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Key points

- Eosinophilia may play a significant role in the pathogenesis of COPD.
- Eosinophilic inflammation in COPD can be steroid responsive; however, eosinophilic inflammation is variable, and caution needs to be taken with measurements and the thresholds used.
- The long-term effects of reducing eosinophil levels in COPD is unclear.

Educational aims

- To explore current knowledge of eosinophils in COPD.
- To explore the relationship between eosinophilia and corticosteroid use.
- To understand the limitations of assessing and using eosinophilia in COPD.

Brian Oliver[1,2], Katrina Tonga[2,3,4], David Darley[3], Sandra Rutting[2], Xin Zhang[5], Hui Chen[1], Gang Wang[5]

wcums-respiration@hotmail.com

https://www.linkedin.com/in/brian-oliver-87b25630/

Review

COPD treatment choices based on blood eosinophils: are we there yet?

Eosinophils are increasingly being recognised as an important characteristic feature of COPD. Patients with COPD and eosinophilic inflammation tend to respond to steroid therapy; however, many questions remain regarding the optimum measurement. Eosinophilic inflammation may be defined based on various sampling techniques, including eosinophil levels in blood, sputum, bronchoalveolar lavage or biopsy, which leads to inconsistencies in its definition. Blood eosinophils may increase in conjunction with sputum eosinophils during COPD exacerbations and therefore may be a good surrogate marker of airway eosinophilic inflammation. However, the timing of the blood eosinophil measurement, the stability of the eosinophil count and the threshold used in different studies are variable. The use of blood eosinophil count to direct biological therapies in COPD has also had variable outcomes. Eosinophilic inflammation has an important role in COPD management; however, its use as the optimum biomarker still needs further investigation.

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What is an eosinophil, and are these cells needed?

Eosinophils are one of several types of leukocyte found in peripheral blood and in tissues, and in some lung diseases they are found in both lung tissue and in the airway and/or alveolar lumen. They are classified and referred to as both granulocytes (due to the numerous granules in their cytoplasm) and polymorphonuclear leukocytes (due to their irregularly shaped nucleus). It is worth noting that the term polymorphonuclear leukocyte sometimes causes confusion as it is used incorrectly to refer only to neutrophils.

Eosinophils are evolutionarily old, being found in "living fossils" such as the tuatara, a type of lizard found in New Zealand [1]. They are also present and functionally similar across multiple species; for example, they are found in zebrafish where they increase in number in response to parasitic worm infections [2]. However, the exact function of the eosinophil remains something of a mystery. Classically, and as alluded to, eosinophils are described as important immune cells that control parasitic worm infections; however, the evidence for this is based on historical pathological studies and may not be correct. For example, studies in mice have shown that the absence of eosinophils promotes the death of the natural mouse worm *Trichinella spiralis* [3], adding further to the mystery of their exact biological role. There is also now the idea that eosinophils are the immunological equivalent of the appendix. This has largely stemmed from the use of anti-interleukin (IL)-5 biologicals for the treatment of allergic disorders including asthma, in which the absence of

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Eosinophilia is common in COPD and has utility in predicting responses to inhaled or oral corticosteroids, but has limitations as a biomarker http://bit.ly/2lQcMpy

eosinophils does not lead to adverse immunological consequences. Of interest in the context of COPD, in which the neutrophil is thought to drive tissue damage, eosinophils have a greater capacity to produce reactive oxygen species [4], and therefore the presence of eosinophils in COPD might have important pathological consequences.

