Interleukin 33: a suitable target for biological therapies of COPD?

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Shareable abstract (@ERSpublications)
Because of the relevant importance of the IL-33/ST2 axis in COPD pathobiology, the future results of AERIFY-1 and AERIFY-2 trials could disclose new information about subgroups of responder patients to biologic therapies for this highly prevalent disease https://bit.ly/3USJCUP

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COPD is a progressive and disabling lung disorder characterised by poorly reversible airflow limitation and mucus hypersecretion, associated with dyspnoea, low exercise tolerance and poor quality of life [1]. Indeed, COPD is one of the main causes of morbidity and mortality worldwide, as well as the most common determinant of chronic respiratory failure [2]. Available pharmacological strategies that are currently used for COPD treatment include bronchodilators and inhaled corticosteroids [3]. However, although these treatments can improve symptoms and decrease exacerbation rate, they do not appear to be able to effectively suppress the underlying pathogenic processes. Among these, smoking-driven oxidative stress and airway inflammation play a key role [4]. In particular, inflammatory mechanisms involve the active participation of the innate immune system, as shown by accumulation within the airways and lung tissue of neutrophils, macrophages, innate lymphoid cells, dendritic cells, natural killer cells, and sometimes also eosinophils and mast cells [5]. Moreover, COPD pathobiology is also dependent on effective crosstalk between innate and adaptive immune mechanisms, leading to recruitment and activation of T helper (Th)1, Th2, and especially Th17 and $CD8^+$ T-lymphocytes [6]. Such immune-inflammatory cells constantly communicate with structural cells, including epithelial cells, fibroblasts, airway smooth muscle cells and endothelial cells, which are responsible for the structural changes that are a hallmark of COPD pathology. The dialogue between immune-inflammatory and structural cells is provided by several mediators such as cytokines, chemokines, growth factors and autacoids [7]. Both inflammatory and structural cells release large amounts of reactive oxygen species, which contribute to amplifying the oxidative stress due to exogenous oxidants derived from cigarette smoke, biomass combustion and air pollution. Airway and lung inflammation and oxidative stress are further worsened by bacterial and viral infections, which represent the most common causes of COPD exacerbations [8].

In regard to this complex pathophysiological network, a central function is exerted by interleukin (IL)-33, a member of the IL-1 family of cytokines whose biological effects are mediated by the suppression of tumorigenicity 2 (ST2) receptor, which is widely expressed among the aforementioned immunoinflammatory and structural cells [9]. IL-33 belongs to the group of innate cytokines known as alarmins, which are produced by the airway epithelium in response to tissue damage triggered by multiple environmental factors such as cigarette smoke, air pollution and infectious agents. In murine experimental models of COPD, as well as in human airway epithelial cells, IL-33 release can be induced by exposure to cigarette smoke [10]. As a consequence, IL-33 intensifies lung inflammation and stimulates mucin production and collagen deposition. IL-33 and its ST2 receptor are highly expressed within epithelial and endothelial cells found in lung biopsies obtained from COPD patients. Furthermore, lung expression of IL-33 is associated with COPD severity and enhanced serum levels of IL-33 are correlated with a high risk of COPD exacerbations [11]. Based on these observations, some anti-IL-33 fully human monoclonal antibodies such as itepekimab, tozorakimab and the anti-ST2 receptor antibody astegolimab have been considered as biological drugs worthy of being tested in COPD patients. Therefore, several phase 1, 2 and

3 clinical trials have been completed or are currently ongoing [12]. Regarding itepekimab, a recent phase 2a trial primarily aimed to evaluate the effects of this biologic on the annualised rate of moderate-to-severe acute exacerbations in COPD patients on standard inhaled treatment. Although the primary endpoint was not reached in the overall study population, a careful subgroup analysis of the results of this trial showed that itepekimab was able to decrease COPD exacerbations and improve lung function in former smokers, rather than in current ones [13]. In order to explain such differences, it has been suggested that the therapeutic failure of itepekimab in current smokers can be due to the toxic effects exerted by tobacco smoke on basal airway epithelial cells, which are the main cellular source of IL-33 (figure 1).

