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. ■

Supported by a grant from AstraZeneca for clinical studies with tezepelumab as part of the WAYPINT trial in patients with chronic rhinosinusitis with nasal polyposis and in the BISA trial with benralizumab in patients with severe eosinophlic asthma, as well as payment for giving talks (B.L.). Also, supported by Sanofi/Regeneron for a clinical study (DISA) in severe asthma with dupilumab and also the SINUS 24 study with dupilumab in patients with chronic rhinosinusitis and nasal polyposis, as well as payment for talks (B.L.).

Originally Published in Press as DOI: 10.1164/rccm.202304-0746LE on June 6, 2023

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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2. Brusselle G, Riemann S. Is efficacy of tezepelumab independent of severe asthma phenotype? *Am J Respir Crit Care Med* 2023;208:1–3.

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

Originally Published in Press as DOI: 10.1164/rccm.202305-0792LE on June 6, 2023

described in other randomized controlled trials, including the DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma) study investigating mepolizumab in severe eosinophilic asthma (3).

How can we explain this disconnect? First, the cellular and molecular mechanisms driving exacerbations versus day-to-day symptoms and QoL might differ (4). Second, in randomized controlled trials of uncontrolled asthma, there is an important improvement in symptoms and QoL in the placebo arm due to a combination of the placebo effect, the Hawthorne effect, and the natural history of the disease. Therefore, even though improvements in asthma QoL scores from baseline to week 52 were observed with tezepelumab in the PATHWAY and NAVIGATOR studies, and were most pronounced in type 2 high asthma, the improvement compared with placebo did not reach the minimal clinically important difference. This contrasts with real-life effectiveness studies that compared clinical outcomes in real-world settings before and during treatment (i.e., pre- vs. posttreatment). Intriguingly, the placebo effect has been shown to have a stronger effect on subjective outcomes such as symptoms and QoL than on objective outcomes such as exacerbations and lung function (5). In conclusion, when investigating the discordance between improvements in exacerbations as opposed to patient-reported outcomes in severe asthma treated with tezepelumab or other monoclonal antibodies, the mechanisms of disease pathophysiology as well as the principles of study design need to be taken into account. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Correspondence and requests for reprints should be addressed to Guy Brusselle, M.D., Ph.D., Department of Respiratory Medicine, Ghent University Hospital, C. Heymanslaan 10, B-9000 Ghent, Belgium. Email: guy.brusselle@uzgent.be.

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Reply to Lipworth and Chan

Christopher S. Ambrose[1], Elliot Israel[5], Karin Bowen[2], Jean-Pierre Llanos[6], Neil Martin[9,10], Bill Cook[1], Åsa Hellqvist[11], Stephanie Korn[12,13], Andrew Menzies-Gow[9,14], Stephanie L. Roseti[3], Nestor A. Molfino[7], Janet M. Griffiths[4], and Jane R. Parnes[8]; on behalf of all authors of Efficacy of Tezepelumab in Severe, Uncontrolled Asthma: Pooled Analysis of the PATHWAY and NAVIGATOR Clinical Trials

[1]Respiratory and Immunology, BioPharmaceuticals Medical, [2]Biometrics, Late-Stage Development, [3]Late-stage Development, [4]Translational Science and Experimental Medicine, Research and Early Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland; [5]Pulmonary and Critical Care Medicine, Allergy & Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [6]Global Medical Affairs, [7]Global Development, and [8]Translational Medicine, Amgen, Thousand Oaks, California; [9]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom; [10]University of Leicester, Leicester, United Kingdom; [11]Biometrics, Late Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [12]IKF Pneumologie Mainz, Mainz, Germany; [13]Thoraxklinik Heidelberg, Heidelberg, Germany; and [14]Royal Brompton and Harefield Hospitals, London, United Kingdom

ORCID IDs: 0000-0003-4175-7336 (C.S.A.); 0000-0002-7785-6881 (J.-P.L.).

From the Authors:

We thank Drs. Lipworth and Chan for their interest in our article published in a recent issue of the *Journal*, which describes a pooled analysis of the PATHWAY (ClinicalTrials.gov ID: NCT 02054130) and NAVIGATOR (ClinicalTrials.gov ID: NCT 03347279) clinical trials, which reported the efficacy and safety of tezepelumab in patients with severe, uncontrolled asthma (1).

Pooling data from the PATHWAY and NAVIGATOR trials increased statistical precision, allowing more accurate assessment of the efficacy of tezepelumab across multiple clinically relevant patient subgroups, including patients with type 2 (T2)-low asthma. The greatest efficacy with tezepelumab was observed in patients with high levels of T2 inflammatory biomarkers: in this subgroup, tezepelumab treatment reduced the annualized asthma exacerbation rate (AAER) by 76–78%, and resulted in clinically meaningful improvements in lung function, asthma symptoms, and health-related quality of life (HRQoL) versus placebo. At the other end of the inflammatory spectrum, as noted by Lipworth and Chan, tezepelumab also demonstrated clinically meaningful reductions in AAERs, including exacerbations associated with hospitalizations or emergency department visits, in patients with low levels of T2 inflammatory biomarkers. Currently, tezepelumab is the only

Supported by AstraZeneca and Amgen Inc.

Originally Published in Press as DOI: 10.1164/rccm.202305-0843LE on June 6, 2023