https://doi.org/10.1016/S2213-2600(21)00182-X

COPD exacerbations: targeting IL-33 as a new therapy

Richard Y Kim, Brian G Oliver, Peter A B Wark, Philip M Hansbro and Chantal Donovan

Current therapies for chronic obstructive pulmonary disease (COPD) aim to control symptoms, improve lung function, reduce acute exacerbations, 1 and decrease mortality. Despite improvements in disease management, available therapies with inhaled corticosteroids and long-acting bronchodilators have modest effects on reducing acute exacerbations of COPD and disease progression and only produce benefits in some people. 2 New and effective therapies for acute exacerbations are needed. Biological therapies that target specific pathways have been successful in several respiratory diseases and are now being assessed in COPD, albeit with little success so far.

Recent evidence highlights the potential for therapeutic blockade of IL-33 in COPD. 3 IL-33 is an alarmin and pleotropic cytokine involved in type 2 immune responses, and the activation, migration, and recruitment of immune cells that can drive disease pathogenesis. 3 IL-33 levels are increased in lung biopsy samples, epithelial and endothelial cells, serum or plasma, and sputum of patients with COPD 456 and correlate with reduced lung function. 5 Lung IL-33 levels are also increased in animal models of cigarette-smoke induced COPD. 7 Collectively, these data suggest that targeting IL-33 in patients with COPD might be beneficial.

In The Lancet Respiratory Medicine , Klaus Rabe and colleagues 8 present data from genetic analyses of gain-of-function and loss-of-function IL-33 mutations and the much anticipated results of a phase 2a randomised, placebo-controlled, clinical trial (NCT03546907) of the IL-33-targeting human IgG4 monoclonal antibody, itepekimab (SAR440340/REGN3500), in 343 patients with COPD at risk of exacerbations (mean age 63·9 years [SD 6·7], 194 [57%] men and 149 [43%] women). As a primary endpoint, this study assessed the annualised rate of moderate-to-severe acute exacerbations of COPD and as a secondary endpoint it assessed improvement in lung function measured as a change in baseline pre-bronchodilator FEV 1 in weeks 16–24 of the trial. Genetic analyses corroborated previous findings of the roles of IL-33 variants in IL-33 bioavailability and asthma risk by independently reproducing findings from two large cohorts (UK Biobank and Geisinger Health Systems) as well as the previously reported association between IL-33 variants, eosinophil counts, and asthma. 9 These confirmatory associations are the positive controls for the study, which goes on to demonstrate that a rare loss-of-function, splice-acceptor allele (rs146597587) and serum IL-33 levels are linked to reduced COPD risk. Conversely, gain-of-function mutations in IL33 and IL1RL1 variants are associated with increased risk. These data suggest that targeting IL-33 might be beneficial and formed the rationale for examining the effects of IL-33 blockade in COPD.

The primary outcome of reducing annualised rate of moderate-to-severe acute exacerbations of COPD was not achieved with itepekimab treatment versus placebo (relative risk [RR] 0·81 [95% CI 0·61 to 1·07], p=0·13). However, subgroup analysis identified the potential benefits of targeting IL-33 in reducing exacerbation frequency and improving lung function versus placebo in former smokers with COPD

(exacerbation frequency treatment effect RR 0·58 [95% CI 0·39 to 0·85], p=0·0061; FEV 1 least squares mean difference 0·09 L [95% CI 0·02 to 0·15], p=0·0076), who are an important clinical subset.

Some important questions remain. What role did the study's recruitment characteristics play in the testing accuracy or power of the intended primary outcome? What confounding effects could the high frequency of moderate-to-severe exacerbations in enrolled patients, and patients with symptoms of chronic bronchitis, have on the reported outcomes?

The placebo control group had an adjusted annualised exacerbation rate (1·61 [95% CI 1·32–1·97]) similar to that reported in placebo groups of two phase 3 clinical trials of mepolizumab in COPD (1·49 [0·65–0·98] and 1·71 [0·68–0·98]). 10 Thus, it is unlikely that the annualised exacerbation rate in the placebo group affected the reported outcomes. Notably, previous data showed, using multivariate logistic regression analysis in patients with stable COPD, that chronic bronchitis is the only clinical parameter significantly associated with high IL-33 levels (odds ratio 1·87 [95% CI 1·14–3·09]). 6 Treating patients with COPD and chronic bronchitis with itepekimab might have more pronounced effects on the outcomes, and future studies might subcategorise patients with chronic bronchitis as a separate variable.

