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Lipworth, Brian; Chan, Rory

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Disconnect for Tezepelumab on Exacerbations, Symptoms, and Quality of Life in Type 2 Low Asthma

Brian Lipworth and Rory Chan

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

To the Editor:

Patients with type 2 (T2) low severe uncontrolled asthma represent an unmet clinical need in terms of available treatment options. In this regard, we were somewhat encouraged by the pooled *post hoc* analysis of the primary endpoint in phase II/III studies with tezepelumab showing evidence of a 37% mean (95% confidence interval, 0–60%) reduction in exacerbations in a subgroup of patients with T2 low asthmas defined by blood eosinophil counts <150 cells/μl and fractional exhaled nitric oxide <25 ppb (1, 2).

However, in such patients with T2 low asthma, there appeared to be a disconnect in regard to a lack of efficacy with tezepelumab for secondary outcomes, including symptom control and quality of life, a key point that was overlooked in an accompanying editorial (2).

Here, for patients with eosinophil counts <150 cells/μl, the mean (95% confidence interval) differences for tezepelumab versus placebo were −0.11 (−0.34 to 0.11) for the asthma control questionnaire and −0.13 (−0.30 to 0.05) for the asthma quality-of-life questionnaire and, for those with fractional exhaled nitric oxide <25 ppb, the respective differences were 0.13 (−0.12 to 0.37) and 0.08 (−0.11 to 0.27), none of which were statistically significant or clinically relevant. Furthermore, in the same biomarker subgroups, the mean differences in prebronchodilator FEV_1 were also not significant, at 0.00 (−0.09 to 0.08) and 0.06 (−0.01 to 0.12), respectively.

We, therefore, believe prospective mechanistic studies are now indicated to look at the effects of tezepelumab in patients with T2 low asthma, perhaps including airway hyperresponsiveness and small-airway function, to see if this might help explain the observed improvements in exacerbations but not symptoms. ■

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Correspondence and requests for reprints should be addressed to Brian Lipworth, M.D., Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK. Email: b.j.lipworth@dundee.ac.uk.

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Reply to Lipworth and Chan

Guy Brusselle[1,2,3] and Sebastian Riemann[1]

[1]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; and [2]Department of Epidemiology and [3]Department of Respiratory Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

ORCID IDs: 0000-0001-7021-8505 (G.B.); 0000-0003-1184-7234 (S.R.).

From the Authors:

Lipworth and Chan highlight an important issue in their letter regarding the *post hoc* pooled analysis of the PATHWAY (Study to Evaluate the Efficacy and Safety of Tezepelumab in Adult Subjects with Inadequately Controlled, Severe Asthma) and NAVIGATOR (Study to Evaluate Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma) studies: in patients with type 2 low asthma, there is a disconnect between improvements in exacerbations (37% reduction) with tezepelumab and the lack of a significant benefit on symptoms and quality of life (QoL) compared with placebo (1). Because of space limitations, we did not discuss this discordance in our editorial (2). However, discordant effects of biological therapies on exacerbations versus symptoms or QoL are not unique to tezepelumab or type 2 low asthma but have been

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