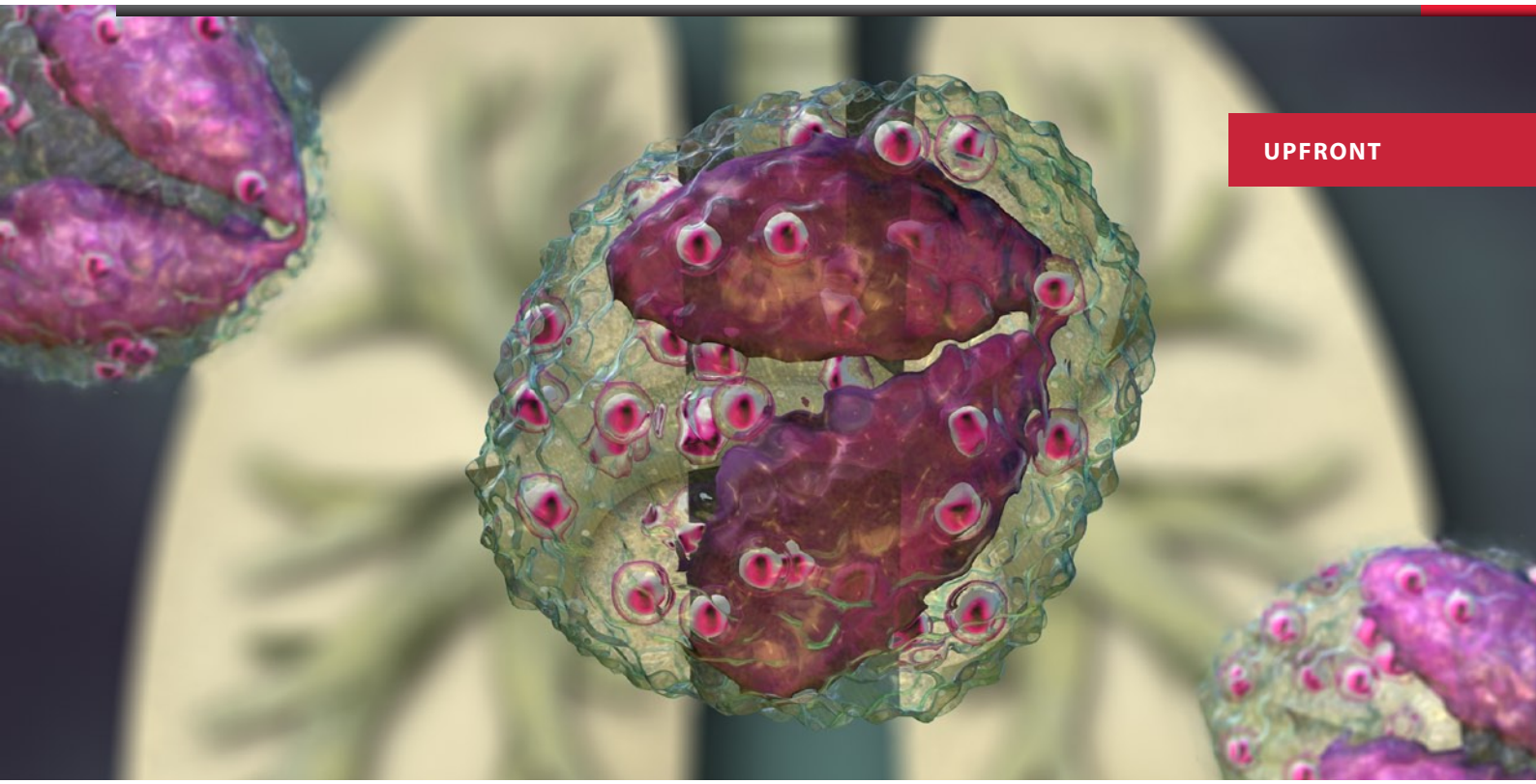

Are blood eosinophil counts helpful in predicting patient responses to **inhaled corticosteroids in COPD?**

The risks and benefits of COPD treatment with inhaled corticosteroids (ICS) are different for individual patients. There is currently debate within the respiratory literature as to whether blood eosinophil counts can be used as a biomarker to determine which patients with COPD are most likely to benefit from treatment with an ICS. In this article, we examine whether there is currently a role for this test in primary care.

