Clinical Preview

Investigating blood eosinophil count thresholds in patients with chronic obstructive pulmonary disease

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Over the last 5 years, there has been a rapid accumulation of data investigating the peripheral blood eosinophil count as a biomarker in chronic obstructive pulmonary disease (COPD). This has largely been through retrospective post-hoc analysis or database association studies; all with similar observations, yet different cut-offs for possible utility. From these data, the blood eosinophil has been shown to predict risk of exacerbation and response to inhaled corticosteroid therapy. However, uncertainty has arisen, perhaps predictably given the heterogeneous nature of COPD, the different study designs and the outcomes studied. Despite this, it is exciting to know that the debate about eosinophils has moved on from whether they are found in COPD or their significance, to at what level eosinophil should be used to make treatment decisions.

In the June issue of The Journal of Allergy and Clinical Immunology, Yun and colleagues, publish a study which goes further to clarify the threshold of the blood eosinophil count and its relevance in COPD. The study incorporated two large, long term, prospective cohorts of very well characterised patients with COPD, to study the relationship of eosinophil counts and exacerbation risk. The Genetic Epidemiology of COPD (COPDGene) cohort was used as a discovery set and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort as a validation set. COPDGene was a multicenter observational study which enrolled over 10,000 smokers with and without COPD in the first phase. In the second phase approximately 5 years later, full blood counts were taken. This resulted in approximately 1500 patients with COPD, with spirometric severity classification of <80% FEV_1 % predicted (GOLD II-IV). Subsequent to the second phase 1113 patients, with COPD and an eosinophil count, were then followed up prospectively for self-reported exacerbation history. ECLIPSE, was a multicenter multinational 3-year

observational study which enrolled approximately 3000 patients with COPD. A full blood count and 3 year-year follow-up in patients with GOLD II-IV was available in 1895 patients for this analysis. Similar to COPDGene, self-reported exacerbations were collected prospectively in ECLIPSE. Patients on oral corticosteroids or with incomplete data were excluded from this current analysis.

In a negative binomial multivariate regression analysis, a range of eosinophil counts, adjusted for known exacerbation risk factors such as a history of reflux, symptoms and lung function, were evaluated for association with exacerbation risk. From the COPDGene analysis, this demonstrated that there was a linear association with absolute eosinophil counts and exacerbation risk. An increase in incidence rate ratio (IRR) of exacerbation risk was associated with absolute eosinophil counts (IRR 2.24, 95% CI 1.35-3.66). At absolute eosinophil counts of ≥200 cells/μL and increasing eosinophil counts, the IRR was significant. In multivariable logistic regression models, an eosinophil cut-off of 300 cells/μL was associated with the greatest sensitivity and specificity (72.6% and 66.0% respectively, area-under-the-receiver-operator-curve of 0.745) for identifying a risk of self-reported exacerbation (≥1 event in the follow-up period). Eosinophilic COPD (defined as ≥ 300 eosinophils/μL) was found to be associated with a worse quality of life and less emphysema scored on CT, in addition to frequent exacerbations (≥2 per year). In the prospective follow-up (equivalent to 1561 person-years), the predictive ability of the eosinophil count was associated with eosinophils at and above the 300 eosinophils/μL cut-off, in addition to a past history of exacerbations.

Following the determination of the cut-off of eosinophils (≥ 300 eosinophils/μL), the ECLIPSE cohort was then used to validate this finding from 1895 COPD patients with complete data. Unlike COPDGene, ECLIPSE did not show worsened quality of life (SGRQ scores) or less emphysema in eosinophilic COPD. Furthermore, the area-under-the-receiver-operator-curve was not significant at identifying an eosinophil count to predict an exacerbation. An eosinophil count (≥ 300 eosinophils/μL remained to be a significant predictor of future exacerbations both at 1 year and the follow-up study period (4981 person-years), and increasing eosinophils were once again associated with increased exacerbations (IRR 1.45, 95% CI 1.09 – 1.93), with significance reached at the cut-off of ≥ 300 eosinophils/μL. The data collected in the

ECLIPSE cohort enabled a further significant analysis to be performed. As blood counts were collected throughout the 4 year follow up period multiple measures of blood eosinophils were available leading to an ability to answer the question relating to stability over time and whether eosinophil stability convey any clinical significance? In general blood eosinophil counts were stable, with an Intra-Class-Coefficient of 0.57. Additionally, in 6.7% of the population with persistent blood eosinophil counts >300 cells/ml, the risk of exacerbation was significantly increased in this group.

This paper provides high quality evidence as to the importance of the blood eosinophil in COPD, both from a discovery and validation set. It is evident that there is an association of exacerbation risk and the peripheral blood eosinophil count; and this risk is greatest in patients with a higher eosinophil count and a history of exacerbations. Although, the number of patients who are in the higher risk category (blood eosinophils≥300 cells/ml and ≥2 exacerbations) is a smaller number to the total population studied (between 2.8-5% overall, but 20% of the frequent exacerbation population), this may focus a future strategy to justify the use of potential anti-eosinophil biological treatment. The observation that measurement of eosinophils are also stable over a period of time introduces further support of the overall findings from COPDGene and ECLIPSE. Subtle differences in the populations studied, i.e. number of active smokers, inhaled corticosteroid use, disease severity and the prospective capture of self-reported exacerbations will account for some differences in the discovery and validation set. Although in clinical practice we seek a cut-off to delineate clear decision-making treatment strategies, it is likely that an approach understanding the risk and the subsequent management of the patient with COPD is perhaps more valid and this paper has further acted on approaches to do this.