# Journal club

Sophie Masterson

## TARGETED TREATMENT FOR CHRONIC COUGH: THE POWER OF PLACEBO SHOULD NOT BE UNDERESTIMATED

Purinergic signalling and sensitisation of $P2X_3$ receptors on the vagus nerve have been implicated in the mechanism of chronic cough. McGarvey *et al* assessed the efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist for the treatment of chronic cough in two phase 3 trials: COUGH-1 and COUGH-2 (*Lancet* 2022;399:909). Both were multinational double-blind, placebo-controlled, parallel group studies comparing 15 mg and 45 mg dosing, 1:1:1 allocation. COUGH-1 ran over a 12-week study period (n=732) and COUGH-2 over 24 weeks (n=1317). Patients with a diagnosis of unexplained chronic cough or refractory chronic cough (despite optimal medical management of associated comorbidity) for over 1 year were included. Current smokers and patients with forced expiratory volume in one second ($FEV_1$):-forced vital capacity ratio <0.6 or abnormal chest imaging were excluded. The primary endpoint was reduction in 24-hour cough frequency in treatment groups versus placebo. Secondary endpoints included clinically significant improvement in Leicester Cough Questionnaire score. Results were similar in both studies: at 12 weeks in COUGH-1, there was a 53% reduction in cough frequency in placebo group, 52% in 15 mg group and 62% reduction in 45 mg group. COUGH-2 reported 57%, 57% and 63% reductions, respectively. Adverse effects predominantly related to taste disturbance: 20% of COUGH-2 participants in the 45 mg group discontinued the study due to adverse events (vs rates of 4.8% in placebo and 7.7% in 15 mg groups). Although 45 mg two times per day of gefapixant achieved a significant relative reduction in cough frequency versus placebo, this was overshadowed by the high rates of adverse effects and significant placebo effect.

## ANTI-INTERLEUKIN-33 IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: SOME PROMISE BUT SMOKING STATUS REMAINS AN IMPORTANT DETERMINANT OF OUTCOME

Itepekimab, an anti-interleukin-33 (IL-33) monoclonal antibody, has demonstrated potential efficacy in the treatment of asthma but has not been studied in patients with chronic obstructive pulmonary disease (COPD). Rabe *et al* (*Lancet Respir Med* 2021;9:1288) performed genetic analyses to investigate the association between IL-33 and COPD, followed by a phase 2a study comparing itepekimab against placebo on annualised COPD exacerbation frequency. Genetic studies of three known functional variants of IL-33 and IL-1RL1 demonstrated association with COPD although weaker than with asthma. Carriers of an IL-33 loss-of-function mutation had lower serum IL-33 levels and a 21% reduced risk of COPD compared with non-carriers (p=0.0049). Trial participants were aged 40–75 years with moderate to severe, symptomatic COPD and a history of exacerbation. They were randomised 1:1 to receive 300 mg itepekimab every 2 weeks (n=172) or placebo (n=171) for a minimum of 6 months alongside their stable maintenance therapy. Itepekimab did not significantly improve exacerbation rates (relative risk 0.81, 95% CI 0.61 to 1.07, p=0.13) or lung function. However, in the predefined subgroup of ex-smokers treatment with itepekimab conferred a 42% reduction in annualised exacerbation frequency (RR 0.58, 95% CI 0.39 to 0.85, p=0.006) and improvement in $FEV_1$ (least squares mean different 0.09 L). Variation in outcomes between groups could be due to a direct pro-inflammatory property of cigarette smoking or reflect the heterogeneous nature of COPD. Although the results in former smokers were encouraging, the primary endpoint was not met. Phase 3 studies are underway.

