Towards the next stage of novel biomarker discussion in COPD: Tekizai-Tekisho

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Biomarkers predicting clinical outcomes reported in COPD but more data needed for their clinical use http://ow.ly/qm2CZ

Forced expiratory volume in 1 s (FEV_1) as a degree of airflow limit2ation has traditionally been regarded as a crucial predictor of mortality in patients with chronic obstructive pulmonary disease (COPD). However, the situation has changed over the past 10 years. Various systemic clinical outcome measurements, such as exercise capacity, dyspnoea, health status, *etc.*, have been found to be associated with mortality [1, 2]. Thus, combined multidimensional disease severity grading protocols have been proposed. To date, the BODE index (body mass index, dyspnoea, exercise capacity and airflow limitation) has led the field as a predictor of disease [3].

Being liberated from the ''FEV_1 supremacy'', COPD has been increasingly recognised as a heterogeneous disease. ''Systemic COPD'' is one of phenotypes associated with elevated markers of systemic inflammation and a high prevalence of comorbidities. The systemic inflammatory phenotype yields poor clinical outcomes with increased mortality and exacerbation frequency [4]. Systemic inflammation in COPD cannot be explained simply by a ''spill-over'' phenomenon of inflammatory mediators from the lungs [5]. Other factors such as bronchial colonisation, obesity, hypoxia and comorbidities are involved. Therefore, a single marker does not seem to be sufficient in assessing systemic effects of COPD, and a combination of multiple markers may have advantages.

Given our recent understanding of this situation, the BODE index may not sufficiently represent factors related to such systemic inflammation. Cross-sectionally, associations between the BODE index and systemic inflammatory biomarkers were not strong [6]. Similarly, from the longitudinal point of view, some serum biomarkers have an additive predictive value of mortality with the BODE index [7, 8]. In addition, regarding comorbidities, Divo *et al.* [9] reported that the qualitative risk stratification comorbidity tool was predictive of risk of death which complimented the BODE index.

In this issue of the *European Respiratory Journal*, Stolz *et al.* [10] have focused on the role of the adrenomedullin (ADM) fragment, proADM, compared to the BODE index in the prediction of clinical outcomes in a multicentre, prospective, observational study. ADM is a ubiquitous peptide synthesised in a number of tissues and cell types and has a range of biological actions including vasodilation, regulation of hormone secretion, cell growth, natriuresis and antimicrobial effects. ADM has increasingly received focus as a potential novel cardiac biomarker in clinical practice, in addition to the conventionally used natriuretic peptides. The present study was performed after a preceding single centre observational study by these authors showed that plasma proADM concentration on admission to hospital for acute exacerbation of COPD was independently predictive of 2-year all-cause mortality [11].

Received: Aug 19 2013 | Accepted after revision: Aug 27 2013

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

STOLZ *et al.* [10] then discovered that proADM itself was most significantly predictive of mortality in patients with stable COPD over other tested blood biomarkers, similarly to the BODE index, and when combined with BODE the predictive power was improved compared to BODE alone (referred to as refined BODE or ''BODE-A'' index) [10]. In addition, beneficially, proADM plus BOD (body mass index, dyspnoea and airflow limitation), ''BOD-A'' index, was more predictive of mortality than the original BODE index. This is good news because the 6-min walking test (6MWT) is time-consuming and difficult to perform, especially in the primary clinic. In turn, this has led to attempts to find other possible multidimensional disease severity staging tests that exclude exercise capacity, such as the ADO index (age, dyspnoea and airflow limitation) or DOSE index (dyspnoea, airflow limitation, smoking status and exacerbation frequency). Although the 6MWT is performed for multiple reasons and cannot be substituted by biomarkers alone in predicting mortality, the use of biomarkers is so straightforward that proADM and its related multidimensional indices are promising outcome measurements in COPD.

