Type 2 inflammation in COPD: is it just asthma?

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Shareable abstract (@ERSpublications)
T2 inflammation is a shared treatable trait of some asthma and COPD patients, but the evidence reviewed here indicates that the nature of T2 inflammation is not identical in COPD and asthma. Eosinophilic COPD is not the same as asthma. https://bit.ly/3XdmwZW

Cite this article as: Beech A, Higham A, Booth S, *et al*. Type 2 inflammation in COPD: is it just asthma? *Breathe* 2024; 20: 230229 [DOI: 10.1183/20734735.0229-2023].

Received: 24 April 2024
Accepted: 7 Aug 2024

Abstract

COPD is a heterogeneous condition, with tobacco smoking being the main environmental risk factor. The presence of type 2 (T2) inflammation is a well-recognised feature of asthma; however, it is now apparent that a subset of COPD patients also displays evidence of T2 inflammation with respect to elevated eosinophil counts and altered gene and protein expression of several T2 inflammatory mediators. T2 inflammatory mediators represent an attractive therapeutic target in both COPD and asthma; however, the efficacy of pharmaceutical interventions varies between diseases. Furthermore, the nature of some shared clinical features also differs. We provide a narrative review of differences in the nature of T2 inflammation between COPD and asthma, which may partly explain phenotypic differences between diseases. We focus on evidence from studies of pulmonary histopathology, sputum and epithelial gene and protein expression, and response to pharmacological interventions targeted at T2 inflammation.

Educational aims

- Briefly describe the prevalence and clinical significance of the type 2 inflammatory endotype in COPD.
- Review the similarities and differences between type 2 inflammatory profiles in asthma and COPD.
- Review current understanding of the co-existence of COPD and asthma in some patients.

Introduction

COPD is a heterogeneous condition arising from a series of complex interactions that occur over a patient's lifetime, with tobacco smoking being the main environmental risk factor [1]. It is characterised by chronic respiratory symptoms and the presence of poorly reversible airflow obstruction. COPD patients have an abnormal immune response within the lungs that persists even upon smoking cessation [1]. There is currently much interest in furthering our understanding of the heterogeneity of COPD airway inflammation, with the aim of implementing precision medicine that individualises treatment based on clinical characteristics (phenotype) combined with biological (endotype) information obtained using biomarkers [2]. The importance of type 2 (T2) inflammation is well recognised in asthma; this terminology is used to describe inflammatory pathways involving mast cells, basophils and lymphocyte subsets that secrete the T2 cytokines interleukin (IL)-4, IL-5 and IL-13 [3]. It is now apparent that a subset of COPD patients has T2 inflammation, as elevated sputum eosinophil counts have been observed in 27–46% of COPD patients during the stable state [4].

Clinical trials conducted ~20 years ago revealed that elevated sputum eosinophil counts were predictive for the response to oral corticosteroids and inhaled corticosteroids (ICS) in COPD patients (reviewed in [4]). These sputum studies showed that a biological characteristic (endotype) could predict an enhanced treatment response. Blood eosinophil counts (BECs) are now used as a practical measure of lung eosinophil levels, as there is an association between these parameters [4]. Figure 1 shows examples of positive staining for eosinophils within the lung from sputum (figure 1a) and the small airways (figure 1b). The initial COPD clinical trials of ICS were conducted in broad populations, showing limited benefit [5]. Numerous clinical trials have subsequently demonstrated the benefit of ICS in COPD patients with increased exacerbation risk, while higher BECs identify individuals within this population who are more likely to respond [4]. Additionally, BEC used in conjunction with exacerbation risk identifies the target COPD population with a positive response to biological treatment targeting T2 inflammation [6]. There is also a relationship between BEC and both future exacerbation risk and lung function decline [4]. The use of BEC in clinical practice as a COPD biomarker is growing, as it is able to provide information on future risk and potential response to pharmacological interventions [7].

Asthma is a disease where the majority of patients have features of T2 airway inflammation, including allergy and/or eosinophilic inflammation [8]. A cardinal feature of asthma is bronchial hyperreactivity with susceptibility to acute bronchospasm after exposure to trigger factors [9]. The differentiation of asthma and COPD is usually straightforward in younger individuals, as allergic asthma occurs in children while COPD is diagnosed in older adults, often after decades of cigarette smoking. Additionally, asthma shows greater variability and reversibility of airflow obstruction and greater bronchial hyperreactivity [9]. However, the clinical presentation of asthma and COPD may be more similar in older individuals, creating difficulty in diagnosis. The term "asthma–COPD overlap syndrome" (ACOS) was introduced to recognise this clinical issue, a joint consensus document from the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) described ACOS as not a single disease entity, but a term applied to patients with clinical features of both asthma and COPD" [10]. The purpose of ACOS was to encourage a deeper understanding of the clinical and biological characteristics of the patient subtypes that exist under this umbrella term, in order to develop discrete management pathways for these subtypes. The purpose was not to lump all the individuals into the same diagnostic bucket and hence same treatment pathway. The most recent GINA and GOLD reports refer to COPD and asthma as two discrete diseases that may occur within in the same individual, and whilst GINA uses the term "asthma–COPD overlap" (ACO) to describe this co-existence, neither report encourages the use of ACOS/ACO as a diagnostic label [1, 9].

