Not just an anti-eosinophil drug: tezepelumab treatment for type 2 asthma and beyond

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To the Editor:

Tezepelumab is a human monoclonal antibody (IgG2λ) approved in several countries and regions, including the USA and the EU, for the treatment of severe asthma. Approval was based on evidence from the phase 2b PATHWAY study (NCT02054130) and the phase 3 NAVIGATOR study (NCT03347279) [1, 2]. Tezepelumab blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine. Questions have been raised about the mechanisms of action of tezepelumab in patients with asthma, particularly regarding the effects beyond reductions in eosinophil counts in the blood and airways [3]. Here, we outline clinical evidence and mechanistic insights from randomised clinical trials supporting the multiple mechanisms of tezepelumab, including those relevant to type 2 (T2)-high and T2-low asthma.

In PATHWAY and NAVIGATOR, tezepelumab reduced the annualised asthma exacerbation rate (AAER) compared with placebo across phenotypes in a broad population of patients with severe, uncontrolled asthma [1, 2]. A reduction was observed in patients with either high or low levels of T2 inflammation biomarkers (blood eosinophils and fractional exhaled nitric oxide (F_{ENO})), although the magnitude of exacerbation reduction was greater among those with high levels. In a pooled analysis, clinically meaningful reductions in the AAER were demonstrated with tezepelumab compared with placebo in patients with high and low blood eosinophil counts (BECs) (high: ⩾300 cells·μL^{-1}; low: <150 cells·μL^{-1}) and F_{ENO} levels (high: ⩾25 ppb; low: <25 ppb), and in a "double T2-low" biomarker subgroup (BEC <150 cells·μL^{-1} and F_{ENO} <25 ppb, excluding patients receiving maintenance oral corticosteroids). A reduction in the AAER compared with placebo was also shown in a "triple T2-low" biomarker subgroup (BEC <150 cells μL^{-1}, F_{ENO} <25 ppb and no perennial allergy, excluding patients receiving maintenance oral corticosteroids), although the confidence intervals were wide owing to small sample sizes (figure 1a).

How might targeting TSLP enable tezepelumab to provide a clinical benefit in both T2-high and T2-low phenotypes? From a T2-high perspective, as a TSLP antagonist, tezepelumab has potent inhibitory effects on key upstream cells involved in T2 inflammation. In PATHWAY and NAVIGATOR, reductions in interleukin (IL)-5 and IL-13 levels were observed with tezepelumab compared with placebo [1, 2, 4]. In patients with symptomatic asthma, reductions in IL-4 levels induced by poly(I:C), an analogue of viral double-stranded RNA, were demonstrated with intravenous tezepelumab 700 mg in the phase 2 UPSTREAM study (NCT02698501) [5]. Furthermore, tezepelumab reduces BECs, airway eosinophil counts, F_{ENO} levels and IgE levels in patients with moderate-to-severe and severe, uncontrolled asthma [1, 2, 4, 6].

In addition to these effects on T2-mediated inflammation, tezepelumab recipients had reduced airway hyperresponsiveness (AHR) compared with placebo recipients in three mechanistic studies [6–8], a finding that has not been consistently demonstrated in placebo-controlled trials of T2-specific biologics [9]. In the phase 2 CASCADE study (NCT03688074), a significantly greater reduction in AHR to mannitol was observed with tezepelumab than placebo (1.41 *versus* 0.57 increase in the doubling dose of the PD_{15} from baseline; p=0.040; PD_{15} being the provoking dose of mannitol required to induce a reduction of ⩾15% in forced expiratory volume in 1 s (FEV_1) from baseline zero mannitol dose, or otherwise a reduction of ⩾10% in FEV_1 between successive non-zero mannitol doses), with more than a one doubling-dose improvement from baseline with tezepelumab [6]. Similarly, in UPSTREAM, tezepelumab reduced the

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Tezepelumab, a biologic therapy for severe asthma, blocks TSLP activity, subsequently downregulating multiple type 2 inflammatory pathways and reducing airway hyperresponsiveness *via* eosinophil-independent effects https://bit.ly/3XGpaV3

