



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

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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 FEV₁ 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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References

1. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B, *et al*. Efficacy of tezepelumab in severe, uncontrolled asthma: pooled analysis of PATHWAY and NAVIGATOR studies. *Am J Respir Crit Care Med* 2023;208:13–24.
2. Brusselle G, Riemann S. Is efficacy of tezepelumab independent of severe asthma phenotype? *Am J Respir Crit Care Med* 2023;208:1–3.

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Reply to Lipworth and Chan

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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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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. ■

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References

1. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B, *et al*. Efficacy of tezepelumab in severe, uncontrolled asthma: pooled analysis of PATHWAY and NAVIGATOR Studies. *Am J Respir Crit Care Med* 2023;208:13–24.
2. Brusselle G, Riemann S. Is efficacy of tezepelumab independent of severe asthma phenotype? *Am J Respir Crit Care Med* 2023;208:1–3.
3. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–659.
4. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, *et al*. After asthma: redefining airways diseases. *Lancet* 2018;391:350–400.
5. Wechsler ME, Kelley JM, Boyd IO, Dutilleul S, Marigowda G, Kirsch I, *et al*. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med* 2011;365:119–126.



Reply to Lipworth and Chan

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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

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