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Serum Eosinophils as a COPD Biomarker: Ready for Prime Time!

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Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease with many subphenotypes that are likely driven by different biologic mechanisms[1]. Though this complexity is poorly understood, defining COPD phenotypes based not only on the severity of airflow obstruction but also by CT characteristics, the presence or absence of cardinal symptoms, or frequent exacerbations has led to a better understanding of disease expression and has helped target treatments[2,3]. Until now however, there have been no serum biomarkers that reliably predict treatment response, are available at the point of care in almost all clinical settings, and can dramatically alter the treatment paradigm for millions of patients. In this issue of Lancet Respiratory Medicine, Watz et al. present their post-hoc analysis of the WISDOM trial[4] demonstrating a robust association between the withdrawal of inhaled corticosteroids (ICS) and an increased risk of moderate-to-severe acute exacerbations of COPD in patients with high baseline serum eosinophil counts. When combined with similar findings from other recent reports, relative serum eosinophilia meets all the criteria for a clinically useful serum biomarker and is ready for prime time use.

The data supporting a role for relative eosinophilia in identifying a steroid-responsive COPD population is remarkably consistent. First, the prevalence of relative eosinophilia has been repeatedly reported to range from 50–70%[5,6], similar to the 54% in the current analysis. Second, no matter the study design (observational or secondary analysis of randomized trial; initiation or withdrawal of ICS therapy), sponsor (constitutional monarchy or rival pharma giants), or patient population (moderate or severe airflow limitation), the clear association between eosinophilia and exacerbation risk, as well as mitigation of that risk with ICS, appears immune to these differing biases [5,7–11]. The results of the current analysis are also entirely consistent with the findings of Bafadhel et al. that systemic steroids improve outcomes in exacerbations associated with serum eosinophils more than 2% while perhaps being detrimental in those with a lower eosinophil count[6].

We expect that our respiratory colleagues will respond with their usual skepticism and highlight numerous imperfections of our newly minted biomarker. First, what is the

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underlying mechanism, given that Watz et al. found no relationship between RAST positivity or IgE levels and the relative benefits of ICS, suggesting this is not atopy-mediated? Second, since the correlation between serum and sputum eosinophilia is not reliable in asthma[12], is poorly described in COPD, and ICS target sputum eosinophils, why would our serum biomarker be at all relevant? And last, if this new fad is so predictive, why was there no benefit on time to first exacerbation between eosinophilia groups? Our responses: 1. Good question. We concede that work still needs to be done. 2. Frankly, we don't care. Induced sputum is difficult to obtain[12], and serum eosinophilia works just fine. 3. The time-to-event endpoint is statistically less useful for capturing the impact of repeated events. The fact that ICS responsiveness could not be predicted by any clinical parameter other than our new biomarker underscores its immediate utility.

Watz and colleagues should be commended for their heroic efforts to define the precise absolute or relative eosinophil threshold to select patients for maintenance ICS therapy. While others have suggested a cut off of 2%[5,7], they argue that this should be raised to 4% where the benefits were most apparent. On close inspection of their results, exacerbation rate ratios approached significance at the 3% threshold (P=0.053), and common sense tells us that the effect on reduction of exacerbations seen above 2% is more likely a continuous effect, proportional to rising eosinophil count. Many investigators, including the authors of this editorial, have called for prospective randomized trials to confirm the predictive utility of serum eosinophils and exactly define its optimum threshold. However, we believe that even well designed studies would fall short of this latter goal and that there is sufficient evidence to support the 2% threshold as an adjunct to clinical judgment in selecting patients for ICS treatment. Furthermore, serum eosinophilia is particularly valuable as a tool to help stop the over prescription of ICS to patients unlikely to benefit[13].

Astute clinicians have known for decades that a significant minority of COPD patients respond very well to ICS, and perhaps now we know who they are. Rather than investing millions of dollars in studies to question this reality, there are clearly more important areas to explore. Though Watz et al. did not find a relationship between serum eosinophils and the effect of ICS withdrawal on FEV_1 decline, this could be in part due to the patients' severe airflow limitation and their concomitant use of both a long acting muscarinic antagonist and a long-acting beta-agonist. Others have found an association between ICS use, increased eosinophils, and less deterioration in lung function in patients with less severe COPD[5,8], and randomized trials are needed to determine if ICS can alter the natural history of disease in this population.

Those of you who take issue with our assertion about the immediate utility of serum eosinophils in COPD can resume your non-winnable debate about what is asthma and what is COPD. Please let us know when it's all settled.

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CONFLICTS OF INTEREST

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