Is tezepelumab more than just an anti-eosinophil drug?

Adil Adatia [1,2], Mustafaa Wahab [1] and Imran Satia [1,2]

[1]McMaster University, Dept of Medicine, Hamilton, ON, Canada. [2]Firestone Institute for Respiratory Health, St Joseph's Healthcare, Hamilton, ON, Canada.

Corresponding author: Imran Satia (satiai@mcmaster.ca)

Shareable abstract (@ERSpublications)
Tezepelumab significantly reduces airway eosinophilia, which is the most likely mechanism by which it reduces the risk of asthma exacerbation in patients with moderate–severe asthma, but has little effect on airway hyperresponsiveness to mannitol https://bit.ly/3xnt5sS

Cite this article as: Adatia A, Wahab M, Satia I. Is tezepelumab more than just an anti-eosinophil drug? *Eur Respir J* 2022; 59: 2101700 [DOI: 10.1183/13993003.01700-2021].

Received: 16 June 2021
Accepted: 23 July 2021

While most patients with mild-to-moderate asthma can achieve disease control using inhaled corticosteroids (ICS), with or without additional controller medication such as long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists [1] or leukotriene receptor antagonists, 5–10% have severe disease and remain uncontrolled despite these therapies. Asthma exacerbations requiring prednisone, emergency department visits and hospitalisations can occur in mild/moderate disease, but they are far more frequent in patients with severe asthma, often requiring maintenance oral corticosteroids (OCS) to prevent such occurrences. Recurrent exacerbations contribute to significant morbidity and (occasional) mortality, and also account for approximately 50% of asthma-related healthcare utilisation costs [2]. Hence, understanding the mechanisms of asthma exacerbations and preventing them has been a major target for scientific understanding and clinical therapeutics.

The fundamental features of asthma are airway inflammation, variable airflow obstruction and airway hyperresponsiveness, but the degree to which each of these components leads to symptoms and exacerbations is incompletely understood. The recent advent of biologic therapy to treat the inflammatory component has revolutionised severe asthma care by reducing exacerbations by approximately 50% in clinical trial settings [3]. The currently approved biologicals target type 2 (T2) inflammatory pathways: the IL-5 pathway (mepolizumab, benralizumab and reslizumab), the IL-4 and IL-13 pathways (dupilumab), and immunoglobulin E (omalizumab). They are efficacious but there are some patients who have a suboptimal or no clinical response in real-world cohorts [4, 5], and there are currently no approved biologicals for severe non-T2 asthma, which represents a significant proportion of severe asthmatics [6, 7]. Thus, there remain major unmet needs in severe asthma care.

One novel treatment approach is to target airway epithelium-derived cytokines implicated in the pathobiology of asthma. Airway epithelial cells produce thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 in response to tissue damage due to allergic, infectious (viral, bacterial, fungal) or irritant (pollution, smoke, diesel) stimuli [8]. These cytokines are thus termed "alarmins" and activate inflammatory pathways involving IL-4, IL-5 and IL-13, culminating in airway inflammation [8]. That TSLP is upstream of these key mediators of airway inflammation makes it an attractive therapeutic target, and indeed tezepelumab, an anti-TSLP monoclonal antibody, has shown promising results in clinical studies. Critically, both phase 2b and phase 3 data showed benefit in patients with high and low blood eosinophil counts, raising the possibility it may be useful in both T2 and non-T2 asthma [9, 10]. Why it may be effective in those classified as non-T2 asthmatics is unclear. One hypothesis is that tezepelumab inhibits mast cells [9], which are key cellular mediators of disordered airway smooth muscle function [11], leading to airway hyperresponsiveness and thus variable airflow obstruction.

In a proof-of-concept study in mild, corticosteroid naïve allergic asthmatics, 700 mg of intravenous tezepelumab (AMG-157) attenuated the early and late phase asthmatic bronchoconstrictor responses and

allergen-induced airway eosinophilia after allergen inhalation challenge [12]. Importantly, there was a small improvement in the methacholine provocative concentration resulting in 20% decrease in FEV_1 (PC_{20}) prior to allergen challenge after tezepelumab treatment. These findings contrast with earlier and subsequent studies of anti-IL-5 biologicals [13, 14], which did not improve allergen-induced bronchoconstriction, thus supporting the hypothesis that tezepelumab may inhibit TSLP-related mast cell activation and hence attenuate airway hyperresponsiveness. In contrast with other biologicals, treating this additional smooth muscle component of asthma pathophysiology might be the mechanism of clinical benefit seen in non-T2 asthma.