Management of patients with chronic obstructive pulmonary disease (COPD) is changing. There is increasing recognition that COPD is a heterogeneous disease which may have distinct phenotypes, a growing realisation that inhaled corticosteroids (ICS) may be overused, new medicines are more readily available (see: "Newly-subsidised medicines for the treatment of patients with COPD", Page 7) and there is some evidence that biomarkers may be able to guide treatment.

The use of biomarkers to enable targeted treatment for patients with COPD is an evolving area of research. The idea that airway inflammation, characterised by elevated eosinophil levels in sputum or blood, may be important in COPD pathophysiology is not new. Initially, research was driven by the observation that corticosteroid treatment modified eosinophilic airway inflammation and was associated with improved outcomes in patients with asthma.[1] This led some researchers to question whether stable patients with COPD and elevated eosinophil levels might respond better to corticosteroids compared with patients without elevated eosinophil levels.[2, 3] Translation of this research into clinical practice is now being discussed in the belief that a raised blood eosinophil level may identify which subset of patients are most likely to benefit from ICS use.[4–6]

The use of blood eosinophil counts to guide ICS treatment is controversial

Despite the promise shown in a number of studies, questions remain as to exactly how blood eosinophil counts could, or should, be applied in clinical practice. For example, should blood eosinophils be assessed by absolute count or relative percentage, and what level should be used as a cut-off,

bearing in mind that most definitions of elevated eosinophil levels in the context of the research are within the "normal" range (see: "Raised eosinophil levels", next page). Also, does a raised eosinophil level detect all patients who are likely to respond to ICS treatment? Should assessment of eosinophils levels only occur when patients are stable, as during COPD exacerbations patients can have elevated levels, and can eosinophil levels guide treatment with oral corticosteroids during an exacerbation? Furthermore, should patients without an increased eosinophil blood level be withdrawn from ICS treatment?

Some respiratory physicians feel more research is required to clinically define elevated eosinophil levels to determine if ICS use in patients with COPD leads to better outcomes.[7, 8]

The concept of COPD phenotypes

Asthma and COPD have traditionally been considered as separate clinical entities; in reality they are both heterogeneous diseases which can be difficult to differentiate. A new taxonomy for chronic airway diseases may eventually be needed to acknowledge this reality as respiratory care becomes increasingly personalised and precise.[9]

The overlap between asthma and COPD has long been recognised, although it was only recently that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy included a clinical definition for identifying patients with Asthma-COPD Overlap Syndrome (ACOS).[10] In addition, other "phenotypes" of COPD have begun to emerge, such as patients with eosinophilic airway inflammation which cannot be attributed to asthma, and patients who have frequent exacerbations.[8, 11] What is not clear is the extent to which these phenotypes reflect the natural progression of COPD, disease severity, responsiveness to treatment and the presence of co-morbidities, and to what extent they are stable and distinct clinical subsets of patients.[8, 12]

The changing role of ICS in COPD

Patients with COPD have been routinely treated with ICS; largely due to the effectiveness of ICS in patients with asthma, rather than clinical evidence of benefit in COPD.[12, 13] Most guidelines now suggest that ICS should only be used for patients with more severe disease who are at risk of exacerbations and for selected patients with ACOS.[10, 14] The legacy of past practice remains, however, and many patients who do not meet these criteria are continuing to be prescribed ICS which may result in more harm than benefit.[13]

