LETTER TO THE EDITOR

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Iftikhar and Colleagues Reply: Methodology Clarified

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We thank Gunsoy and colleagues for their comments on our paper [1] and appreciate the opportunity to further clarify our methods and results. The definitions of asthma exacerbations differed in different studies and was provided in each article mostly in their 'methods' sections. Yes, it is true, that we 'did not extract treatment effects' directly from the source articles. We simply used the asthma exacerbation data reported in each study (see Table for further clarification) in our meta-analysis. We never reported that some biologics increased asthma exacerbations as Gunsoy et al. imply. It is true that 'patient-years' were not provided in each study, which is why we specified in the methods section, that we calculated the patient-years based on the data on follow-up provided in each study. However, it is not true, that exacerbation rates were not reported 'within most studies' (see Table). For Chupp et al. [2], Bel et al. [3], and Castro et al. [4] studies, the asthma exacerbation 'counts'/rates/percentages (definitions and reporting formats of which varied) were reported in the respective papers (see Table).

Our intent for using the approach of calculating 'person years' was to present the data in a uniform format across a range of different studies that differed in their follow-up periods. However, it is understandable how this may have misled some of the readers. We take this opportunity to present the results in the conventional format using just the counts of asthma exacerbations from individual papers (this time, however, excluding Nair [5], Pavord [6], and Hanania [7] studies to avoid any further confusions on calculation of asthma exacerbation counts), and simply calculating odds ratios. The results (see Table) confirm that dupilumab and reslizumab were least associated with asthma exacerbations, and show similar results for mepolizumab. However, these results just like the results of the analysis reported in our original paper have important limitations: (1) only studies from which these data were extractable in a common format were included and others were excluded, (2) since these results are not a 'network' meta-analysis of asthma exacerbations, they do not provide 'indirect estimates' of 'between-drug' comparisons, and (3) since the time when we analyzed the results, two new much awaited studies [8, 9] on dupilumab have been published. With regards to the latter, an updated network meta-analysis is necessary at this time, since in ours, we only included two of the dupilumab studies.

Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Benralizumab studies			
Nowalk 2014	43	47	Subjects with ≥ 1 asthma exacerbation, n (%)—week 24 Table 2 Pg. 18
Park 2016	9	8	Reported as "serious adverse event" Page 141 text
Bleecker 2016	13	19	"Worsening asthma" (during "the treatment period") Pg 2124 3rd para
FitzGerald 2016	4	5	"Worsening asthma" (during "on-treatment period") Pg 2138, para 3
Ferguson 2017	1	2	AE ("worsening asthma" in > 3% pf patients) Pg 573, 2nd para
Pooled odds ratio: 0.80 (0.54–1.19), $p = 0.28$			
Reslizumab studies			
Castro 2011	8	19	"Clinical asthma exacerbation" Pg 1129, 2nd para

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Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Castro 2015 (study 1)	87	89	"Clinical asthma exacerbation" Pg. 358, 2nd para
Castro 2015 (study 2)	83	88	"Clinical asthma exacerbation" Pg. 358, 2nd para
Bjermer 2016	11	19	AE ("worsening of asthma") Pg. 796, Table 3
Corren 2016	13	20	AE (reported as ≥ 3% of patients per MDRA) Pg. 808, Table 3

Pooled odds ratio: 0.58 (0.40–0.83), $p = 0.004$

Mepolizumab studies

Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Bel 2014	3	12	AE ("worsening of asthma") Pg. 1196, Table 3
Flood-Page 2007	14	16	"Exacerbation rates" (reported in %) Pg. 1065
Haldar 2009	10	34	HE per Table 2
Nair 2009	22	90	Exacerbations as defined a priori: 2/9 in mepolizumab; 10/11 in placebo Pg. 989
Ortega 2015	8	15	AE ("worsening of asthma" in > 5% of treatment groups) Supplement Pg. 20, Table S4
Chupp 2017	3	5	AE (worsening of asthma in ≥ 5% of patients) Pg. 395; Pg 398

Pooled odds ratio: 0.24 (0.16–0.35), $p < 0.001$

Dupilumab studies

Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Wenzel 2013	5	42	Exacerbations as defined a priori Supplement Pg. 28, Table S8
Wenzel 2016	13	26	≥ 1 Severe exacerbation event in the 24-week treatment period Table 2, Pg. 36

Pooled odds ratio: 0.22 (0.12–0.40) $p < 0.001$

Lebrikizumab studies

Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Corren 2011	1.8	1.7	HE Pg. 1095
Hanania 2015	20	32	Exacerbations as defined a priori Table 3

Pooled odds ratio: 0.56 (0.30–1.04), $p = 0.06$

Tralokinumab studies

Study ID	Drug events (%)	Placebo events (%)	'Asthma exacerbation' in source articles
Piper 2013	3	4.5	"Protocol defined asthma exacerbations" Pg 333
Brightling 2015	9	13	"Grade 3 treatment-emergent adverse event -worsening asthma" Pg. 697

Pooled odds ratio: 0.66 (0.30–1.42), $p = 0.29$

AE indicates adverse event, *HE* indicates hospitalization event from asthma exacerbation

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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