Therefore, in this issue of *ERJ Open Research*, Rabe *et al*. [14] describe the study designs of the two phase 3 AERIFY-1 and AERIFY-2 randomised, multicentre, double-blind, placebo-controlled trials. The primary purpose of both AERIFY-1 and AERIFY-2 is to verify the efficacy of itepekimab in decreasing the annualised rate of moderate-to-severe acute exacerbations of COPD in former smokers. Secondary endpoints include the eventual effects of itepekimab on lung function, respiratory symptoms and health-related quality of life. Study protocols also refer to the assessment of drug safety. Moreover, a further aim of AERIFY-2 is to evaluate the same outcomes in current smokers with COPD. Based on previous pharmacokinetic and safety evaluations, itepekimab will be administered subcutaneously at dosage schedules of 300 mg every 2 or 4 weeks for a treatment period of 52 weeks. Taken together, AERIFY-1 and AERIFY-2 should enrol >1000 patients. The study rationale underpinning the design of AERIFY-1/2 seems to be well-founded on currently available data. Indeed, these twin trials have been conceived to eventually confirm and extend, in a larger phase 3 sample population, the efficacy and safety of itepekimab. Hence, such an experimental approach might help to further understand the eventual differences characterising the underlying pathogenic mechanisms of COPD in current and former smokers. Another interesting aspect related to the evaluation of an IL-33-targeted therapeutic strategy in COPD patients refers to the possibility of impacting on a broad range of disease inflammatory phenotypes, mainly including the widely diffused cellular pattern sustained by neutrophils and macrophages. This should be an indubitable advantage in comparison with biologics targeting only type 2 inflammation such as dupilumab,

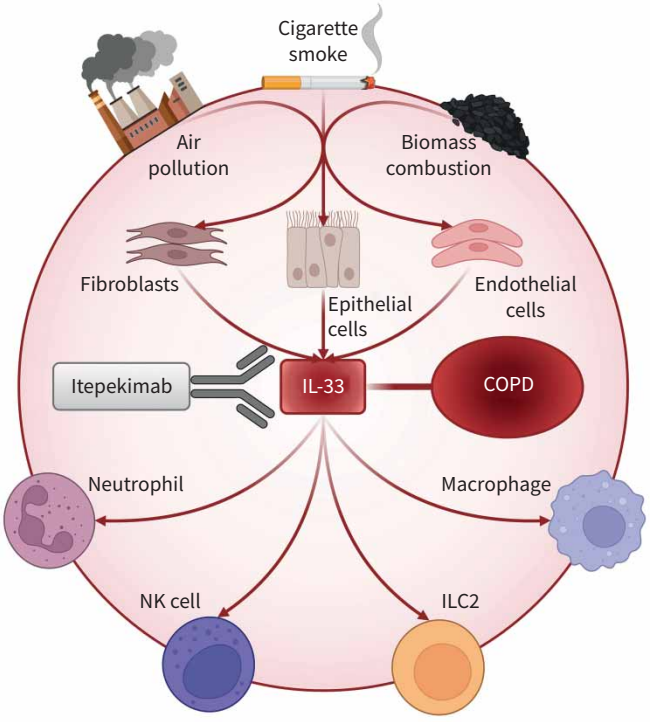

FIGURE 1 Air pollution, cigarette smoke and biomass combustion stimulate lung epithelial cells, fibroblasts and endothelial cells to release high levels of interleukin (IL)-33. This cytokine intensifies airway/lung inflammation in patients with COPD, activating neutrophils, natural killer (NK) cells, type 2 innate lymphoid cells (ILC2) and macrophages. In this regard, itepekimab is a fully human monoclonal antibody that targets IL-33, with potential clinical activity in COPD. Created with BioRender.com.

which has been recently assessed in a minority of COPD patients having ⩾300 eosinophils per microlitre of blood [15]. In fact, IL-33 appears to be involved in the pathobiology of both type 2 (T2) and T2-low airway and lung inflammation.

In conclusion, because of the relevant importance of the IL-33/ST2 axis in the molecular and cellular pathways implicated in COPD pathobiology, the future results of AERIFY-1 and AERIFY-2 trials could disclose new information about potentially larger subgroups of patients responding to biological therapies for this highly prevalent and heterogenous respiratory disease.

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