# Eosinophils as Biomarkers of COPD Exacerbation Risk - Maybe Just for Some?

<table>
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<tr>
<th>Journal:</th>
<th>American Journal of Respiratory And Critical Care Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>Blue-201601-0015ED</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>ED - Editorial</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>04-Jan-2016</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Wedzicha, Jadwiga; Imperial College London, National Heart and Lung Institute</td>
</tr>
<tr>
<td>Subject Category:</td>
<td>7.06 Eosinophils &lt; IMMUNOLOGY AND INFLAMMATION, 9.09 COPD: General &lt; LUNG DISEASES</td>
</tr>
<tr>
<td>Keywords:</td>
<td></td>
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EDITORIAL

Eosinophils as biomarkers of COPD exacerbation risk - maybe just for some?

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Word count 977

COPD exacerbations are responsible for a considerable amount of the morbidity and healthcare costs associated with the condition. Some COPD patients are especially prone to develop exacerbations and have been termed frequent exacerbators (1,2). There has been considerable interest in factors predicting exacerbation frequency and thus applying strategies to reduce the risk of hospital admission. Studies have shown that the strongest predictor of future exacerbation is the exacerbation frequency over the previous year (1,2).

There has been considerable interest recently in the role of the blood eosinophil count in COPD and especially in predicting responses in exacerbation rates with inhaled corticosteroid therapy (3,4). A number of studies have shown that the higher the blood eosinophil count, the greater the exacerbation reduction response to inhaled corticosteroids (3-5). However the study by Pascoe and colleagues (3) described an eosinophil count of 2% or more as predictive of an inhaled steroid response; though this value is generally regarded as being within the normal range for eosinophil count. There have also been suggestions that the blood eosinophil count measured at a COPD exacerbation can direct the use of oral corticosteroids at exacerbation 6).

The role of eosinophils in COPD has thus raised a number of questions and thus the study published in this issue of AJRCCM by Vedel-Krogh and colleagues is of considerable interest (7). This is a large and important study as it describes blood eosinophil counts in COPD patients in the general population using the Copenhagen General Population Study. Cut offs for blood eosinophil levels were studied using total cell counts and also percentage values. The results show that in a general population, blood eosinophil levels above 0.34.10^9
were associated with a 1.76 fold increased risk of severe COPD exacerbations which are those requiring hospitalization. There was a relationship between total blood eosinophil and moderate exacerbations (those requiring oral corticosteroid therapy and/or antibiotics) but the effects were not as marked as in the severe exacerbation group. However the authors also studied a sub-group of patients that they defined as having clinical COPD on the basis of a reduced FEV1, smoking and exacerbation history. The risk of both moderate and severe exacerbations was increased further with higher eosinophil counts in this group but again effects were more pronounced with severe exacerbations.

A cut-off of 2% or more blood eosinophils has been used in other analyses and Vedel-Krogh and colleagues also assessed the value of this cut-off in the Copenhagen study. In this study 64% of the subjects with COPD and 66% of the clinical COPD sub-group had blood eosinophils equal to or above 2%. An increased risk of exacerbations was seen in the clinical COPD cohort but in the whole COPD population there was no increased exacerbation risk with a 2% or greater eosinophil count. When the 2% cut-off was used, the risk of moderate exacerbations was actually increased when the blood eosinophil count was below 2%. This suggests that the 2% cut-off is not as robust as the total eosinophil count in the blood for exacerbation prediction.

There are still a number of issues that need to be resolved regarding eosinophilia in COPD. The presence of eosinophils is not associated with asthma in these patients or the asthma-COPD overlap as asthmatics have been excluded as far as possible in studies. Studies of blood eosinophils in inhaled corticosteroid therapy trials have suggested that the higher the blood eosionophil count the greater the exacerbations frequency and thus the blood eosinophil count may be a biomarker for the presence of a frequent exacerbator. However the data in the study by Vedel-Krogh and colleagues suggests that the association between blood eosinophils and exacerbations is centred around patients who develop severe exacerbations and these patients may have a distinct inflammatory profile making them more susceptible to develop these events.

Most COPD exacerbations are associated with neutrophilic inflammation in the airways due to the presence of viral and bacterial infection (8,9). However increased sputum eosinophil counts may be seen at exacerbations, especially in the presence of a viral infection (9), though not as prominent as the increases in sputum neutrophils. Viral infections are generally associated with more severe exacerbations and also prolonged recovery of exacerbations (10,11) but there is no evidence that the airway inflammatory profile is different between moderate and severe exacerbations as currently defined clinically. Some relationship has been found between airway and blood eosinophils in COPD but the associations are generally weak (12). In the Copenhagen study, COPD patients with higher blood eosinophil counts were more likely to have reported more infections and wheezing during colds, suggesting they may have had increased susceptibility to viral infection (7). The increased blood eosinophil count may reflect a past history of more frequent exacerbations with respiratory viruses and studies are now required to investigate in more detail how eosinophilia is related to viral susceptibility, different degrees of exacerbation frequency and exacerbation recovery.
In the COPD ECLIPSE cohort followed for 3 years, 49% of the COPD subjects had variable blood eosinophil levels above and below the 2% cut-off (13). Thus we need more information on how blood eosinophils change with time and how they relate to exacerbation triggers and their recovery. At least from the data obtained in the study by Vedel-Krogh and colleagues, we now know that we should use absolute blood eosinophil counts in future studies, rather than 2% as a cut off for blood eosinophils in COPD.

Most of the data on relationships between blood eosinophils, exacerbations and corticosteroid sensitivity have come from retrospective analyses of studies and now the study from Vedel-Krogh and colleagues has shown that COPD patients who develop severe exacerbations may have distinct pathophysiological processes and form a specific phenotype. Thus the search for a biomarker of the frequent exacerbator will have to continue and somehow I think that one marker will not be enough.

REFERENCES