Eosinophils, corticosteroids and COPD

Studies in the 1940s and 1950s recognised that raising the levels of endogenous corticosteroids or administration of synthetic corticosteroids decreased eosinophil counts [5, 6] and, over 20 years ago, studies emerged demonstrating a direct pro-apoptotic effect of corticosteroids on eosinophil apoptosis [7]. Therefore, it is not surprising today to find that eosinophilia in a range of diseases is supressed by either inhaled corticosteroid (ICS) or systemic corticosteroid treatment. It would therefore be easy to assume that eosinophilic COPD should be corticosteroid responsive; however, in COPD, the effect of corticosteroid treatment on eosinophil levels and/or clinical outcomes is not as straightforward. Today we acknowledge that COPD is a heterogeneous disease, both in its aetiology and clinical course [8]. What perhaps is more surprising is that eosinophilia, which is typically associated with asthma, occurs in a subset of patients with COPD. In a recent study of patient data from general practice in both the UK and USA (around 43000 patients), eosinophilia was evident in 31% and 25% of the UK and USA cohorts of stable COPD patients, respectively [9], and some studies have reported eosinophilia in up to 40% of patients with COPD [10]. However, COPD studies from the 1990s, often with small numbers of patients, had negative outcomes when looking at the effect of corticosteroid treatment on eosinophilic inflammation [11]. These older studies were used as part of the rhetoric to develop the concept that inflammation in COPD is corticosteroid insensitive, especially when contrasting with the effects of corticosteroid treatment for asthma. The first larger study to show that corticosteroids were effective in eosinophilic COPD was performed by Brightling *et al.* [12] almost 20 years ago. In their study they found that forced expiratory volume in 1 s and symptoms (assessed by the chronic respiratory disease questionnaire) were improved most in patients with stable COPD who had the highest sputum eosinophil counts. This observation was further strengthened by the outcomes of a randomised controlled trial of the treatment of COPD based on either British Thoracic Society guidelines or sputum eosinophil levels [13]. Using sputum eosinophil levels to guide corticosteroid use resulted in a 62% reduction in exacerbations.

The utility of corticosteroids in eosinophilic COPD patients

Following from these initial studies, the positive effect of corticosteroids in eosinophilic COPD patients has been consistently reproduced (for example, when a cut-off of 3% of sputum eosinophils is used) [10, 14, 15] and observed in *post hoc* analyses of recent large clinical trials. *Post hoc* analyses, while informative, are not ideal as disease-modifying factors such as severity or exacerbation frequency might not be fully considered in the analysis. Similarly, in the WISDOM trial, where corticosteroids were withdrawn from COPD patients, baseline eosinophilia predicted ICS withdrawal-related exacerbations of COPD [16, 17]. At this point, you might be wondering why the question "COPD treatment choices based on blood eosinophils: are we there yet?" was raised, if the data are so clear-cut. Unfortunately, there are a number of confounding effects, which need to be considered before answering this question.

The utility of measuring blood eosinophil levels in COPD

The biggest potential confounder to using blood eosinophil levels as a biomarker to guide treatment choices in either stable or exacerbating COPD relates to the measurement of eosinophilia, and the stability or reproducibility of such measurements. Blood eosinophil levels can either be expressed as an absolute count (*e.g.* 150 cells·μL^{-1}) or as a percentage of other cells present. Currently, individual studies define eosinophilia differently, or stratify patients according to eosinophil levels. For example, the groups <2%, ≥2–<3%, ≥3–<4%, <150 cells·μL^{-1}, 150–<300 cells·μL^{-1}, ≥300–<400 cells·μL^{-1} and ≥400 cells·μL^{-1} were used in the *post hoc* analysis of WISDOM [17]. Thankfully, the 2019 treatment guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [18] have recommended blood eosinophil counts ≥300 cells·μL^{-1} in stable COPD as the diagnostic criterion for initiating therapy with ICS/long-acting β-agonist (LABA). However eosinophilia is defined, the utility of the measurement is limited by the stability of the measurement. Landis *et al.* [19] explored the reproducibility of eosinophil counts in peripheral blood in 27557 COPD patients with stable disease in general practice over 1 year and found an intraclass correlation coefficient (ICC) (a measure of how similar the individual measurements are to each other) of 0.64, showing

