Interpreting blood eosinophil counts in health and obstructive lung disease

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Asthma and COPD are prevalent chronic diseases characterised by presence of respiratory symptoms and airflow limitation caused by ongoing inflammatory process in the airways [1, 2]. While the clinical features are reversible or variable over time in asthma [1], they are more persistent and usually progressive over time in COPD [2]. The connection between these two common disorders has been debated thoroughly for many decades with proponents for both “splitting” or “lumping” them into either two distinct or one common entity [3–6]. The clinical heterogeneity of both conditions has also been recognised for a long time, and the fact that some patients show characteristics of both diseases simultaneously resulted in the official introduction of the asthma–COPD overlap label by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma committees in 2014 [7].

The classical view imposes an important distinction in the pathogenesis of asthma and COPD, based on the type of inflammatory response. In most patients with asthma, airway inflammation is characterised by the presence of eosinophils with a typical cytokine pattern (type-2 inflammation), whereas this has not been a prominent feature of airway inflammation in COPD [8]. Nonetheless, during the past two decades, we have also seen some patients with COPD display a type-2 inflammatory response, and a substantial proportion of patients with asthma that do not have type-2 inflammation [9–11]. These observations have led to a proposal of a paradigm shift suggesting that eosinophilic airway inflammation should be considered as an important treatable trait in all types of chronic airways disease, regardless of the asthma or COPD label [12, 13].

Fortunately, it seems that the events taking place in the airways of patients with asthma and COPD are to some degree mirrored in their blood. A number of successful clinical trials sponsored by different companies and using different compounds have suggested that blood eosinophil counts (EOS) are useful in the identification of patients with COPD that will benefit most from inhaled corticosteroid treatment [14, 15], and of patients with asthma suited for treatment with monoclonal antibodies directed against type-2 inflammatory cytokines IL-4, IL-5 and IL-13 [16–18]. Importantly, the results from these clinical trials can now be supported in a real-world setting, where COPD patients with high EOS from a primary care database from the UK have been shown to benefit from inhaled corticosteroid treatment [19]. Based on the available evidence at that time, the GOLD committee in 2019 recommended that EOS higher than 300 cells·µL⁻¹ in patients with COPD and frequent exacerbations despite treatment with long-acting bronchodilators should lead to treatment with inhaled corticosteroids [20]. This was a bold move from GOLD, considering that most of the evidence was based on post hoc analyses of clinical trials rather than on upfront randomisation according to baseline EOS [14, 15]. The most recent recommendations from GOLD acknowledge that the relationship between EOS and the effect of inhaled corticosteroids in COPD.
is likely to be continuous, but a treatment threshold of less than 100 cells·µL\(^{-1}\) is suggested to identify
patients less likely to benefit from the treatment, and higher than 300 cells·µL\(^{-1}\) for patients with greatest
benefit [2]. In severe asthma, an EOS higher than 150 cells·µL\(^{-1}\) is recommended for consideration of
anti-IL5 therapy [17]. It is important to note that these thresholds are below the value of 500 cells·µL\(^{-1}\),
which has traditionally been defined as an abnormal value [21]. This implies that in the right clinical
context, even small variations within normal limits of EOS can provide important information for therapy
guidance by predicting different magnitudes of drug response.

Since EOS is currently the only blood biomarker for the management of COPD and asthma, the study by
Benson et al. [22] in this issue of the *European Respiratory Journal* is of great interest. The authors
conducted a comprehensive literature review and meta-analysis to describe the absolute EOS distributions
in individuals with and without chronic airways disease. By using the PubMed and EMBASE databases
with well-defined search criteria, approximately 6000 studies were identified over 10 years in the period
from 2008 through 2018, with 91 eligible for further assessment after various exclusion criteria
(corresponding to 1.6%). This illustrates the tremendous amount of work the investigators have done that
deserves respect and appreciation. An obvious but nonetheless crucial exclusion criterion during selection
was that studies with EOS as part of the inclusion/exclusion criteria were excluded. In total, 39 of the
studies described EOS in asthma, 12 in severe asthma, 23 in COPD, seven in non-disease controls, and 14
of the studies described EOS in general populations. Sample sizes varied from 200 to approximately 360
000 individuals.

After evaluation of the included studies, the investigators quickly discovered that EOS display a trend
towards a right-skewed distribution in both individuals with and without chronic airways disease, and that
medians or geometric means rather than mean values need to be considered when evaluating potential
thresholds. Interestingly, medians were reported higher in COPD compared to non-disease controls and
general population. As expected, the highest medians were observed in asthma and severe asthma.
Meta-analysis yielded a median of 207 cells·µL\(^{-1}\) (95% CI 203–211 cells·µL\(^{-1}\)) for asthma,
286 cells·µL\(^{-1}\) (95% CI 235–348 cells·µL\(^{-1}\)) for severe asthma, 171 cells·µL\(^{-1}\) (95% CI 159–
184 cells·µL\(^{-1}\)) for COPD, and 157 cells·µL\(^{-1}\) (95% CI 152–163 cells·µL\(^{-1}\)) for non-disease controls and
general population. These results are of considerable interest, as they illustrate for the first time in a
systematic way EOS in patients with asthma and COPD from several studies.

Benson et al. [22] also pursued identification of factors associated with high EOS. Allergy, current
smoking, obesity, male sex and airflow limitation were all associated with higher EOS, and these factors
worked additively [23–25]. We should be aware of these associations when interpreting EOS in patients
with asthma or COPD, but it is disputable how this knowledge will affect decisions regarding therapy.
While presence of allergy is closely associated with type-2 inflammatory response and advocates for
treatment with inhaled corticosteroids, the importance of smoking for EOS and the potential benefit from
inhaled corticosteroid treatment may not be straightforward. A Mendelian randomisation analysis with
more than 100000 individuals from the general population did not find evidence of a causal association
between smoking and EOS [26]. However, a sub-analysis of the IMPACT trial suggested that EOS
threshold for the beneficial effect of inhaled corticosteroid may be higher in current than in former
smokers, which is in line with previous observations of a relative corticosteroid resistance in smokers with
chronic airways disease [27].

Strengths of the study by Benson et al. [22] include a systematic literature search and inclusion of all
available studies focusing on EOS distribution, not only in individuals with chronic airways disease but
also in those from the general population. The investigators should also be recognised for their
contribution in terms of performing a random-effects meta-analysis of medians, a challenge that they have
accomplished with success.

Nonetheless, some limitations of the present study need to be highlighted. It was not possible for the
investigators to evaluate EOS according to medication used; however, it seems that whilst inhaled
corticosteroids reduce airway eosinophilia, their effect on EOS is less well-described and believed to be
modest [28]. Another limitation is that the investigators restricted their search period from 2008 through
2018, thereby excluding earlier studies, which perhaps would have strengthened some of their analyses and
conclusions.

The ability to predict treatment response is key in precision medicine. After many years, while searching
for other biomarkers, we have “rediscovered” EOS, a well-known measurement which is easy to implement
both in hospital- and general practice-settings as a useful biomarker for treatment response in certain types
of COPD and asthma. The study by Benson et al. [22] is an important documentation of our knowledge on the distribution of blood eosinophils in health and obstructive lung disease and reduces some of our knowledge gap regarding this amazing cell.

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References


