Reviewer’s report

Title: COPD exacerbation severity and frequency is associated with impaired macrophage efferocytosis of eosinophils

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Reviewer: H.A.M. Kerstjens

Reviewer’s report:

The authors present the results of a study on macrophage function in relation to eosinophil numbers in 103 patients with COPD. The body of data stems from a cohort followed for a longer period, in whom longitudinal data on clinical characteristics, and sputum was available in stable state and at exacerbations. To this was added, in a subgroup of 17 COPD subjects and 8 normal controls, a prospective study on macrophage efferocytosis, effectively assessing capability to ingest apoptotic eosinophils. In short, efferocytosis was impaired in patients with COPD. When subdividing the COPD group by sputum eosinophil number and macrophage red hue content as indirect measure of efferocytosis, patients with most eosinophils and low efferocytosis had the biggest fall in FEV1 and were most prone for exacerbations.

MAJOR POINTS

1. The remark in the discussion in line 249, that “the majority of subjects had high red hue and normal sputum eosinophil counts suggesting that the contribution of the eosinophil to the total inflammatory burden in COPD might be under-estimated. Indeed, only 18% of subjects had neither high sputum eosinophils nor high red hue” is really very interesting. However, I could not find where it is based upon. The normal values for red hue are not provided. A line of 6% is drawn fig. 2, but not referenced. If it is based on ref 16 in asthma, then it might be a rather poor reference given age differences? Importantly also, I could not find the values of the 8 controls in the current manuscript?

2. How reproducible is the red hue en d especially the efferocytosis measurement, short term? Some indication needs to be provided. And how stable is the phenomenon in COPD patients when in stable phase of their disease.

3. The data on bacterial colonisation are very relevant. I could detect only a written sentence on this (line 176/178) but no further details. Please expand and put into sufficient perspective given the influence colonization might have on macrophage function. This is important also in the discussion where the now unbacked statement is provided in line 255: “However, we have identified that impaired efferocytosis can occur in subjects with low bacterial colonisation.”

MINOR POINTS

1. Line 112. The eosinophils were taken from asthmatics and allergics. Could this
matter to how they are phagocytosed, being different from non/differently primed eosinophils?

2. Line 187/188: no difference between controls and COPD?? There certainly was, as there should be. Given the wording of 4 groups (should be 2 here?) there is perhaps a copy paste problem? Please check and I suspect correct.

3. Table 1. The unit of “exacerbations subjects” is unclear. Number of patients with at least one exacerbation? During ....?

4. The statistical comparison in table 1 on sputum eosinophils should I believe be deleted. The groups were categorized based among others on sputum eosinophil numbers.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests'