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► **To cite this version:**

Arnaud Bourdin, Nicolas Molinari. Non-optimal methodology questions indirect treatment comparison of dupilumab vs. other biologics in severe asthma. *Respiratory Medicine*, 2022, 191, pp.105999. 10.1016/j.rmed.2020.105999 . hal-03548301

HAL Id: hal-03548301

<https://hal.science/hal-03548301v1>

Submitted on 30 Jan 2022

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ARTICLE INFO

Keywords

Benralizumab

Dupilumab

Indirect treatment comparison

Matching-adjusted indirect comparison

Mepolizumab

Severe eosinophilic asthma

To the Editor:

We read with interest the article by Bateman E et al. [1] that attempted to evaluate the relative efficacies of dupilumab vs. benralizumab, mepolizumab, omalizumab, and reslizumab through an indirect treatment comparison (ITC). After careful review, we have concluded the methodology and results lack scientific robustness and credibility because individual trial and patient differences were not considered. Therefore, the conclusions drawn by the authors that “dupilumab was associated with statistically significantly lower annualized severe asthma exacerbation rates compared with benralizumab, mepolizumab, and reslizumab” and “statistically significantly greater improvement in lung function compared with benralizumab and reslizumab (at week 24) and omalizumab (at week 52)” are not credible.

The Bucher methodology [2] employed by Bateman and colleagues failed to meet basic assumptions of an ITC from well-recognized health technology assessment standards. Fundamentally, the Bateman analysis failed to address 1) differences in relevant treatment effect modifiers between studies, such as baseline asthma control, BMI, sex, smoking, background medication requirements, and upper airway disease, presence of nasal polyposis, and use of oral corticosteroids (OCS), and 2) major design differences between trials.

To this point, my colleagues and I published a robust matching-adjusted indirect comparison (MAIC) early in 2020 [3]. Using this gold-standard methodology, we analyzed results from the Phase III benralizumab trials with exacerbation reduction as the primary endpoint (SIROCCO and CALIMA) vs. the Phase III exacerbation trial of dupilumab (LIBERTY ASTHMA QUEST). We found that “substantial heterogeneity and lack of overlap between trial populations precluded matching adjustment.” [3] The dupilumab studies enrolled patients receiving medium-dosage inhaled corticosteroids (ICS) and excluded patients receiving maintenance OCS, whereas the benralizumab primary analysis populations were all uncontrolled on high-dosage ICS/LABA with or without OCS. After matching the populations for treatment modifiers known to impact treatment effect of asthma biologics, we obtained a sample size of 16 patients. The populations were too

dissimilar for meaningful comparison.

MAIC 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, and is widely accepted and used [3–6]. By contrast, Bucher’s method [2], employed by Bateman E et al. [1], erroneously assumes the relative effect of a given treatment is the same across studies, uses relative effects to compare treatments, and does not address treatment effect modifiers (treatment confounders) that may be different between studies.

Comparing efficacy outcomes between substantially different studies using indirect methods is challenging, and their findings can be difficult for physicians and others in the health care community to interpret [7, 8]. We feel that the methodology applied in the current analysis was incomplete, and, therefore, find the stated conclusions on relative efficacy between dupilumab and the other asthma biologics misleading.

Acknowledgments

Medical writing support was provided by Michael A. Nissen, ELS, of AstraZeneca.

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