Pulmonary eosinophilic inflammation is a common feature in patients with asthma, and is associated with a beneficial response to corticosteroids [9]. The efficacy of corticosteroids is reduced in currently smoking and ex-smoking asthma patients compared to never-smokers [11]. There is a reduction in sputum eosinophil counts in smoking *versus* nonsmoking asthma patients [12], suggesting that smoking in asthma skews the airway inflammation profile away from a corticosteroid-responsive T2 environment. Amongst COPD patients, there is also evidence that current smoking attenuates the therapeutic effect of ICS [4].

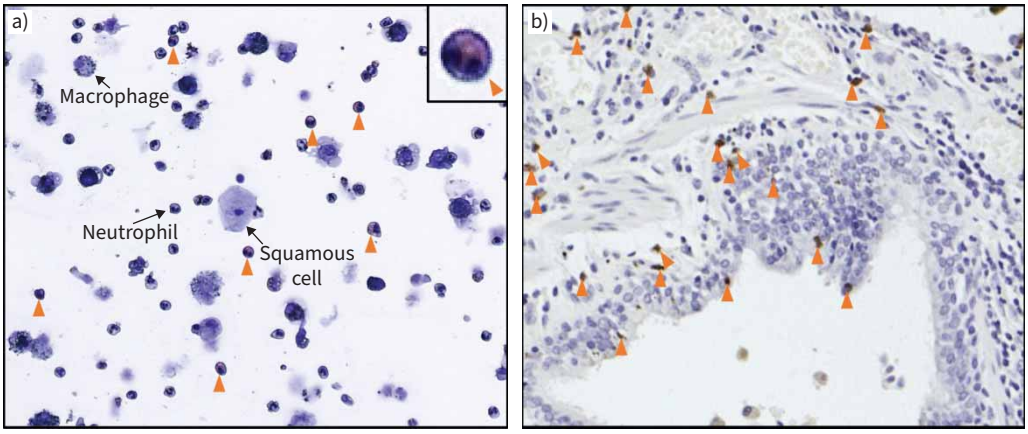

Figure 1 Identification of eosinophils in COPD using a) sputum and b) small airway *via* surgical lung resection. Eosinophils stained using a) eosin and b) major basic protein. Orange arrowheads indicate eosinophils.

While asthma and COPD are recognised as different disease states, there are clearly some similar features. The recognition of the presence of eosinophilic inflammation in a subset of COPD patients has led some to believe that these patients also have asthma, due to the positive therapeutic responses to ICS and biological treatment targeting T2 inflammation. Some asthma patients who also smoke tobacco may develop fixed airflow obstruction and features of COPD (*e.g.* emphysema on computed tomography scanning), and it is then appropriate that these individuals are labelled with having both asthma and COPD. However, for the purpose of clarity, this review will focus predominantly on COPD and asthma as separate disease entities. This is a narrative review of the nature of T2 inflammation in COPD, focusing on similarities and differences to asthma. This review encompasses studies of histopathology, gene expression, T2-related proteins and biomarkers, as well as consideration of the response to pharmacological interventions.

Histopathology studies

In studies using proximal (large) airway biopsies, the numbers of sub-epithelial but not intra-epithelial eosinophils are increased in unselected COPD patients compared to nonsmoking and smoking controls [13]. However, some studies report no difference or lower numbers in COPD patients [14]. In distal (small) airway studies, the numbers of intra-epithelial but not sub-epithelial eosinophils are increased in COPD patients compared to smoking controls [15]. Large airway eosinophil numbers are higher in asthma compared to COPD patients [16], but there is no published direct comparison between asthma and COPD for small airway eosinophil counts. While the overall evidence indicates higher airway eosinophil numbers in asthma *versus* COPD, this reflects the fact that eosinophilic airway inflammation is confined to a COPD subset. The positive correlations between BEC and tissue eosinophil counts in the large and small airways of COPD patients (rho 0.5–0.7; $p<0.001$) [4, 17] highlight that eosinophilic airway inflammation is confined to a COPD subset that can be identified using a blood biomarker.

