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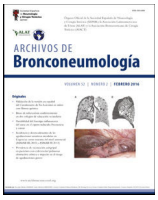

Editorial

Is the Blood Eosinophil Count a Useful Biomarker in COPD? The devil is in the Details!

¿Es el recuento de eosinófilos un biomarcador útil en la EPOC? El problema está en los detalles

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Eosinophils are pleiotropic leukocytes with multiple biological functions.[1] They participate in the initiation and propagation of diverse inflammatory responses, and also modulate adaptive immunity by directly activating T cells. They are derived from bone marrow, and most usually reside in the gastrointestinal tract. The lung is not their natural environment, and their presence in that organ is indicative of an abnormal inflammatory response. Thus, it is entirely logical that increased eosinophils levels in expectorated sputum, bronchoalveolar lavage and/or tissue biopsy have been used to define the presence of pathological processes capable of resulting in disease states, such as asthma, eosinophilic pulmonary syndromes, and certain autoimmune and neoplastic diseases. Many of these pathologies are associated with an increase in peripheral blood eosinophil levels. Pathological eosinophil levels are determined using absolute counts, with mild eosinophilia being defined as 351–500 cells/mm^3, moderate eosinophilia as 500–1500 cells/mm^3, and severe eosinophilia as more than 1500 cells/mm^3. To establish a diagnosis of hypereosinophilia, pathological levels must persist for a number of months.[2] This is an important consideration when interpreting elevated eosinophilic blood count in a particular patient. Finally, blood eosinophil levels are often reported as a proportion of the total number of leukocytes, with values ranging from 1% to 6%.

In COPD, there is widespread consensus on the need for biomarkers that can identify treatable features that can be targeted by specific therapies. In this disease, serum eosinophil level have a good correlation with sputum eosinophils,[3] and are certainly more easily measured. Recent evidence has highlighted the potential use of sputum and serum eosinophil levels as biomarkers of patients likely to suffer from exacerbations and to respond to corticosteroids or other anti-eosinophilic therapies.[4–6] These drugs have been shown to be effective in reducing eosinophil levels and the clinical manifestations of eosinophilic diseases; by and large, the higher the eosinophil count the more effective the therapy. What, then, is the evidence in COPD?

Overall, a retrospective analysis of data obtained in clinical trials suggests an increased rate of exacerbations in patients with blood eosinophilia. Pascoe et al.[7] reviewed the data from 3177 patients with COPD and a previous history of exacerbations treated with either once daily ICS/LABA (Fluticasone/Vilanterol) or LABA (Vilanterol) alone, with 2083 patients (66%) with an eosinophil count of 2% or higher at study entry. All doses of ICS reduced exacerbations by 29% compared with LABA alone (mean 0.91 vs 1.28 exacerbations per patient per year; P<.0001) in patients with eosinophil counts of 2% or higher, and by 10% (0.79 vs 0.89; P=.2827) in patients with eosinophil counts lower than 2%. Reductions in exacerbations with ICS/LABA compared with LABA alone were 24% in patients with baseline eosinophil counts of ≥2 to <4%, 32% for those with counts of 4 to <6%, and 42% for those with eosinophil counts of ≥6%. Siddiqui et al.[8] observed a similar effect using a different combination of twice daily ICS/LABA (beclomethasone/formoterol) versus LABA alone. In this study, patients in the highest quartile of eosinophil count (>281 cell/mm^3) had the greatest benefit both in exacerbation rate as well as health status. Combining the data from three studies using yet another twice daily ICS/LABA combination (fluticasone/salmeterol) compared with LABA alone, Pavord et al.[9] observed a decrease in exacerbation rate, with no impact on lung function decline or health status in 2 of the 3 studies using the 2% threshold. The number of studies supporting such a relationship has increased, with some showing an association between eosinophil levels and improvement in lung function[10] decline, while others confirm the relationship with exacerbations.[11]

Although most clinicians and investigators associate the presence of exacerbations with poor outcomes, this cannot be extrapolated to a similar association between eosinophilia and poor outcomes. Indeed, a review of the results of the ISOLDE study showed that administration of ICS was associated with a slower rate of lung function decline in patients with higher versus lower serum eosinophil levels.[10] In a study of the relationship between eosinophil levels and clinical characteristics in a US population-based cohort, eosinophil >2% was associated with fewer

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co-morbidities.[12] Further, in a recent cohort study of patients with COPD, the presence of eosinophilia was associated with a lower risk of death over 10 years of follow-up.[13]

Overall, interpretation of the data available seems to point to a relationship between eosinophil levels and COPD exacerbations. As is true in eosinophilic diseases, the administration of corticosteroids (or perhaps other immunomodulators) seem to have a beneficial effect on exacerbations in patients with a history of exacerbation and eosinophilia. However, many unanswered questions remain:

1. Is the widely suggested 2% white blood cell cut-off level the right threshold? That value is within normal limits. Indeed, when applied to the general population, this threshold was surpassed in 65% of healthy individuals and 70% of patients with COPD, respectively.
2. Is a single serum eosinophilia measurement sufficient to identify susceptibility phenotypes? There is little information about the stability of serum eosinophil levels over time in COPD.
3. Is the evidence solid enough to warrant a change in clinical practice? So far, no studies in COPD have prospectively evaluated the effect of any particular therapy using blood eosinophils thresholds as an inclusion criterion.
4. Is the eosinophil a friend or a foe? The relationship between eosinophil levels and outcomes other than exacerbations is not known. Whether suppression of eosinophil levels that fall within the normal ranges in the general population carries a risk remains to be seen.

In conclusion, these are exciting times. The possibility that an easily obtained biomarker such as peripheral blood eosinophil count may help determine a patient's risk for certain outcomes and likelihood of responding to specific therapy is very appealing. However, as in many areas in life, "the devil is in the details", and more data is needed before blood eosinophil levels can be used to identify a COPD phenotype amenable to specific immunomodulatory therapy.

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