To test this hypothesis, Sverrild *et al.* [15] conducted the UPSTREAM trial, a double-blind placebo-controlled trial investigating the effect of tezepelumab on airway hyperresponsiveness to mannitol in patients with moderate–severe asthma, irrespective of baseline blood eosinophils. A total of 40 patients were randomised to either tezepelumab 700 mg intravenously or placebo every 4 weeks for three doses, in addition to their standard treatment regimen. The primary outcome was the change in the provocative dose of mannitol causing a 15% reduction in FEV_1 (PD_{15}). Indirect bronchoprovocation challenges, such as mannitol, are thought to cause bronchoconstriction primarily by mast cell mediator release [16], so this challenge allowed for the testing of potential anti-mast cell effects of the drug. The secondary outcomes included airway tissue mast cell infiltration, luminal eosinophilia, fractional exhaled nitric oxide (F_{ENO}) and asthma control.

The trial showed that tezepelumab did improve mannitol PD_{15} by approximately 1 doubling dose more than placebo (1.9 *versus* 1.0), but this difference narrowly failed to reach statistical significance (p=0.06). A significantly greater number of tezepelumab-treated patients achieved a negative mannitol challenge (PD_{15} >635 mg), but this was confounded by a higher baseline PD_{15} in the treatment group. There was a trend towards reduction in total mast cell infiltration in endobronchial biopsies after tezepelumab treatment compared with placebo (p=0.07). However, in the subpopulation with blood eosinophils $\geqslant 0.25\times10^9$ L^{-1} and/or sputum eosinophils ⩾3%, the total mast cell infiltration was significantly reduced in the tezepelumab group. Tezepelumab also significantly reduced eosinophils in the blood, sputum, bronchoalveolar lavage fluid and endobronchial biopsies by approximately 50–75%, and reduced F_{ENO}. No effect was seen on forced expiratory volume in 1 s (FEV_1). A major strength of this study was the sampling of multiple compartments, aside from the bone marrow.

This study provides some interesting insights: 1) tezepelumab seems to work predominantly by significantly reducing eosinophils, but interestingly not down to zero; 2) there is a small shift in airway hyperresponsiveness to mannitol; but 3) this is not entirely explained by a reduction in mast cells in endobronchial biopsies. Rather, it was in the high eosinophil group that a 25% reduction in total mast cells was seen. These data suggest that the primary mechanism by which tezepelumab improves asthma clinical and physiological outcomes is by suppressing airway eosinophilia, and that there might an interactive effect between eosinophils and mast cell activity.

Other factors need to be considered to contextualise the study results with the previous study using the same intravenous dose. First, in the allergen challenge study discussed above, all subjects were mild, corticosteroid-naïve asthmatics whereas the patients in this trial were all treated with inhaled corticosteroids. It is thus possible that tezepelumab does have anti-mast cell effects, but these effects are not additive/synergistic when combined with inhaled corticosteroids. Second, this study used mannitol, which is an indirect bronchial challenge compared with a direct methacholine challenge. The mechanism by with mannitol causes bronchial challenge is thought to be secondary to the osmotic effect, causing degranulation of inflammatory cells in the airways. There may be other cells apart from mast cells or neuronal reflexes which could mediate bronchoconstriction. Third, on average the patients recruited by Sverrild *et al.* [15] had moderate airway hyperresponsiveness to mannitol (PD_{15} <155 mg), though in some subjects it was also mild (PD_{15} >155 mg but <635 mg) [17]. A greater magnitude of effect may have been observed if the trial recruited only those patients with severe airway hyperresponsiveness (PD_{15} <35 mg) to mannitol, who are more likely to have asthma symptoms driven by mast cell activation. Fourth, the magnitude of effect of tezepelumab on mast cell activity may be small and thus could not be detected in a small trial. The larger CASCADE study using tezepelumab 210 mg subcutaneously also showed only a 0.84 doubling dose increase in mannitol PD_{15} [18], suggesting it has a minor effect on mannitol hyperresponsiveness. There was no associated change in chymase- or tryptase-positive mast cells in bronchial biopsies. Interestingly, this dissociation between changes in hyperresponsiveness and tissue mast cell number was also seen in a study of KIT inhibition in asthma [19], so mast cell tissue density may be an insensitive marker of the contribution of mast cells to asthma symptoms.

The results of this study must be contextualised with the recent presentation of the tezepelumab phase 3 trials. In the NAVIGATOR study, tezepelumab administered subcutaneously at the lower dose of 210 mg

showed an overall 56% reduction compared to placebo in the annualised asthma exacerbation rate in moderate-to-severe asthmatics. However, the rate reductions were significantly greater with increasing blood eosinophils (ranging from <0.15 to >0.45×10^9 L^{-1}) and F_{ENO} (<25 ppb to >50) [9]. In patients with blood eosinophils <0.15×10^9 L^{-1} or F_{ENO} <25 ppb, there was only a 39% (95% CI 12–58%) and 32% (8–49%) reduction, respectively, compared with placebo. The SOURCE study evaluated the OCS sparing effect of tezepelumab [20]. Tezepelumab did not have a significant OCS sparing effect in the overall study population, but the odds of achieving a category of greater percentage reduction in maintenance OCS were significant in those with elevated blood eosinophils. Taken together, these data indicate that the effect of tezepelumab is greatest in patients with eosinophilic airway inflammation. It is possible that the lower effects seen in purportedly non-T2 patients may be due to therapeutic benefit in those with eosinophilic airway inflammation not detected by blood eosinophils and/or F_{ENO}.

