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Arnaud Bourdin, Nicolas Molinari

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Indirect treatment comparison of asthma biologics fraught with methodology issues

To the Editor:

We read with interest the article by Busse et al¹ that evaluated the relative efficacies of benralizumab 30 mg, mepolizumab 100 mg, and reslizumab 3 mg/kg through an indirect treatment comparison (ITC). After careful consideration, we have concluded the methodology was lacking, and, therefore, the results and conclusions may not be robust or replicable.

Good practice for ITCs requires fostering homogeneity, exchangeability, and similarity^{2,3} before comparisons are conducted. For an ITC to be considered valid, patient characteristics that may potentially modify treatment effect should be similar between included studies. Patient factors should be identified by quantitative investigation, expert opinion, and literature evidence.⁴ For nonsimilar characteristics, an appropriate matching technique should be undertaken to balance them.⁵ Such matching was conducted in our recently published, matching-adjusted indirect treatment comparison (MAIC), which effectively adjusted for substantial differences between patient characteristics from studies of IL-5/IL-5R α inhibitors.⁶

In the mepolizumab ITC, distributions of treatment-effect modifiers do not appear to have been assessed for included trials. Patient subgroups based on eosinophil counts or asthma control questionnaire (ACQ) scores of more than 1.5 alone did not guarantee all other treatment-effect modifiers were *homogeneously* distributed. It is highly likely that different study populations were unbalanced based on other patient characteristics likely to have possibly influenced clinical response.

ITC validity also depends on whether study populations are *exchangeable*. For example, placebo responses in the included subgroups reveal study effects. Similar placebo event rates (ie, study effects) indicate that populations are exchangeable. Placebo exacerbation rates in the included mepolizumab trials were substantially different than those observed in benralizumab and reslizumab trials. For the mepolizumab ITC, no information on exchangeability was provided.

Trial *similarity* can be considered from clinical and methodological perspectives. *Clinical similarity* refers to similarity in patient characteristics, interventions, settings, length of follow up, and outcomes measured. *Methodological similarity* refers to aspects of trials associated with risk of bias.³ In particular, all eligible trials must be included. The DREAM trial was a pivotal registration study supporting the mepolizumab indication in severe asthma. DREAM should have been included because of its substantial clinical and methodological similarities with other mepolizumab trials included in this ITC. Moreover, studies have indicated that mepolizumab 75-mg intravenous dosing was bioequivalent to the 100-mg subcutaneous dose. Exclusion of DREAM was unwarranted and directly led to selection bias.

A more appropriate approach for understanding responses in different clinical trials is MAIC, which leverages individual

patient data from clinical studies to generate an adjusted trial population that matches important baseline clinical and other features of a second trial population. MAIC methodology matches all possible treatment-effect modifiers, as identified by statistical investigations, literature evidence, and expert opinion.⁴ For asthma, these should include, at a minimum, baseline eosinophil count, baseline exacerbation history, baseline body mass index, maintenance oral corticosteroid use, baseline ACQ score, IgE count, and presence of nasal polyps.⁶

We were unable to replicate results of the mepolizumab ITC via our MAIC analysis, which may reveal trials included in the mepolizumab ITC and corresponding population were non-homogeneous. Finally, the MAIC approach also fits with another indirect meta-analysis.⁷

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Arnaud Bourdin, MD, PhD^{a,b}
Nicolas Molinari, PhD^c

From ^athe Department of Respiratory Diseases, Montpellier University Hospitals, Arnaud de Villeneuve Hospital, ^bINSERM U 1046, University of Montpellier, Arnaud de Villeneuve Hospital, and ^cIMAG, CNRS, University of Montpellier, CHU Montpellier, Montpellier, France. E-mail: a-bourdin@chu-montpellier.fr.

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