The absolute quantity of eosinophils observed in the lung tissue of COPD patients is lower than other cell types such as neutrophils and macrophages [18]. Nevertheless, the number of eosinophils in the lungs varies greatly between individuals, and the subset of COPD patients with higher eosinophil levels has greater T2 inflammation [19–22]. Furthermore, anti-IL-5 receptor-α therapy causes sustained depletion of blood, sputum and airway tissue eosinophil levels alongside clinical benefits in asthma, with potential for benefit in COPD as well (explained in the later section on biological treatments) [23–26]. In COPD patients, large and small airway eosinophilic inflammation demonstrates patchy distribution and spatial clustering with other T2 cell types, including basophils and type 2 innate lymphoid cells (ILC2) [27]. In asthma, increased numbers of intra-epithelial eosinophils are associated with increased expression of IL-5 and increased airway hyperresponsiveness [28]. This may be due to the close proximity of eosinophils to nerves in asthma and the release of nerve-modifying agents, such as major basic protein, which can antagonise muscarinic M2 receptors, leading to innervation of smooth muscle and increased bronchoconstriction [29]. In COPD, the relationship between eosinophil location and their functional role is less clear. Patterns of eosinophilic inflammation in COPD may be determined by micro-environmental cues such as cigarette smoking. For example, the numbers of small airway intra-epithelial eosinophils are lower in current smokers compared to ex-smokers with and without COPD [15]. This may be due to increased activation of eosinophils by tobacco smoke and increased transit into the airway lumen. In support, the numbers of bronchoalveolar lavage eosinophils are higher in COPD current compared to ex-smokers [30], with a concurrent increase in eosinophil activation signals [31].

Increased reticular basement membrane (RBM) thickness is a recognised feature of airway remodelling in asthma and whilst increased RBM thickness has been reported in asthma compared to COPD patients, not all studies report this finding [32]. This may be due to the inclusion of unselected COPD patients: RBM thickness is increased in eosinophil-high (BEC >250 cells·μL^{-1}) compared to eosinophil-low (BEC <150 cells·μL^{-1}) COPD patients [20], suggesting this is a feature of increased T2 inflammation in COPD. Although Liesker *et al.* [32] demonstrated similar RBM thickness in asthma compared to COPD patients, they reported increased collagen I and laminin expression in asthma compared to COPD patients, indicating that the nature of remodelling differs in asthma and COPD. Moreover, Kolsum *et al.* [20] demonstrated increased expression of tenascin C (TNC) in the RBM of eosinophil-high compared to eosinophil-low COPD patients. A potential mechanism to explain this is that eosinophil-derived transforming growth factor-β induces TNC expression in epithelial cells [33].

Smooth muscle hypertrophy has been observed in large and small airways of asthma patients, but this is heterogeneous between individuals [34]. Smooth muscle hypertrophy has also been observed in the large and small airways of COPD patients. Interestingly, COPD patients with greater airway smooth muscle area (>20% of bronchial biopsy area) have greater improvements in lung function following ICS treatment for 12 months, compared to patients with smooth muscle area <20% [35]. The T2 cytokine IL-13 promotes

both smooth muscle proliferation and contractility in asthma [36], and perhaps the COPD findings represent suppression of IL-13-related mechanisms by ICS.

The numbers of goblet cells are increased in asthma patients compared to controls [34] and mucus plugging of the small airways is associated with increased sputum eosinophil counts in asthma patients [37]. *In vitro* studies have demonstrated that IL-13 induces goblet cell hyperplasia in epithelial cell culture [38]. However, in the small airways of COPD patients there is no association between goblet cell remodelling and eosinophil numbers. Furthermore, increased mucus plugging was not related to sputum eosinophil numbers, but was related to sputum neutrophils in COPD [39]. Whilst not conclusive, these data indicate that the role of T2 inflammation in mucus pathophysiology may differ between asthma and COPD patients (figure 2).

Mast cells are tissue-resident granulocytes well known for their role in allergy and asthma [40]. In addition to IgE-mediated inflammation, mast cells also express pattern recognition receptors and can be activated by non-atopic stimuli, such as viruses, bacteria and cytokines [41]. Mast cell numbers are increased in the airways of asthma patients compared to controls [42]. In contrast, studies enumerating mast cells in COPD airways have reported conflicting results [40]. Mast cell numbers are increased in the alveolar tissue of COPD patients compared to controls, with a relationship to disease severity observed [43]. This may be related to mast cell phenotype, as the numbers of tryptase^{+}chymase^{+} mast cells but not tryptase^{+}chymase^{-} mast cells are increased in the alveolar parenchyma of GOLD stage 4 COPD compared to controls [44]. These data suggest a role for mast cells in tissue remodelling in COPD. In asthma, mast cell infiltration of smooth muscle bundles and airway epithelium is related to increased airway hyperresponsiveness, and this may be related to an altered mast cell phenotype with high expression of carboxypeptidase A3 (CPA3) [45, 46]. The difference in the functional role of mast cells in COPD, specifically T2-high COPD, compared to asthma, is probably determined by not only the tissue location (smooth muscle bundles compared to alveolar parenchyma) but also the activating signals, *i.e.* IgE *versus* non-IgE mechanisms. This concept is discussed more in the following section of this review.

