

Precision Medicine in COPD

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The central concept of precision medicine is to take individual variability into account when making management decisions [1]. This is likely to be particularly relevant in heterogeneous conditions such as COPD, the complexity of which is further multiplied by the heterogeneity of exacerbations [2]. Whatever you want to call observable differences between patients - phenotypes or treatable traits [3] - understanding and quantifying these differences, for example using biomarkers, has the potential to bring precision medicine to those living with COPD.

The history of biomarkers in COPD - defined simply as something objectively measured to inform prognosis or treatment response - is not glorious. Where is the respiratory troponin to define acute exacerbation? Where is the respiratory eGFR, a calculation that has surpassed mere measurement of kidney function such that changes in eGFR are now used to define and stage chronic kidney disease? At best we have biomarkers that may permit the use or withholding of therapy in COPD, including corticosteroids via assessment of eosinophils - in stable and exacerbated disease [4,5] – and perhaps antibiotics at exacerbation through assessment of procalcitonin [6]. Why nothing better?

Our ability to sample the airway is certainly part of the problem. For molecular biomarkers bronchoscopy is too invasive, exhaled breath condensate (EBC) insufficiently validated and sputum, even if the patient is producing it or can be induced, a challenging sample to work with: difficult to process and highly variable. A blood marker remains analytically much more preferable, if potentially less lung-specific.

The heterogeneity of COPD contributes to the absence of generic biomarkers too. Was it ever likely that a single marker would diagnose heterogeneous exacerbations in heterogeneous patients [7]? Turn that around, however, and a more positive scenario arises. Heterogeneity provides the possibility that a marker may be useful to predict specific outcomes in specific populations: the essence of precision medicine.

Less obvious than the value of a biomarker in guiding individual treatment or prognosis is the potential value of a biomarker in the conduct of clinical trials. Use of a biomarker to enrich a trial population for subjects more likely to experience the end-point of interest may mean fewer subjects are required, or need to be followed for a shorter time. This increases the efficiency and reduces the cost of clinical research – a valuable development. In the TORCH study [8], for example, only 14% of subjects experienced the primary (all cause mortality) end-point.

It is in this latter context that the paper reported in this issue of the Journal [9] is important. Miller and colleagues report the process through which the COPD Biomarker Qualification Consortium (CBQC) made a case to the FDA, subsequently accepted, around the utility of plasma fibrinogen as a biomarker (used in addition to clinical information) to enrich clinical trials for the key clinical end-points of all-cause mortality and exacerbations. The clinical outcomes have been reported previously [10]. In a total pool of 6376 individuals, plasma fibrinogen >350mg/dl (45% of the population) was associated with an increased risk for hospitalised exacerbation over 12 months (hazard ratio, HR 1.64; 95% confidence interval, CI: 1.39-1.93) and of all-cause mortality over 36 months (HR: 1.94; 95% CI: 1.62-2.31). I applaud the investment in time and money from the COPD Foundation, patient, academic and industry partners who completed the project. Fibrinogen is the first biomarker in COPD to be assessed so rigorously and qualification makes it easier to use fibrinogen in this way for future studies. The present paper will be of most interest to others minded to embark on such a process and the CBQC are pursuing other markers.

Fibrinogen is an acute-phase glycoprotein synthesised in the liver and a key component of the blood coagulation system, forming (insoluble) fibrin on cleavage by thrombin. Fibrin fibres are then cross-

linked by through the action of Factor XIII. Plasma fibrinogen has many of the characteristics of a good biomarker including being relatively easy and reliable to measure in existing practice, and present at a reproducible concentration in stable disease.

The story of fibrinogen in COPD is not new. In 2000, Wedzicha [11] reported elevation of plasma fibrinogen in COPD patients compared to controls, and at COPD exacerbation compared to baseline – especially when exacerbations were associated with sputum purulence. And we have known for some time that elevated systemic inflammation in COPD is associated with adverse outcomes [12]. As a marker of all-cause mortality in COPD, fibrinogen is almost certainly reflecting cardiovascular risk. Fibrinogen is a well-established marker of cardiovascular risk in the general population [13] so perhaps this is unsurprising. Indeed, you might argue that fibrinogen isn't a COPD biomarker at all, rather a marker of co-morbidity, in this case the excess cardiovascular risk observed in our patients with COPD.

The association with future exacerbations is more interesting. It may well be based on prior exacerbation events increasing vascular risk [14], or perhaps the concept that the presentation of exacerbation is more severe in those with underlying ischaemic heart disease [15]. Certainly in the absence of data to suggest that exacerbations are initiated by vascular pathology it seems unlikely that fibrinogen has direct mechanistic involvement and that it therefore may be a druggable target. Of course the best predictor of future exacerbations remains a history of past events [16]; fibrinogen is not offering precision medicine at an individual patient level that surpasses readily available clinical information. The benefit, once again, may be in selecting subjects for recruitment to clinical trials.

Studies are now in progress that will provide proof that biomarker based enrichment of clinical trials in COPD actually works. Don't under-estimate the value in this to the respiratory community, even if our enthusiasm for all-cause mortality as an end-point has perhaps been tempered. But what we really need, still, are better biomarkers of treatment response and prognosis in individual patients. Only then can we achieve our shared goal of improving the lives of all those affected by this most disabling condition. We still await the era of precision medicine in COPD.

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