Reviewer’s report

Title: Blood cells for the differentiation of airway inflammatory phenotypes in COPD exacerbations

Version: 4 Date: 10 Jan 2020

Reviewer: Stephen Bourke

Reviewer's report:

The authors have addressed most of the comments raised.

1. The statement that measurement of sputum is the gold standard test for defining airway inflammation phenotypes has been retained, and the suggested comment I previously mentioned has not been included (at this stage please consider this a discretionary change). A poor correlation between blood and sputum results may lead to a false conclusion that measurement of blood inflammatory cells is not useful. This is clearly incorrect as blood eosinophil count has been shown to be a reliable predictor of response to inhaled corticosteroids when stable and oral steroids during acute exacerbation. Both sputum and blood eosinophils are surrogate markers of airway inflammation; the correlation between both of these biomarkers and airway histology is imperfect. What is most important is that the biomarker accurately predicts steroid treatment response. The biomarker in question must also be easy to measure in routine clinical practice; clearly not true of airway histology, and debatable in the case of sputum.

2. Line 179-180: I am uncertain what the authors mean by the statement: "Bacterial and eosinophilic phenotypes LIKED in the stable state, whereas viral infection was frequently detected in the exacerbation stage". I presume the authors referring to the observation that stable state bacterial colonization predicted bacterial exacerbations and likewise stable state eosinophilic airway inflammation was associated with eosinophilic exacerbations. In contrast viral exacerbations were not related to stable state phenotype but rather represented acquisition of a new pathogen. This is deduced from my understanding of study cited, but is unclear in the submitted text. Please note that bacterial and eosinophilic exacerbations rarely co-existed. Bacterial infection is more likely to be associated with eosinopenia. Consider rewording. Note Prof Bafadhel's study showed a much stronger relation between sputum eosinophilia and blood eosinophils during exacerbations with an AUROC = 0.85. Perhaps worthy of comment, particularly as the study is cited.

3. Line 211 - 215: The authors have simply pasted my comment into the text. The phrase "consider acknowledging…." was advice to the authors that is being followed, but this needs to be reworded: e.g. "we acknowledge…".

In addition further language corrections are required; perhaps best addressed by the copy editor.
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