Pulmonary gene expression and protein studies

Expression of type 2 (T2) inflammatory mediators in COPD and asthma has been assessed using studies of pulmonary gene and protein expression. Some key differences are demonstrated in figure 2. Using a gene

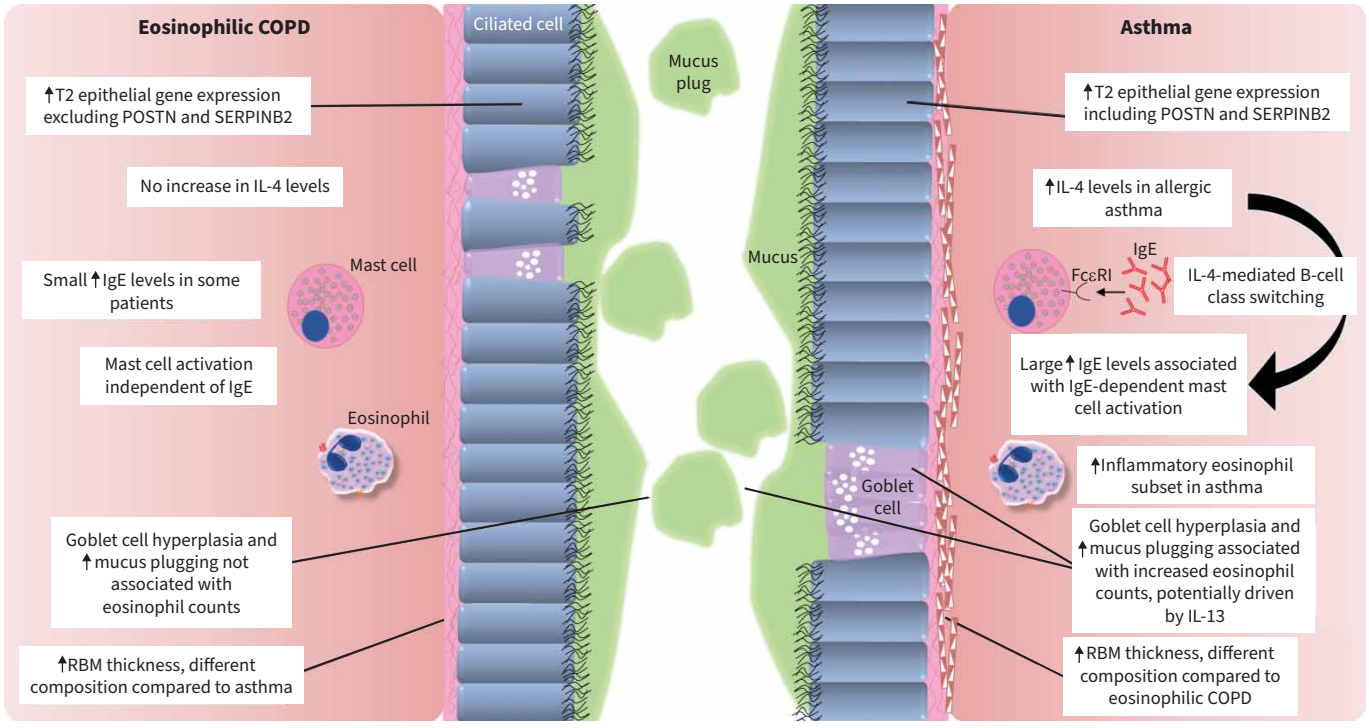

Figure 2 Schematic to show differences in pathophysiology between eosinophilic COPD and asthma. ↑: increased; T2: type 2; POSTN: periostin; SERPINB2: serine peptidase inhibitor B2; IL: interleukin; RBM: reticular basement membrane.

signature derived from T2-high asthma patients, Christenson *et al.* [22] observed increased T2 gene expression in the bronchial brush samples of a subgroup of COPD patients that was not related to a history of asthma. In a separate cohort, these authors observed increased T2 gene expression in bronchial biopsies that was related to blood and pulmonary eosinophils counts but not related to serum IgE levels [22]. Interestingly, the T2 asthma-related genes periostin (POSTN) and serpin family B member 2 (SERPINB2) were not considered optimal markers of T2 inflammation in COPD, due to reduced expression by current smoking.

Using transcriptome analysis of bronchial brush samples from the EvA (emphysema *versus* airway disease) cohort (n=283), George *et al.* [21] identified 12 genes that were associated with BEC in COPD patients, including the IL-13-dependent genes cystatin SN (CST1), chloride channel accessory 1 (CLCA1) and C–C motif chemokine ligand 26 (CCL26). Strikingly, they identified 1197 genes that were associated with BEC in asthma patients, and only one of these genes (CST1) overlapped with COPD gene expression changes [21]. This study highlighted the different nature of airway inflammation in eosinophilic COPD compared to asthma.

A bronchoscopy study (n=41) conducted in COPD patients who were non-atopic and had no history of asthma demonstrated greater eosinophil numbers in bronchial biopsies and bronchoalveolar lavage samples in the eosinophil-high (BEC >250 cells·μL^{-1}) *versus* eosinophil-low (BEC <150 cells·μL^{-1}) group, associated with increased protein levels of the eosinophil survival and chemotactic mediators IL-5 and CCL24 (eotaxin 2) [19]. Using a restricted list of six recognised asthma T2 biomarkers, it was demonstrated that the gene expression of IL-13, CST1, CLCA1 and CCL26 were increased in the eosinophil-high *versus* eosinophil-low group in both bronchial brush and sputum samples, while there were no differences between groups for POSTN and SERPINB2 gene expression. These findings were confirmed in a replication sputum cohort (n=33). The findings indicated that the T2 response in eosinophilic COPD has some similarity to asthma but is not identical.