Why is proADM such a good biomarker in COPD, when it was originally known as a cardiac biomarker? Perhaps we should not be surprised, considering that cardiovascular disease is common and is one of main causes of death in COPD. STOLZ *et al.* [10] have summarised proposed mechanisms in their article, whereby ADM is produced in response to inflammation, infection and hypoxia, which may reflect complex pathogenesis of COPD. Furthermore, in a cross-sectional study [12], increased plasma proADM concentrations were moderately correlated with lower peak oxygen uptake on progressive cycle ergometry in chronic lung diseases (46% COPD) independently of FEV_1, and, in a subgroup analysis, independently of left ventricular ejection fraction. This may indicate that increased plasma proADM partly acts beyond pulmonary or left ventricular functions. Of course, pulmonary hypertension (PH) is an important complication of COPD. However, abnormal haemodynamic vascular responses to exercise or right ventricular dysfunction and remodelling were recently reported to be present even without PH [13, 14], indicating that heart–lung interactions and right ventricular function are noticeable exercise-limiting factors in COPD. Furthermore, an enlarged pulmonary artery on computed tomography, due to several pathological processes besides resting PH, was associated with severe exacerbations of COPD [15]. Thus, ADM may reflect overall impaired cardiopulmonary circulation in COPD, a point which needs further study.

A limitation of the study by STOLZ *et al.* [10] is that the duration of 2 years is relatively short compared to similar studies investigating the association with mortality. In fact, 1- and 2-year mortality rates were low at 4.7% and 7.8%, respectively, indicating that it remains to be elucidated to what extent intervention targeting this biomarker would be beneficial to patients. Although cancer is usually one of the major causes of death in addition to COPD and cardiovascular disease, the study duration in this case may have been too short to permit deaths due to cancer. Therefore, the significance of biomarkers may be different from other studies, and further investigation under various study settings would be needed to confirm future clinical applicability. For example, the recent Spanish COCOMICS study has evaluated and compared the abilities of different multidimensional indices to predict mortality from 6 months to 10 years [16].

Many systemic biomarkers predicting clinical outcomes have recently been reported in COPD. These are mostly based on analysing their relationship with mortality or exacerbations, which will be useful in risk stratification. These studies usually need a large sample size and a long-term follow-up period, and are challenging and exciting for researchers. We should welcome and recognise their efforts when a novel marker is discovered.

However, for clinical applicability of a disease severity marker, clinicians need more information in addition to its predictive property of mortality. This situation might be similar to that in which various novel multidimensional disease indices have been reported for COPD since publication of the original BODE index [17]. Without more robust studies to reveal their properties or characteristics, clinicians might feel rather confused about which, when and how one index should be used, or how it would impact on daily practice. For example, we previously reported that peak oxygen uptake on progressive cycle ergometry and the modified Medical Research Council (mMRC) dyspnoea scale were highly predictive of mortality in COPD [1, 2]. However, endurance procedures would be better at evaluating the effects of bronchodilators on exercise capacity than peak oxygen uptake [18], and, for long-term follow-up of dyspnoea, other multidimensional dyspnoea measurements rather than mMRC (with an approximate five-point scale) would be appropriate [19, 20]. These indicate that, in spite of their excellent predictive properties, their evaluative properties were not as useful, depending on the situation.

A Japanese proverb states: ''Tekizai-Tekisho'' (teki-zai means most appropriate resource, and teki-sho means most appropriate place). The combination of these two phrases translates to ''to place the right resource (human) in the right place'' in English. However, a clear understanding is indispensable to such placement. Therefore, when measuring biomarkers in various clinical settings, it is important to be familiar with their properties or characteristics and confirm their appropriateness to the setting in question. For

clinical researchers, discovery of a novel biomarker is just the start, not the ultimate objective! Considerably more information regarding specificity, responsiveness, stability, superiority and possible beneficial combinations with other markers should be accumulated for clinical applicability going forward. It is not until then that clinicians will gain straightforward access to ''a blood biomarker'' in assessing COPD.

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DOI: 10.1183/09031936.00146013