

Improvements in asthma control and quality of life with benralizumab are unrelated to baseline bronchodilator response



To the Editor:

We read with interest the recent retrospective analysis performed by Mümmeler et al¹ demonstrating no significant differences in forced expiratory volume in 1 second (FEV₁), exacerbations, maintenance oral corticosteroid (OCS) use, and asthma control in patients with severe eosinophilic asthma (SEA) treated with anti-IL5/anti-IL5R α according to the presence or absence of bronchodilator responsiveness (BDR) at baseline using FEV₁ criteria. This is perhaps unsurprising given that BDR to albuterol is mediated by β -2 receptors on airway smooth muscle reflecting airway caliber, whereas response to benralizumab is mediated by eosinophil depletion reflecting type 2 airway mucosal inflammation.

It has previously been shown that both spirometry and airway oscillometry can be used to demonstrate BDR to albuterol in patients with severe asthma with the latter being more sensitive.² Here we report a *post hoc* analysis on a clinical trial (EudraCT No. 2019-003763-22) of 21 patients with poorly controlled SEA who had required 4 courses of OCS over the past year. They were treated with 12 weeks of anti-IL5R α as 3 monthly doses of benralizumab looking at BDR at baseline according to either FEV₁ (200 mL and 12%) or oscillometry (R5 $\geq$ 29%).³

Of the 21 patients, 8 demonstrated BDR using either criterion and 13 did not. There were no baseline differences between those with versus without BDR in FEV₁% predicted, Asthma Control Questionnaire (ACQ), or mini-Asthma Quality of Life Questionnaire (mini-AQLQ) (data not shown). Nonetheless, after 3 doses of benralizumab, mean changes in ACQ and mini-AQLQ exceeded the minimal clinical important difference of 0.5 in both patients with and patients without BDR.

The overall message is clear in that patients with SEA who do not exhibit BDR are likely to benefit from benralizumab reflecting the disconnect between mechanisms acting on airway smooth muscle and type 2 inflammation.

Rory Chan, MBChB
Kirsten Stewart, MBChB
Brian J. Lipworth, MD

Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, United Kingdom.

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Corresponding author: Brian J. Lipworth, MD, Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, United Kingdom. E-mail: b.j.lipworth@dundee.ac.uk.

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Reply to "Improvements in asthma control and quality of life with benralizumab are unrelated to baseline bronchodilator response"



To the Editor:

We thank Chan et al¹ for their comment on our recent article.² In our retrospective registry analysis, we found that the presence or absence of bronchodilator responsiveness (BDR) at baseline was unrelated to the outcome of anti-IL5/anti-IL5R α treatment, that is, improvements of exacerbations, steroid use, asthma control, and forced expiratory volume in 1 second (FEV₁) were similar in both groups. Chan et al corroborate our findings with data from a clinical trial of benralizumab that assessed baseline BDR using spirometry and oscillometry. Similar to our cohort, the majority of patients with severe asthma in that trial had negative BDR at baseline. These patients showed relevant benefits in asthma control and quality of life after only 3 months of benralizumab treatment.

We agree with Chan et al that the mechanism behind the pulmonary function improvement is different for short-acting β -2-agonists (SABA) that confer bronchodilation by the activation of bronchial β -2 receptors compared with anti-IL5/anti-IL5R α treatments that reduce eosinophilic airway inflammation.

Recently, insights into the mechanism of pulmonary function test improvements after anti-IL5/anti-IL5R α have been gained with improvement of small airway dysfunction (SAD) and reduction of mucus obstruction caused by airway eosinophilia being highlighted.^{3,4}

Despite these obvious differences in mode of action of SABA and anti-IL5/anti-IL5R α , positive BDR has been an inclusion criterion for severe asthma trials of biologics up to now because:

- (1) it is used for confirmation of variability of airway obstruction as a feature of asthma as opposed to chronic obstructive pulmonary disease (COPD), and
- (2) it was assumed to increase the likelihood of positive results concerning the FEV₁ end point.

Although this seems understandable from a trial design perspective, it has also led to an exclusion of the majority of

patients with severe asthma encountered in real life. In a recent analysis of the total German Asthma Net severe asthma cohort, we found that 543 of 793 patients had a negative baseline BDR test, similar to the percentage found in the anti-IL5/anti-IL5R α -treated subcohort. Importantly, this absence of BDR was not associated with smoking history or COPD.⁵

Imaging studies may be helpful for both exclusion of differential diagnosis and assessment of airway mucus to predict response to biologics together with T2-biomarkers and physiological measures of SAD, which might reduce over-reliance on classical BDR criteria in the future.

Katrin Milger, MD^{a,b}

Carlo Mümmeler, MD^{a,b}

Nikolaus Kneidinger, MD, PhD^{a,b}

^aDepartment of Medicine V, University Hospital, LMU Munich, Munich, Germany

^bComprehensive Pneumology Center Munich (CPC-M), German Center for Lung Research (DZL), Munich, Germany.

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Corresponding author: Katrin Milger, MD, Department of Medicine V, LMU University Hospital, Marchioninistr 15, 81377 Munich, Germany. E-mail: Katrin.Milger@med.uni-muenchen.de.

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Partial suppression of type 2 inflammation with mepolizumab



To the Editor:

We read with interest the results of the MAPLE trial showing additional suppression by prednisolone of FeNO, blood, and sputum eosinophils in patients taking mepolizumab.¹ These findings illustrate the limited impact of mepolizumab on type 2 inflammation with regard to persistent IL4/IL13 escape in the presence of IL5 blockade.² As such, this reinforces the importance of carefully observing type 2 biomarkers in patients treated with mepolizumab and considering other biologics that have more broad-spectrum effects in suppressing the type 2 inflammatory phenotype. Hence, prospective real-life studies with biologics involving biomarker-directed therapy would help to

elucidate optimal therapy for patients with type 2 high-refractory asthma.

All authors contributed to conceptualization, analysis, investigation, and article writing including review and editing, with B.J. Lipworth additionally providing supervision.

Kirsten E. Stewart, FRCS (ORL HNS)^a

Rory Chan, MBChB^a

Rasads Misirovs, MBBS^a

Brian J. Lipworth, MD^a

^aScottish Centre for Respiratory Research, Ninewells Hospital and Medical School, Dundee, Scotland, United Kingdom.

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Corresponding author: Kirsten E. Stewart, FRCS (ORL HNS), Scottish Centre for Respiratory Research, Mailbox 2, Medical Research Institute, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, United Kingdom. E-mail: Kstewart004@dundee.ac.uk.

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Probiotics in managing pediatric asthma: Is this a viable road?



To The Editor:

We read with great interest the comprehensive review by Fiocchi et al¹ on the use of probiotics in allergic diseases. We certainly agree with several conclusions drawn by these authors. Here, we discuss probiotics in managing children with asthma. As mentioned in this review, a growing body of evidence supports the role of the environmental microbiome in the risk for and severity of allergic diseases and asthma.² Namely, dysbiosis affects the gut-lung axis, promoting the activation of inflammatory pathways.

Moreover, the “microbiota hypothesis” suggested that early-life exposures to certain inflammatory bacteria may influence the composition of the microbiota and consequently promote immune dysregulation toward type 2 immunity. However, supplementing “good bacteria,” such as probiotics, could restore eubiosis and manipulate immune response.³

The benefits associated with probiotic supplementation depend on the multifaceted mechanisms of action, mainly on innate immunity. Probiotics could promote the expansion of type 1