Taken together, evidence from gene and protein expression studies demonstrates that the presence of elevated eosinophil counts in a subset of COPD patients is indicative of an enrichment for a wider T2 inflammatory signature. Whilst elevated cell counts give an indication of presence of inflammation, the enumeration of intact cells may not always reflect the level of cellular activity [47].

In unselected COPD patients, sputum tryptase (TPSB2, which encodes β-tryptase) protein and gene expression levels were similar to controls [48]. However, COPD patients with higher sputum eosinophils (>3%) had sputum tryptase levels higher than control subjects. In the COPD bronchoscopy study already described, mast cell gene expression, including tryptase (TPSAB1, which encodes α- and β-tryptase) and CPA3, was increased in sputum cells and bronchial brush samples of eosinophil-high compared to eosinophil-low patients [40]. However, there was no difference in a gene expression signature for IgE-specific mast cell activation between the groups. This is in contrast to asthma patients, where the same IgE gene signature is increased in eosinophilic compared to non-eosinophilic patients [49]. Mast cells could play a pathological role in COPD patients with eosinophilic inflammation: tryptase reduces epithelial barrier integrity and CPA3 expression is increased in areas of collagen deposition in COPD small airways [50, 51].

Mast cell numbers and mast cell gene expression in COPD are reduced by ICS [52, 53]. The clinical benefit of ICS in COPD patients with increased BEC may therefore be partly related to modulation of mast cell-mediated inflammation.

It has been reported that serum levels of the T2 cytokines IL-5 and IL-13 and the percentage of circulating ILC2 ($Lin^{-}CD45^{+}CD127^{+}CRTH2^{+}$) are significantly higher in COPD patients compared to smoking controls [54]. Interestingly, the levels of IL-4 were not significantly different between COPD patients and controls, a finding also reported in sputum [55]. In contrast, serum and pulmonary levels of IL-4 are increased in atopic asthma patients compared to controls [56], again reflecting potential differences in the underlying pathophysiology of T2 inflammation in COPD and asthma.

IgE levels

There may be a small increase in total IgE levels in some eosinophilic COPD patients [21]. B-cell class switching to IgE-producing plasma cells is regulated by IL-4, the expression of which is increased in asthma patients compared to controls, but is similar in COPD patients compared to controls. Furthermore, increased mast cell activation in asthma is associated with an IgE-dependent mechanism [49], whereas increased mast cell activation in eosinophil-high COPD patients appears to be more independent of IgE signalling [40].

An observational study comparing patients with COPD plus childhood asthma to those with eosinophilic COPD (characterised by a BEC >300 cells·μL^{-1} or a sputum eosinophil count >3%, without history of asthma) demonstrated some phenotypic differences between groups: COPD patients with concomitant childhood asthma were younger and had a higher prevalence of reported allergy (*e.g.* hay fever) with a greater proportion of positive skin prick tests [57].

Eosinophil activation and subsets

While many studies have focused on eosinophil counts in COPD, it is important to investigate eosinophil activation. In a recent study, Mycroft *et al.* [58] observed that the percentage of CD66b^{+} (activation marker) and CCR3^{+} (eotaxin receptor) sputum eosinophils are increased in COPD patients compared to controls, despite similar total eosinophil counts. Increased activation of COPD sputum eosinophils without changes to total cell counts is a concept supported by Louis *et al.* [59], who showed that although sputum eosinophil cationic protein (ECP) levels were higher in COPD patients compared to controls, ECP levels did not correlate with sputum eosinophil cell counts (rho 0.2; p>0.05). In contrast, ECP levels strongly correlated with eosinophil cell counts in asthma patients (rho 0.9; p<0.0001).

In addition to the activation status of eosinophils, one should also consider eosinophil subsets, commonly separated into resident eosinophils (rEos) and inflammatory eosinophils (iEos), based on surface receptor expression and tissue location; eosinophil subsets may be defined using Siglec 8^{+}CD62L^{lo}IL-3R^{hi} (iEos) and Siglec 8^{+} CD62L^{+} IL-3R^{lo} (rEos) [60]. Transcriptome analysis has shown that whereas rEos are enriched for genes involved in tissue homeostasis, iEos are enriched for pro-inflammatory gene expression [60]. Although the percentage of blood iEos is significantly higher in asthma patients compared to COPD patients, IL-5 receptor-α expression is increased on COPD rEos compared to asthma patients. These differences may be determined by the local inflammatory milieu, possibly reflecting the different functions of these cells, *i.e.* protective resident cells *versus* pathological inducible cells. The balance of eosinophil subsets, and the magnitude of activation signals, may also help understand how T2 inflammation differs between COPD and asthma. This may be particularly important in the context of disease-specific stimuli, *i.e.* IgE-mediated *versus* non-IgE-mediated, and the effects of cigarette smoking.

