Stability of eosinophilic inflammation in COPD bronchial biopsies

DOI:

[10.1183/13993003.04167-2020](https://doi.org/10.1183/13993003.04167-2020)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Higham, A., & Singh, D. (2020). Stability of eosinophilic inflammation in COPD bronchial biopsies. *European Respiratory Journal*, 56(6), 2004167. <https://doi.org/10.1183/13993003.04167-2020>

Published in:

European Respiratory Journal

Citing this paper

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Correspondence: Stability of Eosinophilic Inflammation in COPD Bronchial Biopsies

Andrew Higham and Dave Singh

We thank Professor Walters and colleagues for their interest in our recently published research letter “Stability of eosinophilic inflammation in COPD bronchial biopsies” ¹. We would like to provide clarity on several points raised.

Previous bronchoscopy studies have demonstrated increased numbers of eosinophils in the lamina propria of the proximal airways, as well as sputum and bronchoalveolar lavage samples, in COPD patients versus healthy controls ^{2 3}. Walters and colleagues suggest that eosinophil numbers are “low” in the airways of COPD patients. However, these previous publications with different types of airway sampling, and appropriate control groups, show the opposite to be true.

A large population study showed that blood eosinophil counts are raised in COPD patients compared to healthy controls; this finding was replicated in a retrospective cohort analysis ^{4 5}. Higher blood eosinophil counts in COPD patients are associated with more eosinophils in the lungs, whether measured in sputum or bronchoscopy samples ^{6 7}. This association supports the use of blood eosinophils as a surrogate biomarker of lung eosinophil counts, with numerous analyses showing that higher blood eosinophil counts are associated with a greater response to inhaled corticosteroids (ICS) in COPD patients with a history of exacerbations ⁷. There is considerable variation between COPD patients in the numbers of eosinophils in the blood or tissue ^{2 3 6 7}; this variation (between individuals) is clinically relevant, as it is associated with a differential response to ICS. We agree with Walters et al

that airway tissue eosinophil counts are a reflection of blood eosinophil counts, and this relationship supports using blood eosinophil counts as a predictive pharmacological biomarker in COPD patients.

Clinical trials performed approximately 20 years ago showed that COPD patients with higher sputum eosinophil counts had a greater clinical benefit from corticosteroid treatment ⁷. These studies highlight the value of splitting the COPD population using lung eosinophil numbers. It is clear that some COPD patients have eosinophilic inflammation present in the lungs, which is related to a differential response to ICS treatment. Jogdand et al recently investigated eosinophil counts in the proximal airways and distal lung samples, and showed that higher eosinophil counts (compared to controls) were present in a subset of COPD patients ⁸. Walters et al suggest there are low eosinophil numbers present in COPD airways. This statement is true for some COPD patients, but clearly not correct for others.

Jogdand et al demonstrated the presence of eosinophil rich microenvironments in the small airways of a subgroup of COPD patients, describing patchy lung tissue eosinophilia associated with increased T2 markers ⁸. We also noted spatial variation in the presence of eosinophils in the proximal airways; a subgroup of COPD patients had higher submucosal eosinophil counts which varied considerably between airways ¹. Overall, our findings coupled with Jogdand et al indicate that eosinophilic inflammation is patchy in the lung tissue, and underscores the value of multiple sampling to study tissue eosinophils.

Walters et al state that COPD airway wall eosinophil counts are lower than other immune cell types such as neutrophils and lymphocytes. While this is true, it does not mean that eosinophils have no role in the pathophysiology of COPD. The multiple studies showing that sputum and blood eosinophil counts are associated with a differential response to ICS cannot

be ignored, and the question is whether ICS are treating lung eosinophils themselves or T2 inflammation associated with eosinophils ⁹. There is also emerging data that patients with higher sputum eosinophil counts have a different microbiome, with reduced presence of *Haemophilus influenza*, suggesting an interaction between the microbiome and inflammation in COPD ¹⁰.

Walters et al raise a point about Bland-Altman analysis, with regard to log transforming data when the differences are proportional to the mean. The original paper by Bland and Altman focuses on clinical measurements such as oxygen saturation and peak expiratory flow rate; they advocate log transformation to improve the estimates of limits of agreement (LOA), but they also add a note of caution for log transformation in instances where the relationship is more complex ¹¹. Our data concerning repeated eosinophil measurements demonstrates a more complex pathophysiological phenomenon than the repeatability of peak flow rates, and log transformation would not have helped to interpret that data. The key point about the plots we presented was to highlight a relationship between the differences and the mean. We used intraclass correlation coefficient and within subject standard deviation to provide additional objective analysis of what was obvious to the eye; lower levels of submucosal eosinophilic airway inflammation in COPD patients are highly stable over time, while higher levels of eosinophilic airway inflammation are more heterogeneous throughout the bronchial tree, with greater variation over time.

Andrew Higham¹

Dave Singh^{1,2}

1. The University of Manchester Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK.

2. Medicines Evaluation Unit, The Langley Building, Southmoor Road, The University Hospital of South Manchester, Manchester, UK.

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