COPD exacerbation phenotypes: the next frontier

Angela Moran MBChB, FRACP

Ian D Pavord FMedSci

Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, NDM Research Building, Old Road Campus, University of Oxford, Oxford OX3 7FZ

Correspondence to ian.pavord@ndm.ox.ac.uk

Chronic obstructive pulmonary disease (COPD) has been a high burden to health systems globally for many years and continues to have unmet need.(1) It is a heterogeneous condition with differing mechanisms of disease in different subsets of patients. One development in recent years has been the identification of the peripheral blood eosinophil count as a simple, clinically accessible biomarker of a clinically important inflammatory phenotype of the condition: eosinophilic COPD. There is now consistent and compelling evidence that the blood eosinophil count is an independent prognostic biomarker of the risk of severe exacerbations of COPD and a predictive biomarker of the reduction in risk of exacerbation seen with inhaled corticosteroids (ICS) and anti-IL-5 in both asthma and COPD.(2) As a result, COPD treatment guidelines have changed and, for the first time in airway disease, ICS treatment to prevent exacerbations is now recommended only in patients with the appropriate biomarker profile.(3)

Perhaps surprisingly, given that the blood eosinophil count was first identified as a promising biomarker of eosinophilic airway inflammation in an exacerbation cohort, there has been less interest in biomarker directed management of these events. As a result, management of exacerbations of COPD has not changed in the last 20 years and remains very much of the one size fits all type. Progress in this area is, however, a priority as severe exacerbations resulting in hospital admission are responsible for the bulk of the disease-related health care costs, morbidity and mortality.

Previous work has identified four distinct biologic exacerbation clusters (bacterial, viral, eosinophilic and pauci-inflammatory). The 30% of patients with eosinophilic exacerbations were indistinguishable from the others in terms of cross-sectional clinical characteristics but a longitudinal analysis suggested that eosinophilic exacerbations involved a bigger fall in lung function but a much faster recovery with oral corticosteroid treatment than non-eosinophilic events.(4) The most plausible explanation is that eosinophilic exacerbations are more responsive to corticosteroids. Studies showing a clear link

between eosinophilic airway inflammation and a greater response to oral corticosteroids in stable COPD and the six-fold higher rate of treatment failure when exacerbations associated with a blood eosinophil count >2% are treated with placebo compared to prednisolone are entirely consistent with this interpretation.

Given this background then, might the blood eosinophil count be an independent predictor of hospital length of stay in patients with an exacerbation of COPD treated with prednisolone? In this issue of Respirology, the authors of a prospective observational study from Hong Kong have addressed this question by assessing the blood eosinophil counts in subjects admitted with acute exacerbations of COPD as a predictive biomarker of length of stay. A secondary aim of the study was to look for an association between blood eosinophil count at the index event and the risk of repeated exacerbations and mortality over the subsequent year. They studied 346 patients admitted with an acute exacerbation of COPD, who were treated with a standard course of systemic corticosteroid and antibiotics. A blood test was taken at admission and lung function measurements and symptom questionnaires were administered after 8 weeks. The main finding was that the blood eosinophil was negatively associated with length of hospital stay. Receiver operating characteristic curve (ROC) analysis was used to determine that the optimally predictive blood eosinophil cut-off values was $<0.144 \times 10^9$/L or <2%, a value identical to the differential count found to exclude eosinophilic airway inflammation with a high sensitivity (ref Bafadhel et al AJRCCM 2010). Readmission rate and mortality were assessed at 1 year. The majority of subjects were male and elderly with severe airflow obstruction. Nearly half had readmissions within the 12 months and the mortality rate was just under 10%. This was not significantly different between those with eosinophilic and neutrophilic exacerbations.

