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Eosinophils and therapeutic responses to steroids and biologics in COPD: a complex relationship

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The treatment of the inflammatory component of COPD has undergone significant changes over the past two decades. Inhaled corticosteroids were commonly used, just as they were in asthma, until their use was discouraged by large clinical trials such as the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease[1] and the Copenhagen Lung Health Study,[2] which demonstrated modest to no short-term improvements in lung function, with minimal effect on long-term decline associated with ongoing smoking. The trial designated ISOLDE[3] suggested that the benefits are limited to patients with severe airflow obstruction and frequent exacerbations. The use of inhaled steroids was further supported by retrospective and case-control studies that suggested that they reduced mortality from COPD.[4] Seminal observations from Suissa et al.[5] identified "an immortal time bias" in these observational studies that would reduce the benefits attributed to the use of inhaled corticosteroids. With increasing recognition of adverse effects, particularly pneumonias with the use of inhaled corticosteroids,[6] international guidelines, quite correctly, recommended against the regular use of high doses of inhaled steroids in most patients with COPD.[7]

It is therefore clinically important to be able to identify biomarkers or predictors of response to glucocorticosteroids in patients with COPD so that they are used judiciously. Approximately 25-30% of patients with COPD have raised numbers of circulating eosinophils,[8] and 8-10% may have persistently elevated eosinophil numbers in their sputum.[9] Although the correlations between eosinophil numbers in blood and sputum[10] or tissue[11] are poor, both are predictors of exacerbations[12] and of response to corticosteroids (both oral and inhaled).[13-15] Early clinical studies[13] demonstrated that improvement in FEV_1 and symptoms with prednisone use in those with sputum eosinophils greater than 3% is more significant than that demonstrated with any currently approved bronchodilator for COPD. More recent studies have demonstrated that not only are eosinophils (> 2%) in circulation a predictor of response to corticosteroids,[16,17] but the use of corticosteroids in those with lower eosinophil counts show a signal to harm as well.[16]

However, unlike in asthma, eosinophils may not be directly contributing to exacerbations as the results of clinical trials regarding anti-IL-5 monoclonal antibodies in patients with COPD and raised circulating eosinophil numbers of > 150 or 300 cells/μL have been disappointing. Clinical trials using mepolizumab demonstrated modest non-statistically significant reduction in exacerbations,[18] while larger trials using benralizumab did not meet the primary endpoint of exacerbation reduction.[19] In the METREX (ClinicalTrials.gov number NCT02105948) clinical trial (n = 230 in the eosinophilic arm, and n = 604 in the non-eosinophilic + placebo arms) 100 mg s.c. mepolizumab was associated with an 18% reduction in exacerbations (p = 0.04). However, in the replicate METREO (ClinicalTrials.gov number NCT02105961) trial, the same dose of mepolizumab (n = 223 in the eosinophilic arm, and n = 226 in the non-eosinophilic + placebo arms) was associated with a non-statistically significant 20% reduction in exacerbation frequency (p = 0.07). Paradoxically, the 14% reduction in exacerbations observed with the higher dose of 300 mg s.c. mepolizumab was not statistically significant (p = 0.14). In the much larger clinical trials with benralizumab—GALATHEA and TERRANOVA (ClinicalTrials.gov numbers NCT02138916 and NCT02155660, respectively)—neither the lower dose of 30 mg s.c. nor the higher dose of 100 mg s.c. were associated with statistically significant reductions in exacerbations, although higher blood eosinophil numbers were associated with greater reduction in exacerbation frequency. While these large anti-eosinophil clinical trials failed to show a significant clinical benefit, a relatively small Canadian study in which 147 patients discharged from an ER were randomly assigned to daily doses of prednisone 40 mg or placebo demonstrated significant reductions in relapse, as well as improvements in FEV_1 and in symptoms.[20] Indeed, we had demonstrated, in 20 patients with severe COPD and CT-confirmed emphysema, a > 300 mL improvement in FEV_1 with a short five-day course of prednisone, but no improvement in FEV_1 after six months of treatment with mepolizumab 750 mg i.v. monthly.[21]

Despite observations that small studies of 20-150 patients have demonstrated a benefit of steroids use in those with increased blood or sputum eosinophils, large studies with 600-4,000 patients could not demonstrate benefits from powerful anti-eosinophil biologics, suggesting that steroids might be acting on some other cells or pathways that are upregulated along with eosinophils. Eosinophils may not directly be contributing to exacerbations but work as a biomarker for another process that is being targeted by steroids. We are not currently certain what these cellular or other immunological processes might be. Steroid withdrawal studies such as that carried out by the GLUCOLD study group[22] provide us some evidence that CD8+ cells or mast cells may increase with steroid dose reduction and are associated with worsening of symptoms. Indeed, there is evidence of an association of mast cells with alveolar septae in patients with centrilobular and paraseptal emphysema.[23] Mast cells, eosinophils,[24] and basophils[25] may be activated by IL-33

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to secrete IL-13 that can stimulate mucus secretion or directly stimulate macrophages to release matrix metalloproteinase-12. The recent demonstration that, unlike anti-IL-5 biologics, anti-IL-4R biologic dupilumab could reduce exacerbations by a third in patients with COPD,[26] eosinophilia, and history of bronchitis would suggest that this strategy might be effective in those patients with raised IL-13 activity in the airway[24] and consequent mucus secretion contributing to symptoms and exacerbations.

Other strategies such as targeting IL-33 signalling[27,28] have suggested modest improvements in former smokers and those with low blood eosinophils. There is also speculation that the benefits of IL-33 blockade might be influenced by a complex interacting network involving the microbiome and airway inflammation.[29] Eosinophilia observed in blood (or even in sputum) may not always be a pathological process but could also be a reflection of airway microbial dysbiosis[30] that could also be modulated by inhaled or oral corticosteroids. The association between airway eosinophilia in COPD and mixed viral and bacterial infections was demonstrated almost two decades ago,[31] and this may not be critically dependent on IL-5.[32]

In summary, epithelial alarmin activation by multiple stimuli including cigarette smoke, pollutants, and certain microbes could recruit eosinophils into the airway in patients with COPD. While increased eosinophils in blood and COPD are predictors of exacerbations and response to corticosteroids, these effects may not be directly modulated by eosinophils. Therefore eosinophil-specific therapies may not have much clinical effect unless the patients have concomitant asthma. However, targeting the IL-13 pathway, particularly in those with eosinophilia, might lead to clinical benefits by possibly reducing airway mucus secretion. This needs to be proven. Additionally, targeting this pathway or the IL-33 pathway might decrease the rate of decline of FEV_1 (or increase in airspace) by reducing airway metalloproteinase activity. The beneficial effects might be modulated by airway microbial dysbiosis. It is indeed a complex interplay of pathological processes.

CONFLICTS OF INTEREST

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