontrolled (≥1.5 ACQ score) eosinophilic asthma patients, stratified by blood eosinophil counts*	Severe patients with asthma including patients with <1.5 ACQ score (who were randomized into mepolizumab studies but not into benralizumab studies) and noneosinophilic patients (who were randomized into benralizumab studies) who are not eligible for mepolizumab or benralizumab
Intervention	Mepolizumab 100 mg SC Benralizumab 30 mg Q8W	Mepolizumab 100 mg SC & 75 mg IV Benralizumab 30 mg Q8W
Comparator		Standard of care
Outcomes	Clinically significant exacerbations Exacerbations requiring ED visit/hospitalizations Lung function ACQ score	Clinically significant exacerbations Exacerbations requiring ED visit/hospitalizations Lung function
Studies	MENSA (100 mg SC) MUSCA (100 mg SC) SIROCCO (30 mg Q8W) CALIMA (30 mg Q8W)	DREAM (75 mg IV) MENSA (100 mg SC, 75 mg IV)† SIROCCO (30 mg Q8W) CALIMA (30 mg Q8W)

ED, Emergency department; IV, intravenous; PICOS, Population, Intervention, Comparator, Outcome, Studies; Q8W, every 8 weeks; SC, subcutaneous.

*Further stratification by exacerbation history provided in appendix.

†MUSCA excluded although in scope of PICOS. Results with MUSCA are included in appendix.

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