The risks and benefits of ICS in COPD

Epidemiological evidence and the retrospective analysis of several large randomised controlled trials indicate that the use of an ICS, either alone or in combination with a long-acting beta$_2$ agonist (LABA), increases the risk of patients with COPD developing pneumonia.[10, 15] The long-term use of ICS is also associated with an increased prevalence of oral candidiasis, hoarse voice, skin bruising and possibly reduced bone density.[10] Respiratory physicians in New Zealand now tend to reduce or withdraw ICS treatment in patients with COPD, rather than initiate it. One study reported that in stable patients with severe COPD withdrawal of ICS resulted in no difference in the exacerbation rate compared with patients who continued ICS treatment.[16]

The decision to prescribe an ICS needs to balance the risks and the benefits for individual patients. Approximately fourteen patients need to be treated for one year to prevent one COPD exacerbation (number needed to treat [NNT]= 14).[17] For the same period there will be one additional case of pneumonia for every 20 – 30 patients treated with an ICS (i.e. number needed to harm [NNH] may be as low as 20).[17] When the heterogeneous nature of COPD is considered, however, these numbers are less helpful as not all patients with COPD will receive the same benefit from ICS treatment.[12] The availability of a reliable biomarker to help predict response to ICS would assist clinicians and patients in making better treatment decisions.


For further information on COPD, see: "The optimal management of patients with COPD – Parts 1 & 2", BPJ 66 (Feb, 2015).

The role of eosinophilic airway inflammation in COPD

Eosinophilic airway inflammation is generally considered to be a hallmark of patients with asthma rather than COPD, however, it is also found in patients with COPD.[10, 18] Elevated sputum eosinophil levels, due to eosinophilic airway inflammation, are found in up to 80% of corticosteroid-naïve and 50% of corticosteroid-treated patients with asthma, compared with between 10 and 40% in patients with COPD.[18] This data was taken from stable patients, but there is also evidence that patients with COPD have elevated sputum eosinophil levels during exacerbations.[18]

Blood eosinophil levels have been suggested as a practical, quick, cost-effective surrogate marker for sputum eosinophil levels as sputum samples for eosinophil analysis are often unavailable outside of a research setting.[5, 6] However, there are difficulties with using blood eosinophil levels as a biomarker in this context, including:

- The link between eosinophilic airways inflammation and blood eosinophils has been questioned with one study reporting only a moderate correlation between the two[18]
- An individual's blood eosinophil levels change over time and are influenced by COPD phenotype, medicines and co-morbidities, e.g. obesity[18]

- Depending on what cut-off is used, a large number of patients with COPD may have "elevated" blood eosinophil counts; a review of three large trials found that 57–75% of patients with COPD had blood eosinophil levels ≥ 2%.[6]

Research has been hampered by methodological problems

In addition to the problems relating directly to eosinophil levels, issues have been raised regarding the methodology of some of the research that has been conducted, including:

- Variability in the outcomes used to measure ICS treatment efficacy, e.g. a decrease in exacerbations or a slower rate of decline in FEV_1.[6, 19]
- Inconsistencies in the medicines that are used. Some studies have used ICS monotherapy, others have used combination medicines, e.g. a LABA/ICS;[6, 19] earlier studies used oral corticosteroids[2]
- The exclusion of patients with mild COPD and those with any features suggestive of asthma, i.e. patients with ACOS type COPD

More research is required before eosinophil testing becomes a routine part of management

There is currently a lack of consensus amongst respiratory physicians, in New Zealand and worldwide, regarding the usefulness of blood eosinophils as a marker for ICS responsiveness in patients with COPD. The research appears to suggest that COPD patients with a blood eosinophil level > 2% may benefit from ICS (or combination) treatment. However, it remains unclear whether a blood eosinophil level >2% will identify all patients with COPD who will respond to an ICS. To date, no prospective randomised controlled trials have been published. Expert opinion currently suggests that it is premature to offer specific advice on the usefulness of a raised blood eosinophil level to guide individual ICS treatment in primary care; this issue will be revisited if the evidence-base for the recommendation changes.[6–8]

