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LETTER

Letter to the Editor Regarding "Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab"

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Dear Editor,

We read with interest the paper by Menzies-Gow et al. [1] aimed at assessing the impact of benralizumab on clinical remission in patients suffering from severe asthma. The study [1] was a post hoc analysis including selected pooled patients from the SIROCCO [2], CALIMA [3], and ZONDA [4] trials. The analysis was performed by applying a composite definition of severe asthma clinical remission adapted from Delphi documents [5, 6] and results were reported in a descriptive manner with no statistical analysis.

Post hoc analyses are characterized by intrinsic weaknesses such as type I error and the possibility of being misinterpreted [7]; furthermore, Delphi methods are limited by the fact that they are subjective by nature and based on opinions of people who should be expert in a specific field [8]. The misuse of these techniques may result in biased clinical evidence.

However, when conducted properly, both post hoc analyses and Delphi surveys may lead to clinically valuable insights and recommendations [7, 9, 10]. In fact, high-quality evidence may originate from prespecified post hoc analyses [11] and by strictly applying the criteria resulting from consensus frameworks [5, 6], conditions not fully met in the study by Menzies-Gow et al. [1]. As a matter of fact, the authors performed an unplanned (non-prespecified) pooled post hoc analysis by applying, in an arbitrary way, a combination of criteria for the definition of severe asthma clinical remission derived from two different Delphi processes [5, 6]. The four-item composite definition of clinical remission used in the pooled post hoc analysis [1] was not fully consistent with the criteria proposed by the Delphi studies [5, 6], as shown in Table 1.

Looking at one of the primary Delphi publications [6], only zero exacerbation and zero corticosteroids (OCS) use can be considered major criteria of clinical remission; conversely, the Asthma Control Questionnaire (ACQ) and forced expiratory volume in 1 s (FEV_1) identified minor criteria. Moreover, regardless of the weight of criteria, both the Delphi documents [5, 6] required that the improvements in each

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Table 1 Criteria for defining the composite definition of severe asthma clinical remission used in the pooled post hoc analysis by Menzies-Gow et al. [1] and comparison with the reference Delphi documents [5, 6]

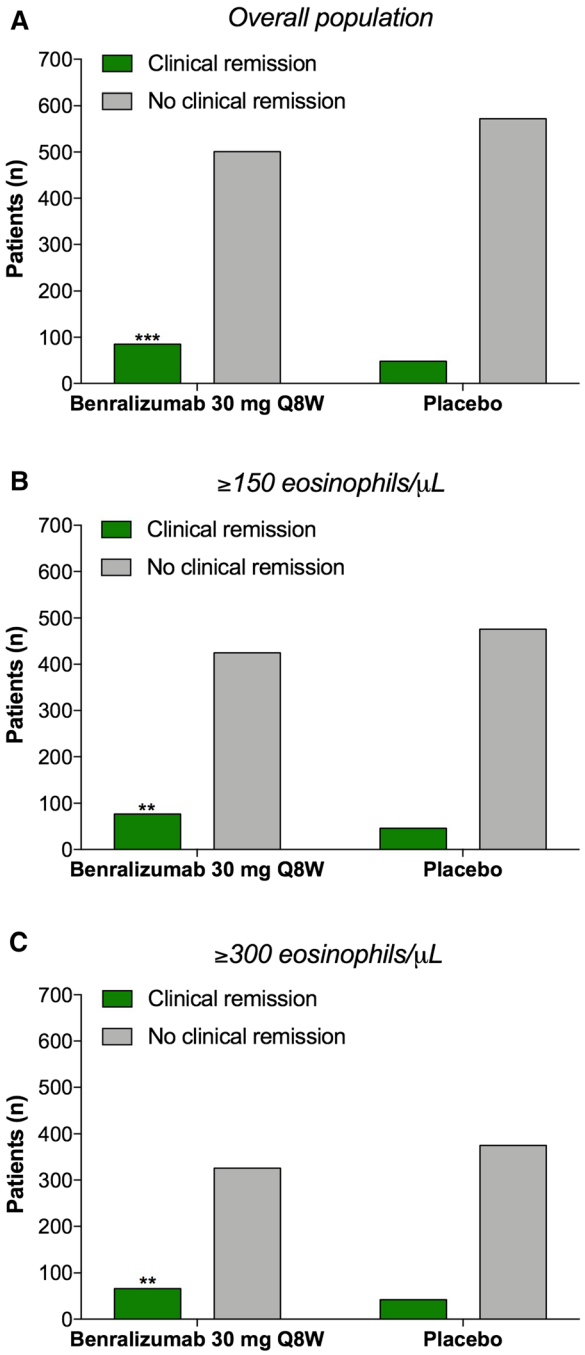
Items	Composite definition of severe asthma clinical remission used by Menzies-Gow et al. (all criteria needed) [1]	Severe asthma remission and/or super-responder criteria from Delphi processes [5, 6]	Consistency
Daily symptoms	ACQ score $\leq$ 0.75 at 6 and 12 months	ACQ score $\leq$ 0.75 or $<$ 1.0 for $\geq$ 12 months	Yes at 12 months, no at 6 months
Exacerbation	Zero exacerbations at 6 and 12 months	Exacerbation elimination for $\geq$ 12 months	Yes at 12 months, no at 6 months
OCS	Zero OCS use at 6 and 12 months	Cessation of maintenance OCS for $\geq$ 12 months	Yes at 12 months, no at 6 months
Lung function	Pre-BD FEV_1 increase $\geq$ 100 mL at 6 and 12 months	$\geq$ 500 mL improvement in FEV_1 for $\geq$ 12 months	No