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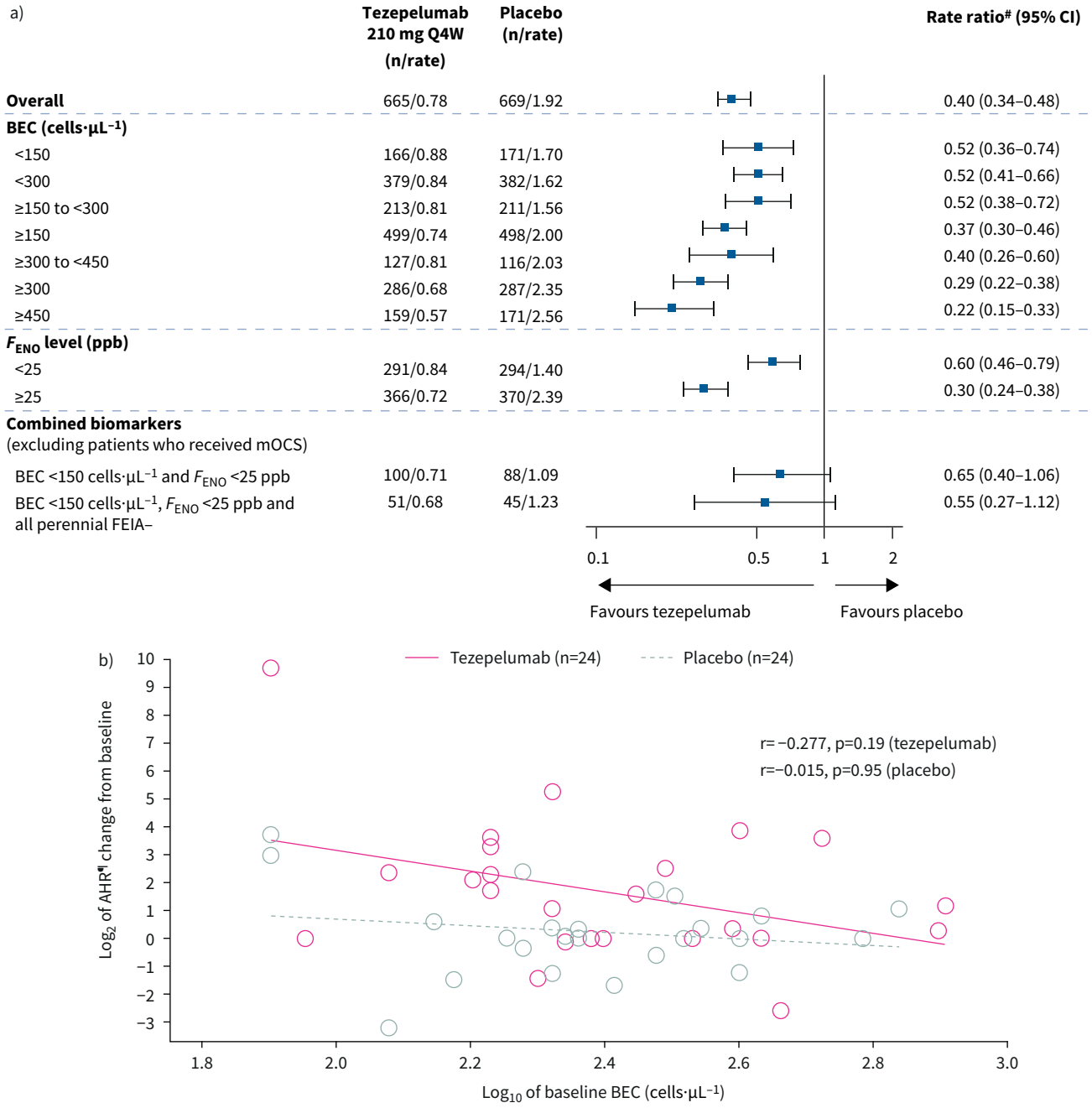

FIGURE 1 a) Annualised asthma exacerbation rate over 52 weeks with tezepelumab *versus* placebo in the overall pooled population and in individual and combined biomarker subgroups (PATHWAY and NAVIGATOR studies). b) Change from baseline to the end of treatment in airway hyperresponsiveness (AHR) score by baseline blood eosinophil count (BEC) (CASCADE study). Only patients with non-missing results for both baseline BEC and AHR score change from baseline to end of treatment are presented. Baseline was defined as the last non-missing measurement recorded on or before the date of randomisation. #: rate ratio is displayed on a log scale; data are from a negative binomial regression analysis with treatment, study (PATHWAY or NAVIGATOR), history of exacerbations (⩽2 or >2 in previous 12 months), subgroup and treatment-by-subgroup interaction as covariates. ¶: AHR is expressed as doubling dose units for the PD_{15} of mannitol (defined as the provoking of mannitol required to induce a reduction of ⩾15% in forced expiratory volume in 1 s (FEV_1) from the baseline zero mannitol dose, or otherwise a reduction of ⩾10% in FEV_1 between successive non-zero mannitol doses). FEIA: fluorescence enzyme immunoassay; F_{ENO}: fractional exhaled nitric oxide; mOCS: maintenance oral corticosteroid; Q4W: every 4 weeks; r: Spearman's rank coefficient.

proportion of patients with AHR to mannitol compared with placebo [8]. Lastly, tezepelumab reduced AHR measured by challenge with methacholine [7], which acts directly on airway smooth muscle. Supportive of an eosinophil-independent mechanism, the effect of tezepelumab in reducing AHR to

mannitol in CASCADE was independent of baseline BECs (figure 1b). The precise mechanism of tezepelumab's reduction of AHR, particularly the influence of TSLP on mast cell function, is being examined in ongoing studies.

These effects of tezepelumab differ from the more restricted effects of other biologics approved for the treatment of severe asthma, which target specific T2 inflammatory pathways (IgE, IL-5, eosinophils or IL-4/13). For example, the IL-5 receptor-targeting, anti-eosinophil agent benralizumab reduces BECs but does not affect levels of F_{ENO} or IgE [10], and the anti-IL-4/13 dupilumab reduces levels of F_{ENO} and IgE but not airway eosinophil counts or BECs (although this is under further evaluation) [11]. The relatively circumscribed T2 mechanisms of these biologics probably explain their failure to reduce the AAER meaningfully in patients with T2-low asthma.

In summary, tezepelumab blocks TSLP activity and, as a result, downregulates multiple T2 pathways and reduces AHR. The broad mechanism of action and clinical efficacy of tezepelumab are distinct from the targeted T2 effects of other biologics. Although future research may help to further elucidate the full mechanisms of action of tezepelumab, current clinical evidence suggests a collective mechanism beyond airway eosinophils and T2 inflammation.

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