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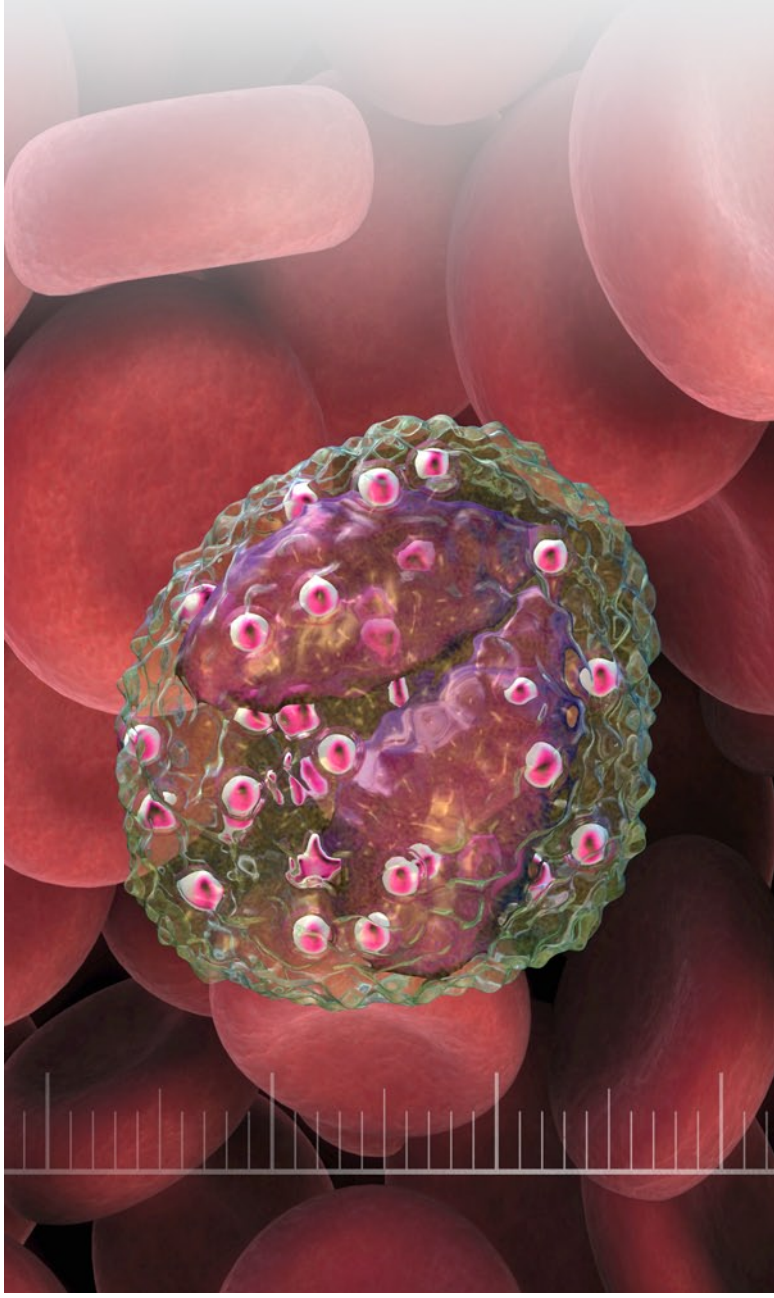
Raised eosinophil levels

Eosinophils typically account for 1–6% of an individual's total white blood cell count.[20] The >2% cut-off used by many researchers investigating ICS response in patients with COPD therefore falls within the normal range.[18] The reference range for eosinophils in adults on full blood count is $0 - 0.5 \times 10^9$/L.[21] Most research in the context of COPD focuses on a "raised blood eosinophil level" rather than "eosinophilia" *per se*. Alternative causes for elevated blood eosinophil counts include: allergies, skin diseases, e.g. eczema, parasitic infections of the gastrointestinal tract, e.g. hookworm, reactions to medicines, e.g. aspirin, malignancy, as well as a range of non-parasitic infections, e.g. scarlet fever, and autoimmune disorders.[21]



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