Exhaled nitric oxide fraction

The exhaled nitric oxide fraction (F_{ENO}) is an established biomarker of T2 inflammation in asthma. The enzymatic production of nitric oxide is regulated by several nitric oxide synthases, with the most pronounced and sustained production regulated by inducible nitric oxide synthase (iNOS). The production of nitric oxide by bronchial epithelial cells can be regulated by T2 cytokines, IL-4 and IL-13, which upregulate iNOS. A gene expression microarray study demonstrated that the NOS2 gene (encoding for iNOS) was strongly correlated with F_{ENO} in asthma, together with other T2-related genes including POSTN, CLCA1 and SERPINB2 [61]. Additionally, F_{ENO} levels are closely related to eosinophil numbers in some [62] but not all studies in asthma, corroborating evidence that F_{ENO} is a biomarker of T2 inflammation that can be independent of eosinophil counts. The measurement of F_{ENO} in asthma is of some diagnostic and prognostic relevance, with a cut-off between 40 and 50 ppb proposed as a subsidiary in the diagnosis of asthma in patients with other supporting features [9].

Elevated F_{ENO} measurements are observed in a subgroup of COPD patients and, importantly, this holds true in patients without a concomitant diagnosis of asthma [63]. In the National Health and Nutrition Examination Survey (NHANES) study, the mean±SD F_{ENO} in COPD patients without a history of asthma was 15.8±13.6 ppb, while the prevalence of F_{ENO} >25–50 ppb was ∼13% and F_{ENO} ⩾50 ppb was ∼2% [63]. Tobacco smoking represents an important confounding factor in the assessment of F_{ENO} [64]. The partial inhibition of nitric oxide production elicited by tobacco smoke may be attributed to the reduction in nitric oxide synthases and/or other T2 inflammatory mediators implicated in nitric oxide production [65]. Ex-smoking COPD patients display higher F_{ENO} levels compared to current smokers [66]. Mean±SD F_{ENO} levels in current smokers and ex-smokers with COPD have been reported as 8.9±5.0 ppb and 18±16.9 ppb, respectively [63]. Nevertheless, there is a subgroup of current smoker COPD patients who have elevated F_{ENO} levels, and this is greatest in patients with higher BEC (>300 cells·μL^{-1}) [66]. Interestingly, electronic cigarette use does not alter the interpretation of F_{ENO} levels in COPD, probably due to the differences in chemical composition between tobacco and electronic cigarette liquid [67].

In COPD, an association between elevated BECs and elevated F_{ENO} has been observed, a finding that was more pronounced in ex-smokers [66]. Some studies have shown an association between sputum eosinophil counts and F_{ENO} levels in COPD, although not all studies have demonstrated this relationship [66]. Whilst F_{ENO} levels are used as a surrogate for airway eosinophilic inflammation, there is evidence that F_{ENO} levels and eosinophil numbers do not always correlate in both asthma and COPD. This may

be due to several factors, including suppression by current smoking and the heterogeneity of eosinophilic inflammation, which is more variable at higher counts [4]. Furthermore, whilst current smoking is now recognised as an important confounding factor in F_{ENO} levels, it has historically not always been appropriately corrected for. Alternatively, F_{ENO} levels may represent a mechanism of T2 inflammation that is different from eosinophilic inflammation. In support of this, monoclonal antibodies that block IL-5 fail to significantly suppress F_{ENO} in unselected asthma patients, despite reducing eosinophil numbers [68].

A large prospective cohort reported an association between elevated F_{ENO} and exacerbation risk [69], although inconsistent results have been reported elsewhere [70]. Nevertheless, F_{ENO} is a biomarker that can be used to detect T2 inflammation in COPD, particularly in ex-smokers.

Pharmacological interventions

ICS

ICS have anti-inflammatory effects and are used as part of COPD treatment in combination with a long-acting β-agonist (LABA) or LABA plus long-acting muscarinic antagonist [1]. As already discussed, BECs are a predictive biomarker for ICS benefit amongst COPD patients with increased exacerbation risk. Interestingly, a review of placebo-controlled clinical trials involving airway sampling shows that there was no reduction in bronchial mucosal or sputum eosinophil counts in the majority of studies [71]. Instead, there was more evidence for a reduction in lymphocyte and mast cell numbers. Overall, this suggests that BECs identify COPD patients with (T2) corticosteroid-responsive inflammation, but that eosinophil trafficking into the lungs is not the primary target. These analyses of cell numbers do not exclude an effect of ICS on eosinophil activation.