that there is good reproducibility, but a subgroup of COPD patients have variable eosinophilia. Negewo *et al.* [20] found a better ICC of 0.8 of blood eosinophils over a median 28-day period in stable COPD, suggesting that blood eosinophil levels are very stable in the short term (1 month) in people with stable disease. Oshagbemi *et al.* [21] also carried out a study of eosinophil level reproducibility in general practice, including 39824 COPD patients and 90772 patients without COPD over a 10-year period. COPD patients were excluded if they had an exacerbation within 30 days of the start of follow-up. In their cohort, 34.9% of COPD patients and 25.8% of patients without COPD had eosinophilia (defined as counts $>0.34\times10^9$ cells·L^{-1}). The stability of eosinophilia was higher in patients without COPD, and in patients with COPD stability was around 85% at 6 months, declining to 62% at 2 years, progressively declining in subsequent years [21]. Other studies have found lower reproducibility of eosinophil counts in peripheral blood measurements. For example, analysis of a subgroup of COPD patients (334 patients) in the COSYCONET study [22] over routine visits at 0, 6 and 18 months found that 26% of patients were non-eosinophilic at all three visits; however, only 5% of COPD patients were persistently eosinophilic. Interestingly, 28% of patients were eosinophilic at one study visit [22]. While the study visits were scheduled, patients were not excluded if they were exacerbating. The COSYCONET study analysis defined eosinophilia as ≥300 cells·µL^{-1}, but when eosinophilia was defined as ≥2% in blood (or sputum) in a retrospective analysis of the ECLIPSE study [23], 37.4% of 1483 COPD patients had stable blood eosinophilia. This assessment was made based on an initial measurement of eosinophils at the first study visit in patients with stable COPD and compared to measurements at years 2 and 3. Sputum eosinophilia was markedly less reproducible, but valid measurements were available for approximately 10% of patients. Therefore, it is clear that if blood eosinophil levels alone were used to guide therapy, there would be some element of chance as to whether a given patient would be classified as eosinophilic or not. In asthma, there is good evidence to show that the use of β-agonists as monotherapy has pro-inflammatory effects, for example by inducing sputum eosinophilia [24, 25]. Interestingly, this pro-eosinophilic effect of β-agonists as monotherapy has not been studied in COPD patients; however, they are safe and effective treatments for COPD [26].

The utility of measuring blood eosinophils to guide therapy is likely to vary depending upon the clinical status of the patient, *i.e.* whether their COPD is stable or they are experiencing an exacerbation. Two studies in 2019 have both investigated eosinophilia during exacerbations. MacDonald *et al.* [27] compared clinical characteristics of hospitalised patients with exacerbations of COPD who had low (<50 cells·µL^{-1}), normal (50–150 cells·µL^{-1}) or high (>150 cells·µL^{-1}) numbers of eosinophils. Low eosinophil numbers were associated with infection, longer hospitalisation and reduced mortality compared to patients with high eosinophil counts. Sivapalan *et al.* [28] reported the results of an open-label non-inferiority trial of using eosinophilia (>300 cells·µL^{-1}) to guide prednisolone therapy in COPD exacerbations. They found no significant differences in mortality or days out of hospital between the groups, with reduced corticosteroid exposure in the eosinophilia-guided group. In a non-inferiority study, the lack of statistical difference between groups shows that the investigative treatment is as effective as the established treatment group. Therefore, Sivapalan *et al.* [28] demonstrate the utility of measuring sputum eosinophils to guide prednisolone therapy in COPD exacerbations. However, follow-up was only for 30 days, and therefore the long-term effects of reduced corticosteroid use during exacerbations remains to be determined. In the study by Sivapalan *et al.* [28], six patients died in the eosinophil-guided reduced corticosteroid group and four in the usual therapy group. While this difference was not statistically significant, mortality is a signal that needs to be closely followed in future studies of this nature.

Eosinophil-targeted therapies in COPD

So far, we have discussed the potential utility of using eosinophils to guide corticosteroid treatment; however, biological therapies targeting eosinophilia are emerging as useful add-on therapies for the treatment of severe asthma. Mepolizumab and benralizumab are the two leading anti-IL-5-based therapies, and the utility of both drugs has been investigated in multiple phase 3 clinical trials of COPD [29, 30]. For an excellent overview of the mepolizumab trials, see the review by Long and Wall [31]. The studies of both benralizumab [29] and mepolizumab [30] recruited eosinophilic COPD patients with a history of exacerbations, who were either receiving guideline-based inhaled treatment (benralizumab) or triple therapy (mepolizumab). The outcomes of treatment with the two therapies were different. Mepolizumab reduced exacerbation frequency in eosinophilic patients, but not in all patients. Benralizumab, however, did not affect exacerbation frequency. The major difference in the two studies was the definition of eosinophilia: in the mepolizumab clinical trials eosinophilia was defined as >220 cells·µL^{-1}, while in the benralizumab clinical