The findings on length of stay are consistent with those of a recent retrospective case note review of patients attending the emergency department of a single hospital with an acute exacerbation of COPD, although this larger study found a higher mortality rate in non-eosinophilic exacerbations.(5) In another study, a higher short-term treatment success rate was seen in patients with blood eosinophils >=2% but these patients had an increased relapse risk subsequently.(6) There is therefore mounting and increasingly robust evidence that acute eosinophilic COPD exacerbations are associated with a shorter hospital length of stay, even if severe, almost certainly because these events are more corticosteroid responsive.(7)

As we move into an age of increased understanding of the pathophysiological mechanisms involved in COPD and biomarkers of these mechanisms, what are the implications of these findings in clinical practice? The study adds to the growing body of evidence that eosinophilic exacerbations of airways disease are very treatment responsive and have a good short term prognosis. It suggests that the blood eosinophil count could be used to identify patients suitable for early discharge or ambulatory care, although some caution is required when extrapolating the findings of the Hong Kong study as it is single centre study involving an ethnically different and male predominant population.

The study supports calls to move away from our current classification system for obstructive airways disease towards a new system where a higher priority is given to determining the mechanistic pathways involved. There is now abundant and convincing evidence that this approach would improve outcomes for individuals by allowing better prediction of their outcome and likely treatment response.(8) There are, however, a number of areas where evidence is lacking and new studies are needed. First, is it possible to withhold corticosteroids in patients with low blood eosinophil counts? An initial study suggested that it is, and raised the possibility that oral corticosteroids were associated with a worse outcome compared to placebo in patients with an eosinophil count <2%.(9) A subsequent

meta-analysis and a recent large randomised controlled trial of oral corticosteroid treatment directed by daily blood eosinophil counts after an initial single dose have not found worse outcomes, but neither study showed any advantage over placebo of conventional oral corticosteroids in patients with low eosinophil counts.(10) (11) Second, what about a situation where a patient has been rendered blood eosinophil low by treatment with anti-IL-5? There is mounting evidence that exacerbations in this situation are non-eosinophilic, less severe in terms of fall in symptom scores and PEF, and slower to recover with standard prednisolone treatment.(12) Might it be that this treatment is no longer necessary when circulating eosinophils have already been depleted? Finally, if the effects of prednisolone are dependent on depletion of circulating eosinophils, then why not do this more completely, more safely and for longer with an as needed injection of an anti-IL-5 monoclonal antibody? These and other questions will be important to answer over the next few years but it is already clear that we are heading towards a new frontier of precision, biomarker directed, phenotype specific treatment of one of the most common and important acute medical problems.

References

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. Global Health, Epidemiology and Genomics. 2018;3.
2. Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, et al. Blood eosinophil levels as a biomarker in COPD. Respiratory Medicine. 2018;138:21-31.
3. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. The European respiratory journal. 2019;53(5).
4. Ghebre MA, Pang PH, Diver S, Desai D, Bafadhel M, Haldar K, et al. Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles. Journal of Allergy and Clinical Immunology. 2018;141(6):2027-36.e12.
5. Russell REK, Beer S, Pavord ID, Pullinger R, Bafadhel M. The acute wheezy adult with airways disease in the emergency department: A retrospective case-note review of exacerbations of COPD. International Journal of COPD. 2019;14:971-7.
6. Prins HJ, Duijkers R, Lutter R, Daniels JM, van der Valk P, Schoorl M, et al. Blood eosinophilia as a marker of early and late treatment failure in severe acute exacerbations of COPD. Respiratory Medicine. 2017;131:118-24.
7. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JEA, Morgan MD, Brightling CE, et al. Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. Chest. 2016;150(2):320-8.

8. Agustí A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. Precision medicine in airway diseases: moving to clinical practice. The European respiratory journal. 2017;50(4).
9. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: A randomized placebo-controlled trial. American Journal of Respiratory and Critical Care Medicine. 2012;186(1):48-55.
10. Bafadhel M, Davies L, Calverley PMA, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: A further analysis. European Respiratory Journal. 2014;44(3):789-91.
11. Sivapalan P, Lapperre TS, Janner J, Laub RR, Moberg M, Bech CS, et al. Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. The Lancet Respiratory Medicine. 2019;7(8):699-709.
12. Shrimanker R, Pavord ID, Yancey S, Heaney LG, Green RH, Bradding P, et al. Exacerbations of severe asthma in patients treated with mepolizumab. European Respiratory Journal. 2018;52(6).