In conclusion, tezepelumab significantly reduces airway eosinophilia, and most likely this is the primary mechanism by which it reduces the risk of asthma exacerbation in moderate–severe asthmatics. It appears to have a minimal effect on airway hyperresponsiveness to mannitol, though additional studies in subjects with severe airway hyperresponsiveness would be informative. Whether tezepelumab is truly effective in non-T2 asthma requires further study in patients with uncontrolled symptoms without sputum eosinophilia. Without a single therapeutic strategy that can ameliorate the myriad biological pathways leading to the asthma phenotype, careful consideration of the specific mechanisms contributing to symptoms and exacerbations in each patient is required to choose the most effective therapy.

Conflict of interest: A. Adatia was supported by the Canadian Institutes of Health Research/Canadian Allergy, Asthma, and Immunology Foundation/AstraZeneca/Allergen NCE Emerging Scientist Award in Allergic Asthma. M. Wahab has nothing to disclose. I. Satia is currently supported by the E.J. Moran Campbell Early Career Award, Department of Medicine, McMaster Univesity and previously reports grants from the ERS (RESPIRE3 Marie Curie Award), BMA James Trust Award, North West Lung Centre Grant; personal fees and sponsorship to attend meetings from Merck MSD, Genentech, AstraZeneca and GSK, outside the submitted work.

References

1 Kim LHY, Saleh C, Whalen-Browne A, *et al.* Triple *vs* dual inhaler therapy and asthma outcomes in moderate to severe asthma: a systematic review and meta-analysis. *JAMA* 2021; 325: 2466–2479.
2 Chen S, Golam S, Myers J, *et al.* Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. *Curr Med Res Opin* 2018; 34: 2075–2088.
3 McGregor MC, Krings JG, Nair P, *et al.* Role of biologics in Asthma. *Am J Respir Crit Care Med* 2019; 199: 433–445.
4 Mukherjee M, Forero DF, Tran S, *et al.* Suboptimal treatment response to anti-IL-5 monoclonal antibodies in severe eosinophilic asthmatics with airway autoimmune phenomena. *Eur Respir J* 2020; 56; 2000117.
5 Eger K, Kroes JA, Ten Brinke A, *et al.* Long-term therapy response to anti-IL-5 biologics in severe asthma-a real-life evaluation. *J Allergy Clin Immunol Pract* 2021; 9: 1194–1200.
6 Woodruff PG, Modrek B, Choy DF, *et al.* T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; 180: 388–395.
7 Simpson JL, Scott R, Boyle MJ, *et al.* Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006; 11: 54–61.
8 Mitchell PD, O'Byrne PM. Epithelial-derived cytokines in asthma. *Chest* 2017; 151: 1338–1344.
9 Menzies-Gow A, Corren J, Bourdin A, *et al.* Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021; 384: 1800–1809.
10 Corren J, Parnes JR, Wang L, *et al.* Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017; 377: 936–946.
11 Brightling CE, Bradding P, Symon FA, *et al.* Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002; 346: 1699–1705.
12 Gauvreau GM, O'Byrne PM, Boulet LP, *et al.* Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014; 370: 2102–2110.
13 Leckie MJ, ten Brinke A, Khan J, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; 356: 2144–2148.
14 Gauvreau G, Sehmi R, FitzGerald J, *et al.* The effect of benralizumab on allergen-induced responses in subjects with mild allergic asthma. *J Allergy Clin Immunol* 2021; 147: Suppl, AB157.
15 Sverrild A, Hansen S, Hvidtfeldt M, *et al.* The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J* 2022; 59: 2101296.
16 Anderson SD. Indirect challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010; 138: 25S–30S.

17 Brannan JD, Koskela H, Anderson SD. Monitoring asthma therapy using indirect bronchial provocation tests. *Clin Respir J* 2007; 1: 3–15.
18 Diver S, Khalfaoui L, Emson C, *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: 1299–1312.
19 Cahill KN, Katz HR, Cui J, *et al.* KIT Inhibition by imatinib in patients with severe refractory Asthma. *N Engl J Med* 2017; 376: 1911–1920.
20 Wechsler M, Menzies Gow A, Brightling CE, *et al.* Oral corticosteroid-sparing effect of tezepelumab in adults with severe asthma. *Am J Respir Crit Care Med* 2021; 203: A1197.