## AIR FILTERS IN COPD: GREATEST BENEFIT WHEN USED LONGER

Poor indoor air quality has been associated with increased symptom burden in COPD. In the CLEAN AIR Study, Hansel *et al* (*Am J Respir Crit Care Med* 2022:205;421) examined whether the use of a high-efficiency particulate absolute (HEPA) filter would improve respiratory morbidity in ex-smokers with COPD. The primary outcome was improvement in St George's Respiratory Questionnaire (SGRQ) scores. Ex-smokers with COPD ($FEV_1$ ≤80% predicted), with home particulate matter 2.5 levels >10 ($PM_{2.5}$<10 is WHO-recommend air quality target), were randomised 1:1 to receive active or sham HEPA filters. Groups were generally well matched although the active group had a higher proportion of white participants (74.1% vs 55.2%) and those earning ≥$30 000/year (43.1% vs 31.0%). Device efficacy was confirmed with significant reductions in $PM_{2.5}$ and nitrogen dioxide in the active group. At 6 months, there was no difference in SGRQ total score −1.55 (95% CI −5.75 to 2.65, p=0.465). However, there was improvement in SGRQ symptoms subscale, rescue inhaler use (incidence rate ratio 0.54, p=0.011), moderate exacerbation frequency (IRR 0.32, p=0.033) and Breathlessness Cough and Sputum Score. Furthermore, a per-protocol analysis of participants who had used at least one device for 80% of the time over the 6-month trial period demonstrated a significant and clinically important reduction in SGRQ scores: −4.76 in active versus sham groups (95% CI −9.12 to −0.34, p=0.035). Indoor air filters are an environmental intervention that can improve respiratory-associated quality of life although benefit is most likely in those indoors for the longest time and who use the device for the majority of that period.

## MORTALITY IN COPD EXACERBATION REQUIRING NON-INVASIVE VENTILATION: SIMPLE TOOL CAN HELP WITH OUTCOME PREDICTION

Use of non-invasive ventilation (NIV) in acute exacerbation of COPD (AECOPD) with acute hypercapnic respiratory failure (AHRF) has been shown to reduce the need for invasive ventilation and mortality. Despite this, reports suggest that NIV is underused with substantial variation in application. Hartley *et al* (*Eur Respir J* 2021:58;2004042) propose the Non-Invasive Ventilation Outcome (NIVO) score, a clinical prediction tool for in-hospital mortality in patients with AECOPD and AHRF. The derivation set consisted of a retrospective cohort of AECOPD with AHRF (n=489) from a two-site UK hospital trust. Eight variables were identified then validated through prospective analysis at 10 other UK centres (n=733). Variables identified in the derivation stage were validated using inpatient mortality as the dependent variable, with significance confirmed through multivariate, logistic regression analysis. The NIVO score consists of seven items, scoring a maximum of 9 points and includes chest radiograph consolidation, Glasgow Coma Scale score ≤14, atrial fibrillation, pH <7.25, time to acidaemia >12 hours, extended Medical Research Council dyspnoea (eMRCD) score 5a or 5b. Time to acidaemia and eMRCD 5a each score 2 points, eMRCD 5b scores 3. Scores are stratified into risk categories with corresponding in-hospital (low, 0–2=5%; medium, 3–4=17%; high, 5–6=41% and very high, 7–9=71%) and 90-day mortality prediction (low, 0–2=16%; medium, 3–4=33%; high, 5–6=50% and very high, 7–9=80%). The data confirm the poor outcomes in the short and medium term of some patients with AHRF secondary to an AECOPD, however, it guides the clinician by indicating the relative limited use of some commonly used clinical indicators such as $FEV_1$ or home oxygen use in supporting decision-making in this group. The final tool is suitable for use at the bedside using readily available data and as such can guide informed decision-making around ventilatory support in AECOPD with AHRF.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Not applicable.

**Provenance and peer review** Commissioned; internally peer reviewed.



**To cite** Masterson S. *Thorax* 2022;**77**:948.

*Thorax* 2022;**77**:948.
doi:10.1136/thorax-2022-219478

**Correspondence to** Dr Sophie Masterson, Barts Health NHS Trust, London, UK; smasterson1@nhs.net