ACQ Asthma Control Questionnaire, *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 s, *OCS* oral corticosteroids

item should be assessed for at least 12 months. Thus, since the ZONDA [4] study lasted 28 weeks, this trial should not have been included in the post hoc analysis [1]; nor should the data at 6 months for the SIROCCO [2] and CALIMA [3] studies. Menzies-Gow et al. [1] correctly reported that all the four items were concurrently necessary to define clinical remission in severe asthma. This approach was consistent to the framework for the clinical remission in asthma and/or the assessment of criteria for defining super-responders [5, 6], but the increase in FEV_1 should have been defined as $\geq$ 500 mL [6] and not as $\geq$ 100 mL as set by Menzies-Gow et al. [1].

Overall, across all the results reported by the authors [1], only those shown in Fig. 4B and Supplementary Tables 1 and 2 (clinical remission at 12 months) may be suitable for an appropriate post hoc analysis. However, since Menzies-Gow et al. [1] reported in the methods that only patients from SIROCCO [2] and CALIMA [3] studies not receiving OCS were included in the pooled post hoc analysis and that patients who were receiving OCS at baseline were excluded, it is unclear why the item "No OCS" was considered in these figures and tables.

In any case, if one ignores the unclear point concerning the OCS use in the SIROCCO [2] and CALIMA [3] studies and assuming an increase in $FEV_1 \geq 100$ mL as a valid remission criterion, the data reported in Fig. 4B and Supplementary Tables 1 and 2 remain useful for an independent statistical analysis and clinical interpretation. In this respect, the Fisher's exact test and the relative risk (RR) analysis showed that, when compared to placebo, benralizumab 30 mg every 8 weeks (Q8W, first three doses 4 weeks apart) elicited significant severe asthma clinical remission in the overall pooled population from SIROCCO [2] and CALIMA [3] studies (Fig. 1a; RR 1.87, 95% confidence interval [CI] 1.34–2.62, $P < 0.001$). Similar results were found also in the patient subgroup with blood eosinophil count $\geq$ 150 cells/μL (Fig. 1b; RR 1.74, 95% CI 1.23–2.45, $P < 0.01$) and $\geq$ 300



◀**Fig. 1** Fisher's exact test comparing the number of severe asthmatic patients treated for 12 months with benralizumab 30 mg Q8W or placebo achieving the clinical remission according to the four-item composite definition proposed by Menzies-Gow et al. [1] (zero exacerbations and zero OCS use and ACQ-6 $\leq$ 0.75 and pre-BD FEV_1 increase $\geq$ 100 mL). The analysis was performed on the overall population from SIROCCO [2] and CALIMA [3] studies (**a**) and in subgroup populations with blood eosinophil count $\geq$ 150 cells/μL (**b**) and $\geq$ 300 cells/μL (**c**). $^{**}P < 0.01$ and $^{***}P < 0.001$. *ACQ* Asthma Control Questionnaire, *BD* bronchodilator, FEV_1 forced expiratory volume in 1 s, *OCS* oral corticosteroids, *Q8W* every 8 weeks, first three doses 4 weeks apart

cells/μL (Fig. 1c; RR 1.67, 95% CI 1.17–2.40, $P < 0.01$).

Interestingly, these statistically significant results are worth of an objective clinical interpretation via the analysis of the number need to treat (NNT), an absolute measure providing the clinically beneficial effect of a medical intervention in a specific population [12, 13]. It resulted that 15 (95% CI 10–32) patients had to be treated with benralizumab 30 mg Q8W to have one patient achieve clinical remission compared to placebo over 12 months, with no significant difference according to the levels of blood eosinophil count ($\geq$ 150 eosinophils/μL: NNT 15, 95% CI 9–42; $\geq$ 300 eosinophils/μL: NNT 15, 95% CI 9–53).

Post hoc analyses are neither necessary nor forbidden, but if carried out they should fulfill strict criteria and be built on solid scientific background [7]. Here we have provided evidence that a well-performed pooled post hoc analysis of SIROCCO [2] and CALIMA [3] studies may provide scientific findings useful from both a statistical and clinical point of view. Although the concept and definition of clinical remission in asthma have yet to be refined and validated through studies designed ad hoc, generally they include the absence of significant symptoms, no exacerbations, no use of OCS, and large improvement in lung function after at least 12 months of treatment [5, 6]. In this context, benralizumab 30 mg Q8W was effective in eliciting clinical remission of severe

asthma in one patient out of 15, at least according to the four-item composite definition proposed by Menzies-Gow et al. [1]. Certainly, airway inflammation and remodelling may be present also during clinical remission of atopic asthma [14]; however, such an NNT value looks of remarkable clinical impact since it resulted from the concurrent presence of four different remission criteria in the same patient.

Concluding, the data resulting from our independent post hoc analysis further supports the clinical benefit of benralizumab 30 mg Q8W after 12 months of treatment in severe asthmatic patients, but the obtained NNT value should be applied with caution to real-life clinical settings because it originated from the pooled analysis of randomized controlled trials. In all likelihood, post-marketing trials reporting open patient-level data available for independent research could definitively assess, in an unbiased manner, the real percentage of severe asthmatic patients treated with benralizumab achieving clinical remission.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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