



Methodological Concerns of a Recent Network Meta-analysis Assessing Biologics for Eosinophilic Asthma

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A network meta-analysis assessing the comparative efficacy of anti IL-4, IL-5, and IL-13 drugs for treatment of eosinophilic asthma by Iftikhar et al. [1] was recently published online in *Lung* and concluded that “only reslizumab and dupilumab were associated with statistically significant reductions in asthma exacerbation rates” versus placebo. These conclusions contradict previous analyses which show a beneficial effect of all biologics considered against placebo on exacerbation reductions, and we suspect that this may be due to inappropriate data extraction and analysis methods used in the current study.

Firstly, asthma exacerbations were specified as an endpoint but the definition of an exacerbation in the study lacks critical details. It is not clear from the article whether all clinically significant (also referred to as severe) exacerbations (SE), or only those requiring emergency department and/or hospitalisation (HE), were of interest. In addition, the authors did not extract treatment effects (i.e. rate ratios) and their standard error directly from the source articles as was done for other endpoints. Instead, their Methods describe that asthma exacerbation counts and “patient-years” were used to calculate rate ratios. However, neither patient-years nor exacerbation counts are reported within most studies included in the analysis. It is therefore unclear where any of the inputs used for these calculations were extracted from, nor is the method used to calculate the rate ratios and their standard errors provided.

To illustrate our concern, Table 1 compares the data from three included studies as reported in the original source article and by Iftikhar et al., attempting to replicate the result (it

should be noted that this issue applies to most, if not all, of the studies in the meta-analysis). As it is unclear what the definition of asthma exacerbations was, we present results both for SE and HE.

In each instance, we were unable to obtain the data used by the authors to calculate the rate ratio. Additionally, it seems possible that data relating to different exacerbation outcomes were extracted. We were therefore unable to replicate the authors’ results. There are also inconsistencies in the data reported, for example, despite Chupp et al. having a study size over fourfold compared to Bel et al., results estimated by the authors for the latter appear to have smaller confidence intervals (see table). This does not seem plausible. More worryingly, the CIs estimated by the authors for the majority of studies are substantially wider than those reported in the original study—it is not clear why this is the case.

In summary, the available information is insufficient to replicate the authors’ results, and it appears likely that some data were extracted or calculated erroneously. It is therefore necessary for the authors to provide more details on their definition of asthma exacerbations, what exacerbation-related data were extracted for each study, and how the reported results were calculated and the meta-analysis performed. The validity of this analysis is therefore very questionable.

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Table 1 Comparison of data reported for asthma exacerbations within source publications and by Iftikhar et al. [1]

Study/biologic	N (as reported in source publication)	RR (95% CI) reported in Iftikhar et al.	RR (95% CI) reported in source publication	Asthma exacerbation counts	Patient follow-up (patient-years)
Chupp et al. (2017) [2]/ Mepolizumab	551	0.421 (0.004, 43.102)	SE: 0.42 (0.31,0.56) HE: 0.31 (0.08,1.24)	Not reported	Not reported
Bel et al. (2014) [3]/Mepolizumab	135	0.300 (0.033, 2.729)	SE: 0.68 (0.47,0.99) HE: Not reported	Could be extracted from Fig. 2B	Not reported
Castro et al. (2015) [4]/ Reslizumab	953	0.640 (0.526, 0.778)	SE: 0.46 (0.37,0.58) HE: 0.66 (0.38, 1.16)	Not reported	Not reported

RR rate ratio, CI confidence interval, SE severe exacerbation, HE hospitalisation exacerbation

Compliance with Ethical Standards

Conflict of interest All authors are employees and own shares of GSK.

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