ICS exert their effects on T2 inflammation in asthma, as demonstrated by Woodruff *et al.* [72], who assessed forced expiratory volume in 1 s (FEV_1) improvement with ICS in patients characterised by T2-high *versus* T2-low bronchial epithelial gene signatures using relative expression of IL-13-inducible genes (POSTN, SERPINB2 and CLCA1). Patients with T2-high asthma showed positive improvements in FEV_1 over 8 weeks of treatment, while there was no improvement in the T2-low group. Furthermore, in asthma patients with a mast cell subtype characterised by TPSB1 and CPA3 in sputum, a reduction in expression of CPA3 (amongst other genes) was also observed in response to ICS [46]. In COPD, a *post hoc* analysis of bronchial epithelial gene expression following treatment with ICS-containing therapy revealed a reduction in relative expression of a mast cell activation signature driven by three genes: TPSB2, IL1RL1 (IL-33 receptor) and CPA3 [52]. Overall, these studies show that ICS target T2 inflammation in both asthma and COPD, but that the nature of the T2 inflammation targeted varies between these conditions.

F_{ENO} levels have shown discriminative ability in predicting enhanced short-term responses to ICS in asthma [73], while a reduction in F_{ENO} levels was observed over 12 months in response to ICS compared with non-ICS treatment [74]. However, current guidelines take a cautious approach, as larger confirmatory randomised controlled trials are still required. The predictive ability of F_{ENO} levels with regard to ICS effects in COPD is less clear, as there is a limited number of studies. In observational research studies, no differences in F_{ENO} levels are observed between ICS users and non-users [66]. A short-term reduction in F_{ENO} levels has been observed in current and ex-smoking COPD patients treated with ICS-containing therapy, although this effect was limited to patients with elevated F_{ENO} at baseline [75]. Inconsistent findings have been reported regarding the relationship between baseline F_{ENO} values and improvement in FEV_1 with ICS-containing therapy. Overall, there is some promise regarding the use of F_{ENO} to predict ICS response in COPD, but the relationship is affected by confounding factors including smoking status.

Biological treatments

Monoclonal antibodies targeting T2 inflammation are well established in the treatment of severe asthma, including antibodies directed against IL-5 or IL-5 receptor-α (mepolizumab/reslizumab and benralizumab, respectively), the high-affinity IgE receptor (FcεRI; omalizumab), shared IL-13/IL-4 receptor (dupilumab) or thymic stromal lymphopoietin (TSLP; tezepelumab). Higher baseline F_{ENO} measurements have been demonstrated to predict a greater clinical response in asthma to omalizumab, tezepelumab and dupilumab [76]. Moreover, F_{ENO} has been established as a parameter for initiation of dupilumab when levels are $\geqslant$25 ppb in patients with allergic and non-allergic eosinophilic asthma [9]. Additionally, mucus plugging was considerably reduced 16 weeks following initiation of dupilumab therapy, accompanied by a reduction of residual ventilation defects [77].

Mepolizumab was evaluated in COPD patients at risk of exacerbation in the METREX/METREO phase 3 studies (reviewed in [4]). Whilst mepolizumab treatment resulted in reduced BECs, the primary end-point analyses failed to demonstrate a reduction in exacerbation rates. Nevertheless, in a pre-specified meta-analysis, exacerbation reduction was observed for mepolizumab, restricted to a selected subgroup of patients with the highest BECs. In the primary end-point analyses, benralizumab did not lead to a significant reduction in exacerbation rates in the GALATHEA and TERRANOVA studies, investigating different treatment regimes in COPD patients at risk of exacerbation [78]. A *post hoc* analysis of both trials revealed a significant treatment effect in a subpopulation of patients at risk of exacerbation, high BEC and receiving inhaled triple therapy [25]. The group mean findings presented thus far in trials of mepolizumab and benralizumab suggest a lower effect of these agents in eosinophilic COPD compared to asthma [24, 79], therefore also suggesting a less dominant role for eosinophils in COPD pathophysiology compared to asthma. However, overall mean results in these studies may not reflect individuals with better responses, as shown in *post hoc* analysis in both asthma and COPD [25, 80].

IL-13-driven pathways may contribute to mucus secretion and airway remodelling in COPD patients with elevated eosinophil counts [6]. These findings are interesting in the context of the first positive results for the use of dupilumab in COPD. The phase 3 BOREAS study investigated the administration of dupilumab in COPD patients with a history of exacerbations and BEC $\geqslant$300 cells·μL^{-1} [6]. In this selected population, a 30% reduction in annual exacerbation rates was observed compared to placebo, and was accompanied by improvements in lung function, health-related quality of life and respiratory symptoms. There was also evidence that eotaxin 3 (CCL26), pulmonary and activation-regulated chemokine (PARC/CCL18), IgE levels and F_{ENO} showed greater numerical reductions upon 52 weeks of treatment when compared to placebo. However, there appeared to be little difference in BEC between groups. Comparable results have recently been reported from the NOTUS study with a similar design, where a 34% exacerbation rate reduction was observed for patients treated with dupilumab *versus* placebo [26]. Whilst encouraging, the exacerbation reduction observed in selected COPD patients (30% [6]) is smaller in magnitude compared to selected asthma patients (up to 67% exacerbation reduction in uncontrolled moderate-to-severe asthma patients with a baseline BEC $\geqslant$300 cells·μL^{-1} [81]); the effects of IL-13/IL-4 receptor blockade therefore differ between COPD and asthma.