The promising results with itepekimab in former smokers, but not current smokers, raises the possibility that existing therapy in the former smoker subcategory (inhaled corticosteroids, long-acting b2-agonists [LABA] or long-acting muscarinic receptor antagonists [LAMA]) contributed to the beneficial effects of itepekimab. Small sample sizes in the two double therapy subgroups precluded examination of the potential influence of either double therapy on the efficacy of itepekimab. These data also highlight other avenues of investigation that can be pursued in the future, where subcategorising former smokers with exacerbations that required steroid only, antibiotics only, or both steroid and antibiotics, might provide additional clues as to which type of exacerbation is reduced by itepekimab and inform new additions to existing clinical guidelines.

Furthermore, does itepekimab exert steroid-sparing effects? The data from this study encouragingly indicates this possibility, and examining the annualised rate of moderate-to-severe acute exacerbations of COPD that require systemic corticosteroids (either alone or in combination with antibiotics) in a larger cohort will enable interrogation of this clinically important possibility. In a recent phase 2 study of itepekimab in people with asthma (NCT03387852), itepekimab was not as effective as the monoclonal therapy, dupilumab. However, it is unclear whether the combination of itepekimab and dupilumab was additively or synergistically beneficial. What effects would the combination of itepekimab and another monoclonal antibody have on acute exacerbations of COPD? Future studies that explore this question could also incorporate biomarker-driven recruitment of patients with gain-of-function mutations in IL33 and IL1RL1 variants.

Significantly, this study links the loss-of-function, splice-acceptor allele (rs146597587) with reduced COPD risk and highlights the potential therapeutic use of adding a biologic (such as itepekimab) to standard treatment regimens in former smokers with COPD. A phase 3 itepekimab clinical trial (NCT04701983) will assess the efficacy of itepekimab in former smokers in acute exacerbations of COPD, and an examination of the mechanisms through which itepekimab might impart steroid-sparing effects will add further gravity to these outcomes.

We declare no competing interests.

References

1. Halpin DMG, Criner GJ, Papi A, et. al.: Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2021; 203: pp. 24-36.
View In ArticleCross Ref
2. Lipson DA, Crim C, Criner GJ, et. al.: Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020; 201: pp. 1508-1516.
View In ArticleCross Ref
3. Donovan C, Hansbro PM: IL-33 in chronic respiratory disease: from preclinical to clinical studies. ACS Pharmacol Transl Sci 2019; 3: pp. 56-62.
View In Article
4. Byers DE, Alexander-Brett J, Patel AC, et. al.: Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease. J Clin Invest 2013; 123: pp. 3967-3982.
View In Article
5. Kearley J, Silver JS, Sanden C, et. al.: Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. Immunity 2015; 42: pp. 566-579.
View In ArticleCross Ref
6. Kim SW, Rhee CK, Kim KU, et. al.: Factors associated with plasma IL-33 levels in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2017; 12: pp. 395-402.
View In Article
7. Donovan C, Starkey MR, Kim RY, et. al.: Roles for T/B lymphocytes and ILC2s in experimental chronic obstructive pulmonary disease. J Leukoc Biol 2019; 105: pp. 143-150.
View In ArticleCross Ref
8. Rabe KF, Celli BR, Wechsler ME, et. al.: Safety and efficacy of itepekimab in patients with moderate to severe COPD: a genetic analysis and randomised, double-blind, phase 2a trial. Lancet Respir Med 2021; published online July 21. https://doi.org/10.1016/S2213-2600(21)00167-3
View In Article
9. Smith D, Helgason H, Sulem P, et. al.: A rare IL33 loss-of-function mutation reduces blood eosinophil counts and protects from asthma. PLoS Genet 2017; 13:
View In Article
10. Pavord ID, Chanez P, Criner GJ, et. al.: Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med 2017; 377: pp. 1613-1629.