trials eosinophilia was defined as ≥150 cells·μL^{-1} at screening or ≥300 cells·μL^{-1} during the previous year. Exacerbation frequency in the placebo groups also differed (around 1.7 per year for mepolizumab *versus* 1.2 for benralizumab). Could these differences explain the differences in the study outcomes? Perhaps, and we are sure that these differences will be used as points of debate for some time to come. However, what is clear is that the effectiveness of these two therapies in COPD is markedly reduced in comparison to their effectiveness in asthma, and neither is likely to transform the management and outcomes of COPD patients.

COPD treatment choices based on blood eosinophils: are we there yet?

To date, the evidence suggests that measuring eosinophil levels to help guide therapy is useful, both in the context of initiating combined ICS/LABA, and in the potential reduction of corticosteroids. However, each patient is different, and a holistic view of their COPD needs to be taken before considering changes to their therapy. Ideally, this should include multidimensional assessment, as comorbidities are common in people with obstructive lung diseases [32]. The concept of identifying and treating both comorbidities and lung disease in COPD has given rise to the concept of treatable traits, which is described in detail in an excellent article by McDonald *et al.* [33]. Simplistically, this method identifies the clinical components of disease (pulmonary and nonpulmonary) in a patient that are treatable (for example high blood pressure or sputum eosinophilia) and treats these traits using a multidisciplinary approach.

The future of eosinophils in COPD management

The recent negative findings from the benralizumab trials may leave the reader with the impression that targeting eosinophils in COPD has limited utility. However, this is clearly not the case for decisions around introducing ICS/LABA, or reducing or increasing the dose of corticosteroid given in stable COPD. In these situations, there is good evidence that using eosinophil levels to guide corticosteroid treatment has beneficial outcomes. We recommend inclusion of measurement of eosinophils in induced sputum where possible, and the inclusion of blood eosinophil levels at routine clinical visits, as understanding how eosinophil levels are changing in response to treatment, or at the time of an exacerbation, is perhaps more useful than a single historical or current measurement of eosinophil levels. The use of a cut-off point (*e.g.* more or less than 300 cells·μL^{-1}) is useful, but in our opinion eosinophil levels should be considered as a continuous variable. For example, an increase of counts from 80 to 280 cells·μL^{-1} would suggest a greater corticosteroid dose is needed, but if the decision was based on a cut-off point of 300 cells·μL^{-1} no change in dose would occur.

As to the future of the eosinophil as simply a biomarker of corticosteroid responsiveness or a pathogenic cell in COPD, future studies are needed. For example, the lack of effect of benralizumab in reducing exacerbation frequency, despite reducing eosinophilic inflammation, is reasonable evidence to suggest that exacerbations of COPD are not driven by eosinophils as they are in asthma. However, this does not mean that, for example, reducing eosinophil levels in mild COPD would not be effective in reducing the rate of progression of COPD. It might also be the case that better phenotyping and selection of patients is needed to select patients who will benefit from eosinophil-targeting biological therapies.

Affiliations

Brian Oliver[1,2], Katrina Tonga[2,3,4], David Darley[3], Sandra Rutting[2], Xin Zhang[5], Hui Chen[1], Gang Wang[5]

[1]School of Life Sciences, Faculty of Science, University of Technology Sydney, Sydney, Australia. [2]The Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia. [3]Dept of Thoracic and Transplant Medicine and St Vincent's Clinical School, St Vincent's Hospital, University of New South Wales, Sydney, Australia. [4]Faculty of Medicine and Health, University of Sydney, Sydney, Australia. [5]Dept of Respiratory and Critical Care Medicine, Clinical Research Centre for Respiratory Disease, West China Hospital, Sichuan University, Chengdu, China.

Conflict of interest

None declared.

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