Journal club

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may offer a useful point of care test to identify eosinophilic driven exacerbations. However, although the clinical utility of this approach needs to be tested to ensure patient outcomes are maintained, it may enable more focused use of steroids and antibiotic therapy and is an important step towards personalised medicine in patients with difficult asthma.

TEZEPELUMAB IN SEVERE ASTHMA: REDUCED EXACERBATIONS IN FREQUENT EXACERBATORS

Biological therapies targeting the type 2 (T2) inflammatory pathway have become incorporated into guidelines for the management of atopic asthma but have not consistently shown benefits in those patients with asthma without evidence of ongoing eosinophilic inflammation. Tezepelumab targets thymic stromal lymphopoietin which activates inflammation beyond the T2 pathway. Menzies-Gow *et al* (*N Engl J Med*, 2021, DOI: 10.1056/NEJMoa2034975) investigated the impact of tezepelumab on patients with asthma already established on medium-dose or high-dose inhaled corticosteroids and two exacerbations in the previous year in a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. A total of 1061 patients underwent randomisation with 528 receiving tezepelumab and 531 placebo. Tezepelumab treatment reduced the annual exacerbation rate (0.93 compared with 2.10; rate ratio 0.44, 95% CI 0.37 to 0.53; $p < 0.001$) with improvement also seen in subgroup analysis of patients with a low serum eosinophil count (< 300 cells/ μ L). Furthermore, a significant improvement was seen in prebronchodilator FEV₁ at week 52 compared with baseline (0.23 L tezepelumab, 0.09 placebo, $p < 0.001$). Reduction in serum eosinophil counts and fraction of exhaled NO (FeNO) levels from baseline were documented as early as week 2 in the treatment arm and were sustained throughout the trial. Additionally, there were reductions in total serum IgE levels, indicating that tezepelumab targets multiple pathways to derive clinical benefit.

TEZEPELUMAB IN SEVERE ASTHMA: SUPPRESSES EOSINOPHILIC AIRWAY INFLAMMATION EVEN IN PATIENTS WITH LOW BASELINE T2 MARKERS

While clinical efficacy data for tezepelumab is accumulating, there remains interest in the mechanism of action to allow for better targeting of this therapy. Diver *et al* (*Lancet Respir Med*, 2021 doi.org/10.1016/S2213-2600(21)00226-5) report the results of a double-blinded, randomised placebo-controlled phase 2 trial, the CASCADE study. The study protocol recruited adult patients with moderate-to-severe asthma and evidence of poor control to receive

tezepelumab (randomised $n = 59$; completed $n = 48$) or placebo (randomised $n = 57$; completed $n = 51$) every 4 weeks for a planned 28 weeks followed by a 12-week follow-up period. The study protocol required amendment due to the COVID-19 pandemic to allow for ongoing treatment until follow-up testing could be completed. The study used bronchial biopsies to investigate the inflammatory profile of patients and had preplanned subpopulation analyses according to FeNO (< 25 or ≥ 25 ppb) and serum eosinophil levels (< 150 , 150 – 300 and > 300 cells/ μ L). The results demonstrated a nominally significant reduction in submucosal eosinophils in tezepelumab-treated patients compared with placebo ($p < 0.001$) consistent across all T2 subgroups. There was no evidence of reduction in other inflammatory cells. Reassuringly, tezepelumab was safe and well tolerated with no safety concerns raised. The study provides evidence of the mechanism of action of tezepelumab including efficacy in patients with a low T2 profile.

MEPOLIZUMAB IN SEVERE ASTHMA: INSIGHT INTO DIFFERENT EXACERBATION PHENOTYPES

Despite the impact of eosinophil depleting therapies such as mepolizumab, patients with severe asthma continue to suffer exacerbations, although there are increasing data to suggest that distinct phenotypes may exist that could be used to make therapeutic decisions such as use of acute or long-term antibiotics. In the MEX study, McDowell *et al*. (*Lancet Respir Med*, 2021, doi.org/10.1016/S2213-2600(21)00004-7) performed an exploratory analysis using prospectively collected data during exacerbations in patients with severe asthma treated with mepolizumab. The aim was to produce detailed phenotyping of the exacerbations. To assess the inflammatory characteristics of the exacerbations, sputum from the patient's first exacerbation was divided according to high or low sputum eosinophil count (cut-off point 2%). No difference in sputum characteristics was seen in those who exacerbated versus those who did not and the time to exacerbation was unaltered by degree of sputum eosinophilia or time from mepolizumab treatment. Analogous to chronic obstructive pulmonary disease (COPD), exacerbations were more likely in patients with a history of exacerbations prior to study entry. FeNO correlated with sputum eosinophilia at exacerbation ($r = 0.56$, $p < 0.0001$) with a low FeNO discriminating between exacerbation phenotype (FeNO ≤ 20 ppb negative predictive value (NPV) for eosinophilic sputum 100%, 95% CI 80% to 100%; ≥ 50 ppb positive predictive value (PPV) for eosinophilic sputum 77%, 95% CI 60% to 90%). The investigators conclude that measurement of FeNO at exacerbation

DUPILUMAB IN MODERATE TO SEVERE ASTHMA: BIGGEST BENEFIT IN THOSE WITH MOST INFLAMMATION

Interleukin (IL)-4 and IL-13 are important drivers of the T2 inflammatory pathway and patients with T2 inflammation often have more severe disease and are more likely to suffer exacerbations. Dupilumab is a biologic targeting this T2 inflammatory pathway and has been shown to reduce asthma exacerbations in patients with moderate-to-severe asthma in the Liberty Asthma QUEST study. The original study used dupilumab 200 mg and 300 mg fortnightly and pooled these treatments for this analysis. Corren *et al* conducted a post-hoc analysis of 1902 patients (dupilumab $n = 1264$, placebo $n = 638$) from this phase 3 study (*Eur Respir J* 2021 DOI: 10.1183/13993003.04498-2020) examining exacerbation frequency, lung function and quality of life stratified by markers of T2 inflammation (eosinophil count, inhaled corticosteroid dose and FeNO). Dupilumab reduced the rate of asthma exacerbations, improved prebronchodilator FEV₁ at 12 weeks and the Asthma Control Questionnaire 5 scores at 24 weeks, irrespective of exacerbation frequency in the past year (≥ 1 , ≥ 2 or ≥ 3), baseline FeNO levels, baseline eosinophil count (≥ 300 vs ≤ 150 cells/ μ L) or baseline inhaled corticosteroid dose (medium vs high). The magnitude of impact was greatest in those patients with high levels of T2 inflammation and failed to reach statistical significance in those with the lowest levels. It is important to acknowledge that this post-hoc analysis was not powered for these analyses and that no corrections for multiplicity were made. However, it emphasises the clinical outcomes of dupilumab treatment and that those with more severe T2 inflammation may reap additive benefits.

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