

To The Editor:

The relationship between blood eosinophils and risk and treatment outcome in COPD is a continuous, not dichotomized. The implications for analysis and utilization.

We would like to congratulate Bafadhel et al on their excellent paper examining the response to Budesonide and blood eosinophils counts (on line version 10th Jan) in COPD. In clearly demonstrating the continuous nature of the relationship between blood eosinophil count and the risk of exacerbations as well the benefit of inhaled corticosteroids in COPD, they have helped clarify a point that we alluded to in our original paper¹ that the nature of the response is “graded” dependent on the eosinophil count. The use of a cutoff point in our paper has frequently been misunderstood, and has prompted much irrelevant debate about the relevance of the cut off for allocating treatment and the stability of the biomarker over time. We would like to clarify the choice of the cut point in our original paper was intended to allow comparison with previously published work and did not and does not reflect or infer any belief that at the 2% blood eosinophil count, or any other specific eosinophil level, there is a sudden step wise change in the relationship between blood eosinophils with either risk or benefit, as would be seen with a dichotomized variable.

When consistency of eosinophil measures over time are analysed, in a non-dichotomized fashion, the blood eosinophil count is as stable as many commonly used biomarkers. It is more useful to interpret biomarker results as reflective of a tendency, e.g. those with a low value will typically have low values. The critical test here is not repeatability, but whether one measurement predicts outcome/benefit better than no measurement; or alternatively how much more predictive value is gained from using two or more serial measurements. We believe that the eosinophil count as a predictor of risk and benefit has passed that first test and we hope that in time the usage will evolve to provide a more predictive inflammatory endotype marker, whether through repeated tests or other methods is yet to be seen.

The decision to treat should not ideally depend on a “one size fits all” cut-off, but is dependent on many factors such as the risk the subject has of developing the outcome, individual risk of treatment related adverse outcomes and patient preference to name but a few. In our view this is the very nature of personalized medicine. We foresee that blood eosinophils will be used like serum cholesterol, which is a continuous variable, and the decision to treat is made in the clinical context of age, co-morbidities and cardiovascular risk. Similarly, we envisage blood eosinophils along with other clinical characteristics being assessed with previous exacerbation history, history of pneumonia and BMI to inform on ICS treatment needs. For COPD, this process could be operationalized in non-specialist settings using a risk based treatment algorithm, similar to those used very successfully for cardiovascular risk reduction.

The critical observation is that cut offs used with biomarkers that behave as a continuous variable are by their very nature arbitrary in the same way that “normal values” are arbitrarily defined for many biological variables used in medicine, in neither case does that undermine their utility.

We also note with interest the observation on the relationship of the blood eosinophil count and smoking status, which may turn out to be an important clinical characteristic, that in time could also inform on the appropriate treatment in a clinical algorithm. It is especially intriguing that smoking status

appears to interact with the eosinophil count and may in part explain the biology underlying the absence of ICS response in some subjects. The observation is similar in nature to the one we described² in a data-driven cluster analysis of fluticasone furoate/vilanterol studies, with the potentially important difference that we showed a difference to the response in the low Eos group dependent on pack years rather than current smoking status. We observed that heavy smokers had little benefit in the low eosinophil group relative to lighter smokers, while ICS related risk reduction in the high eosinophil group was not related to the degree of exposure to tobacco smoke. Whether these similar but different findings relate to the different interventions, the patient groups or merely methodological differences remains to be seen.

Funding: GSK

Steve Pascoe¹, Ian Pavord², David Hinds³, Nicolas Locantore⁴, Neil Barnes¹

¹*Respiratory Medical Franchise, GSK, Brentford, UK* ²*Respiratory Medicine Unit, Nuffield Department of Clinical Medicine, University of Oxford, Old Road Campus, Oxford, UK* ³*Worldwide Epidemiology, GSK, Research Triangle Park, North Carolina, USA* ⁴*GSK R&D, Collegeville, Pennsylvania, USA*

1. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435-442
2. Hinds DR, DiSantostefano RL, Le HV, Pascoe S. Identification of responders to inhaled corticosteroids in a chronic obstructive pulmonary disease population using cluster analysis. *BMJ Open*. 2016;6

Author Conflict of Interest Information:

Author	COI
Neil Barnes	Employed by GSK, stocks in GSK
David Hinds	Employed by GSK, stocks in GSK
Nicholas Locantore	Employed by GSK, stocks in GSK
Steven Pascoe	Employed by GSK, stocks in GSK
Ian Pavord	Speaker's honoraria from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis and GSK, honoraria for attending advisory board panels from Almirall, AstraZeneca, Boehringer Ingelheim, Dey Pharma, GSK, MSD, Schering-Plough, Novartis, Napp Pharmaceuticals and RespiVert, and has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, GSK and Napp Pharmaceuticals