

Reply to “Have we reached our final destination with biologics in severe uncontrolled asthma?”



To the Editor:

We thank Lipworth and Chan¹ for their thoughtful comments on our rostrum article “Super-responders to biologic treatment in type 2-high severe asthma: passing fad or a meaningful phenotype?”²

Results from the DESTINATION trial³ on the reduction of the annualized exacerbation rates in patients with T2-high severe asthma confirm how effective a strategy based on the block of upstream alarmins could be. What would be interesting to assess in real-life prospective studies is the number of patients with super-response (SR) and clinical remission after tezepelumab administration. Following the findings from the SOURCE study,⁴ only patients with blood eosinophils ≥ 150 cells/ μ L experienced a significant reduction of oral corticosteroid (OCS) use, which is unsurprising considering the impact of tezepelumab on T2 biomarker reduction.⁵ Accordingly, the OCS cessation criterion should be carefully evaluated in SR/remission classifications because patients with a T2-low endotype treated with tezepelumab could not fulfill this point despite a significant clinical and functional improvement. Moreover, considering the lack of specific non-T2 biomarkers to assess tezepelumab response, some useful clues could arise from airway hyperresponsiveness (AHR) assessment. As shown in the CASCADE trial,⁵ AHR is markedly decreased in the tezepelumab arm, suggesting that the block of thymic stromal lymphopoietin can improve this feature with mechanism independent from eosinophilic inflammation. Although this last statement needs further compelling evidence to be proven, it would be fascinating to understand whether the AHR decrease after tezepelumab administration could be a reliable biomarker to assess SR in patients with T2-low severe asthma.

Finally, DESTINATION results revealed a significant reduction of exacerbation rates in patients with concomitant severe asthma and chronic rhinosinusitis with nasal polyps (CRwNP). Despite the large confidence interval due to the small sample size, these data confirm how a good control over upper airways inflammation can significantly affect severe asthma outcomes. Future studies should translate this concept into the specific SR/remission criterion, considering the importance of CRwNP in severe asthma response to biologics.

Andrea Portacci, MD
Giovanna Elisiana Carpagnano, MD, PhD

Institute of Respiratory Disease, Department of Translational Biomedicine and Neuroscience, University “Aldo Moro”, Bari, Italy.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication February 27, 2023; accepted for publication February 28, 2023.

Corresponding author: Andrea Portacci, MD, University “Aldo Moro”, Piazza Giulio Cesare 11, 70124 Bari, Italy. E-mail: a.portacci01@gmail.com.

REFERENCES

1. Lipworth B, Chan R. Have we reached our final destination with biologics in severe uncontrolled asthma? *J Allergy Clin Immunol Pract* 2023;11:1575-6.
2. Portacci A, Dragonieri S, Carpagnano GE. Super-responders to biologic treatment in type 2-high severe asthma: passing fad or a meaningful phenotype? *J Allergy Clin Immunol Pract* 2023;11:1417-20.
3. Menzies-Gow A, Wechsler ME, Brightling CE, Korn S, Corren J, Israel E, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. *Lancet Respir Med*. Published online January 23, 2023. [https://doi.org/10.1016/s2213-2600\(22\)00492-1](https://doi.org/10.1016/s2213-2600(22)00492-1)
4. Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S, Welte T, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. *Lancet Respir Med* 2022;10:650-60.
5. Diver S, Khalfaoui L, Emson C, Wenzel SE, Menzies-Gow A, Wechsler ME, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2021;9:1299-312.

<https://doi.org/10.1016/j.jaip.2023.02.030>