The search for novel therapies in COPD has involved targeting alarmins, which are epithelium-derived cytokines. There are promising early results concerning the targeting of IL-33 pathways in COPD: a phase 2a study with the anti-IL-33 monoclonal antibody itepekimab showed exacerbation rate reduction in former smokers, although not in the overall population [82]. Interestingly, itepekimab lowered BECs, with an associated increase in lung function. Another anti-IL-33 agent, tozorakimab, significantly reduced serum IL-5 and IL-13 levels in a phase 1 study in COPD patients [83]. The IL-33 receptor antibody astegolimab demonstrated a reduction of exacerbation rates in a subgroup with low BECs (<300 cells·μL^{-1}) but not in the overall intention-to-treat population. Following the success in asthma, results from the tezepelumab COPD exacerbation study (COURSE), investigating the efficacy and safety of tezepelumab in COPD, are awaited.

Conclusion

Although some biomarkers of T2 inflammation in asthma are similarly expressed in COPD, current evidence suggests that T2 inflammation in these two diseases is not identical. In asthma, POSTN and SERPINB2 are biomarkers of T2 inflammation, but their role in COPD is less prominent. The stark contrast in the number of bronchial brush genes associated with BEC in COPD and asthma (12 *versus* 1197, respectively) and the lack of overlap between diseases suggests that different signalling pathways are related to T2 inflammation in COPD *versus* asthma. This is probably related to differences in environmental cues, such as the role of atopy and increased IgE-mediated mast cell activation in asthma, *versus* cigarette smoke-related toxicity and oxidative stress coupled with non-IgE-related mast cell activation in eosinophilic COPD.

Table 1 Take-home messages: key differences between eosinophilic COPD and asthma

Relative efficacy of biological treatments is lower overall in COPD compared to asthma; however, response varies between individuals, according to the nature and degree of inflammation
Differences in type 2 epithelial and sputum gene expression profiles
Greater mast cell activation by IgE in asthma
Increased inflammatory eosinophil subset in asthma
Differences in the pathophysiology of mucus hypersecretion

COPD and asthma display some shared phenotypic traits, although the nature of these traits appears to be subtly different between diseases. Airflow obstruction is more variable in asthma and there is greater bronchial hyperreactivity, while airflow obstruction and symptoms are more persistent and poorly reversible in COPD. Furthermore, whilst biological treatment is promising in eosinophilic COPD, the relative efficacy when compared to use in asthma appears to be lower; these differences are likely to reflect immunological differences in the lungs. T2 inflammation is clearly a shared treatable trait of some asthma and COPD patients, but the evidence reviewed here indicates that the nature of T2 inflammation is not identical in COPD and asthma (table 1). Eosinophilic COPD is not the same as asthma.

Key points

- COPD and asthma share some phenotypic traits in clinical characteristics and treatment response; however, there are subtle differences.
- Whilst T2 inflammation is present in some COPD and asthma patients, the nature of inflammation is distinct between COPD and asthma with respect to inflammatory mediators and pathophysiology.

Self-evaluation question

Can you describe the differences in nature of T2 inflammation between eosinophilic COPD and asthma?

Author contributions: All authors contributed to conceptualisation, literature searches, manuscript writing and editing. All authors reviewed, commented on and agreed to the final version of the manuscript.

Conflict of interest: D. Singh has received sponsorship to attend and speak at international meetings, honoraria for lecturing or attending advisory boards from the following companies: Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Teva, Theravance and Verona. F. Trinkmann reports grants from AstraZeneca, Bayer Boehringer Ingelheim, Chiesi, Novartis, Roche, BMBF, DZL, Markedsmodningsfonden and E+H Knorr Stiftung, as well as consulting fees and honoraria from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Fisher & Paykel, GlaxoSmithKline, Janssen-Cilag, Merck Healthcare, Novartis, Omron, OM-Pharma, Roche, Sanofi, Aventis and Thorasys, and travel support from AstraZeneca, Actelion, Bayer, Berlin Chemie, Boehringer Ingelheim, Chiesi, Mundipharma, Novartis, Pfizer and TEVA. V. Tejwani reports grants from NIH NHLBI and payment or honoraria from Thermofisher. A. Beech, A. Higham and S. Booth have no conflicts of interest to declare.

Support statement: D. Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

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Suggested answer

Whilst T2 inflammation is present in some COPD and asthma patients, the nature of inflammation is distinct between COPD and asthma with respect to inflammatory mediators and pathophysiology. Differences in inflammatory mediators relate to type 2 epithelial and sputum gene expression profiles, mast cell activation by IgE and characteristics of eosinophil subsets, whilst the pathophysiology of mucus hypersecretion appears to be different between asthma and COPD.