Clinical Preview

Investigating blood eosinophil count thresholds in patients with COPD

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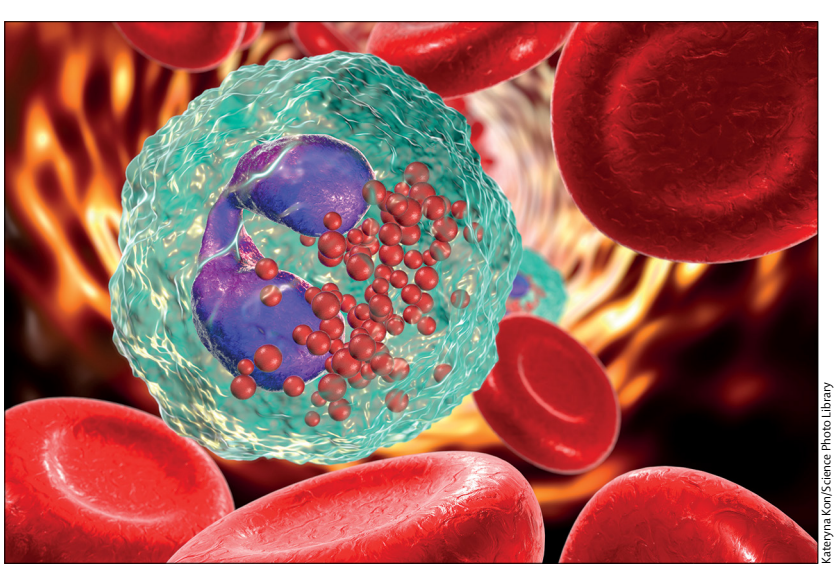
For the **paper by Yun and colleagues** see *J Allergy Clin Immunol* 2018; **141:** 2037–47

Over the past 5 years, data investigating peripheral blood eosinophil count as a biomarker in chronic obstructive pulmonary disease (COPD) have been rapidly accumulating. This accrual of data has largely been through retrospective post-hoc analyses or database association studies, which all have similar observations but different cutoffs for possible utility. From these data, the blood eosinophil count has been shown to predict risk of exacerbation and response to inhaled corticosteroid therapy. However, uncertainty has arisen about the reliability of data, perhaps predictably given the heterogeneous nature of COPD, the different study designs, and the outcomes studied. Despite this uncertainty, the progress that has been made with eosinophils in COPD is encouraging; it is accepted that eosinophils have an important role in COPD and research now focuses on what eosinophil cut-off should be used to guide treatment decisions.

In the June issue of the *Journal of Allergy and Clinical Immunology*, Yun and colleagues published a study that further clarified the threshold of the blood eosinophil count and its relevance to COPD. The study used two large, long-term, prospective cohorts of well characterised patients with COPD to study the relation between eosinophil counts and exacerbation risk. The Genetic Epidemiology of COPD (COPDGene) cohort was the discovery set, and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort was the validation set. COPDGene was a multicentre observational study that enrolled more than 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 FEV_1 <80% predicted (GOLD classification 2–4). After the second phase, 1113 patients with COPD and a recorded eosinophil count were then followed up for self-reported exacerbation history. ECLIPSE was a multicentre, multinational, 3-year observational study that enrolled approximately 3000 patients with COPD. A full blood count and 3 year follow-up in patients with COPD (GOLD classification 2–4) was done in 1895 patients. Similar to COPDGene, self-reported exacerbations were collected prospectively in ECLIPSE. Patients on oral corticosteroids or with incomplete data were excluded from the analysis by Yun and colleagues.

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 assessed for association with exacerbation risk. From the COPDGene cohort, this analysis showed that there was a linear association between 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 at least 200 cells per µL and increasing eosinophil counts, the IRR was significant. In multivariable logistic regression models, a 300 cells per µL eosinophil cutoff was associated with the greatest sensitivity (72·6%) and specificity (66·0%) for identifying a risk of self-reported exacerbation of at least one event in the follow-up period (area under ROC of 0·745). Eosinophilic COPD (defined as ≥300 eosinophils per µL) was found to be associated with a worse quality of life and less emphysema scored on CT, in addition to frequent exacerbations (at least two per year). In the follow-up (equivalent to 1561 person-years), the predictive ability of the eosinophil count was associated with eosinophil counts of at least 300 per µL, in addition to a past history of exacerbations.

Following determination of the eosinophil cutoff (≥300 per µL) with COPDGene, the ECLIPSE cohort of 1895 patients with COPD was then used to validate this finding. Unlike COPDGene, ECLIPSE did not show worsened quality of life (St George's Respiratory Questionnaire scores) or less emphysema in eosinophilic COPD than in non-eosinophilic COPD. Furthermore, the area under the ROC was not significant at identifying an eosinophil count to predict an exacerbation. An eosinophil count of at least 300 per µL remained a significant predictor of future



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exacerbations both at 1 year and at 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 cutoff of at least 300 eosinophils per µL. As blood counts were collected multiple times throughout the 3-year follow-up in the ECLIPSE study, stability of eosinophil counts and their clinical significance could be measured over time. In general, blood eosinophil counts were stable, with an intraclass coefficient of 0·57. Additionally, in 6·7% of the population with persistent blood eosinophil counts greater than 300 cells per ml, the risk of exacerbation was significantly increased.

Yun and colleagues provide high quality evidence for the importance of blood eosinophil counts in COPD, both from a discovery set and validation set. An association of exacerbation risk and peripheral blood eosinophil count is evident, and exacerbation risk is greatest in patients with a higher eosinophil count and a history of exacerbations. Although the patients in the higher risk category (blood eosinophils ≥300 cells per ml and at least two exacerbations) are a much smaller percentage of the total population studied (between 2·8–5% overall, but 20% of the frequent exacerbation population), findings might focus a future strategy for the use of anti-eosinophil drugs for treatment. The observation that eosinophil counts 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, such as the 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 cutoff to delineate clear decision-making treatment strategies, it is likely that understanding the risk and the subsequent management of the patient with COPD is perhaps even more valid, and this study adds weight to this approach.

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