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## Asthma-like features and COPD

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Features of asthma such as bronchodilator reversibility, atopy, early onset symptoms, airflow obstruction in the absence of an appropriate smoking history and eosinophilia are recognised to be prevalent in patients with COPD<sup>1,2</sup>. However, whether there is clinical value in identifying these features, or in considering one or more of them as representative of a distinct clinical syndrome such as the asthma COPD overlap syndrome (ACOS), is much less clear. This would be the case if the measures provide a unique perspective on prognosis and/or on likely response to an established or experimental treatment (theragnostic).

Some useful insight is provided by a study reported in this issue of the journal. Suzuki and colleagues<sup>3</sup> report on a retrospective analysis of asthma-like features in patients in the Hokkaido COPD cohort, a 10-year prospective observational study of patients with COPD. The study included 268 patients with respiratory-specialist diagnosed COPD. Three asthma-like features were assessed: bronchodilator reversibility, defined as a post-salbutamol improvement in FEV<sub>1</sub> of  $\geq 200$ ml and  $\geq 12\%$ ; blood eosinophils  $\geq 300$ cells/ $\mu$ l; and atopy as indicated by specific IgE in the serum against one of 14 common inhaled antigens. Patients with a past history of asthma were excluded after a careful review of the clinical history by the treating respiratory physician. Despite this, 135 (50%) of the patients had one or more asthma-like feature.

The authors' analysis suggests that high blood eosinophils, but not bronchodilator reversibility or atopy, was associated with a slower decline in FEV<sub>1</sub>. No asthma-like feature was individually associated with exacerbations or all-cause mortality. However, when more than one feature was present there was a lower 10-year all-cause mortality compared to those with one or no asthma-like features. The negative findings on bronchodilator reversibility and atopy are broadly consistent with much of the existing literature<sup>1,2,4</sup>. Findings with the blood eosinophil contrast with other larger but shorter intervention and epidemiological studies, which show that patients with COPD and asthma plus evidence of eosinophilic airway inflammation have a higher risk of exacerbation<sup>1,5-7</sup>, a more rapid decline in FEV<sub>1</sub><sup>6,8</sup> and increased mortality rates<sup>9</sup>. A possible explanation for the benign outcomes reported in this study is that patients

with higher blood eosinophils are more treatment responsive<sup>1,10</sup>. If this is the case then inhaled corticosteroid (ICS) use is unlikely to have made an important contribution because only 14% of the cohort received this treatment. The study illustrates well one of the central problems with cross-sectional and longitudinal analysis of biomarker performance when the biomarker is prognostic and theragnostic but not that responsive to treatment, as is the case with the blood eosinophil count. Important prognostic information will be lost if the population are already treated.

Regarding our second use of biomarkers, that of predicting a treatment response, it is not possible to draw any firm conclusions from an observational study such as this. More useful information is available from four recent re-analyses of large trials of ICS-containing treatments in COPD that have shown a compelling and close relationship between the blood eosinophil count and the reduced risk of exacerbations seen with the addition of an ICS<sup>1,5,10</sup> or the increased risk of exacerbation when ICS are replaced with an additional long-acting bronchodilator<sup>11</sup>. In all analyses the efficacy of ICS was absent or minimal in the 30-40% of patients with a blood eosinophil count <2% (equivalent to about 150 cells/ $\mu$ l), but increases progressively above this level. The blood eosinophil count also has utility as a marker of the response to oral corticosteroid therapy given to hasten recovery at the time of an exacerbation with, again, benefits of treatment confined to subjects with a blood eosinophil count  $\geq$ 2%<sup>12,13</sup>. Finally, there is a relationship between the blood eosinophil count and reduced decline in lung function with ICS in patients with COPD. In a re-analysis of the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, Barnes et al<sup>8</sup> showed that in the placebo treated group the rate of decline in FEV<sub>1</sub> was greater in patients with an eosinophil count  $\geq$ 2% than those with a count <2% (74.5 vs 51.3 ml/year) whereas in the ICS treated patients the excess decline was reduced substantially in the  $\geq$ 2% group (to 40.6 ml/year) but not in the <2% group (54.2 ml/year).

Thus the evidence for use of blood eosinophil count as a theragnostic marker seems solid. Can the same be said for the other biomarkers investigated by Suzuki and colleagues? We suspect not as neither measure is related to the blood eosinophil count or to the effects of ICS on the long-term outcomes in COPD<sup>1</sup>. There is some evidence that the bronchodilator response is related to the increase in FEV<sub>1</sub> after

treatment with ICS<sup>1</sup>, and allergy to a more complete suppression of symptoms with ICS<sup>4</sup>. However, neither lung function improvement nor symptom control are major goals of ICS treatment in patients with COPD. For measures that figure so highly in our current criteria to stratify airways disease it is remarkable how little useful prognostic and theragnostic information these measures provide.

It is interesting that of the 135 patients with at least one asthma-like feature the majority had only one feature (71%) and very few had all (5%). This lack of segregation, and the very different relationship with ICS treatment response, suggests that these markers represent discrete, mechanistically distinct disease pathways. This is an important consideration given that all are potential qualifying measures for a diagnosis of ACOS. The difficulty is that once this label is applied, there will be an assumption of homogeneity. We believe that this assumption, which also occurs in patients labelled as having asthma or COPD, is becoming an important barrier to progress against key outcomes in airways disease. For example, it was the main reason why the beneficial effects of oral corticosteroids<sup>14</sup> and anti-IL-5 in eosinophilic airways disease<sup>15,16</sup> were missed initially. We suspect that the time has come to move beyond arbitrary labels and toward a position where the goal of assessment is to identify treatable pathways causally linked to important clinical outcomes<sup>17</sup>. At a time when we are moving towards precision medicine, it seems a retrograde step to create a new diagnosis which does not have one underlying targetable molecular pathway.

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