Eosinophilic airway inflammation in COPD

Shironjit Saha
Christopher E Brightling

Institute for Lung Health, University Hospitals of Leicester, Leicester, UK

Abstract: Chronic obstructive pulmonary disease is a common condition and a major cause of mortality. COPD is characterized by irreversible airflow obstruction. The physiological abnormalities observed in COPD are due to a combination of emphysema and obliteration of the small airways in association with airway inflammation. The predominant cells involved in this inflammatory response are CD8+ lymphocytes, neutrophils, and macrophages. Although eosinophilic airway inflammation is usually considered a feature of asthma, it has been demonstrated in large and small airway tissue samples and in 20%–40% of induced sputum samples from patients with stable COPD. This airway eosinophilia is increased in exacerbations. Thus, modifying eosinophilic inflammation may be a potential therapeutic target in COPD. Eosinophilic airway inflammation is resistant to inhaled corticosteroid therapy, but does respond to systemic corticosteroid therapy, and the degree of response is related to the intensity of the eosinophilic inflammation. In COPD, targeting treatment to normalize the sputum eosinophilia reduced the number of hospital admissions. Whether controlling eosinophilic inflammation in COPD patients with an airway eosinophilia will modify disease progression and possibly alter mortality is unknown, but warrants further investigation.

Keywords: COPD, sputum eosinophilia, corticosteroids

Introduction

Chronic obstructive pulmonary disease is a common condition predominantly caused by smoking. It is a major cause of mortality, and in 1999 there were approximately 30 000 deaths due to COPD in the UK. This represented 5.1% of all deaths (5.9% of all male deaths and 4.3% of all female deaths) (NICE 2004). COPD is the major cause of respiratory failure and is a common cause of chronic disability. In contrast to asthma, COPD is characterized by irreversible airflow obstruction. The physiological abnormalities observed in COPD are due to a combination of emphysema and obliteration of the small airways. These two pathologies are distinct in that emphysema can occur without narrowing of the small airways, and vice versa, although the conditions usually coexist. Small airway narrowing is a consequence of inflammation, increased airway muscle mass and fibrosis in the airway wall, and the accumulation of inflammatory mucus exudates in the lumen. Subsequent increased airway wall thickness is associated with worsening disease severity as defined by the Global Initiative of Obstructive Lung Disease (GOLD) stage (Hogg et al 2004).

There is considerable interest in airway inflammation in COPD. This interest has been fuelled by the desire to modify airway inflammation in COPD in the anticipation that this will have an impact on lung function decline and exacerbations, which are the major determinants of the morbidity and mortality associated with this disease. Neutrophils, CD8+ T lymphocytes, and macrophages have been implicated in the disease pathogenesis of COPD, whereas, asthma is regarded as a T_h2-mediated

Correspondence: Christopher E Brightling, Institute for Lung Health, Clinical Sciences Wing, University Hospitals of Leicester, Groby Road, Leicester, LE3 9QP, UK
Tel +44 116 287 1471
Fax +44 116 258 3950
Email ceb17@le.ac.uk

eosinophilic disease. Indeed, the presence of eosinophilic inflammation is often viewed as a distinguishing feature between asthma and COPD.

The development of sputum induction as a non-invasive test of airway inflammation has enabled clinicians to study the phenotype of airway inflammation in patients with airway disease. The sputum differential cell count has been defined in large normal populations (Belda et al 2000). The normal sputum eosinophil count is <1.1%. A sputum eosinophil count >3% was associated with a good response to corticosteroids in asthma (Pavord et al 1999) and COPD (Pizzichini et al 1998). The application of sputum induction has led to the recognition that eosinophilic inflammation is present in only 50% of cases of asthma (Douwes et al 2002) and in about 20%–40% of cases of COPD (Saetta et al 1994; Confalonieri et al 1998; Pizzichini et al 1998; Brightling, Monteiro, et al 2000; Brightling et al 2005). Hence there is considerable overlap in the presence of eosinophilic airway inflammation in COPD and asthma, as illustrated in Figure 1 (Brightling, Monteiro, et al 2000; Green, Brightling, Woltmann, et al 2002).

In this review we briefly summarize eosinophil biology, describe the inflammatory profile of COPD in stable disease and exacerbations and its response to treatment with particular reference to the eosinophil, and explore the potential role of a sputum eosinophil count in the management of COPD.

Eosinophil biology

Eosinophils are end-stage cells derived from the bone marrow under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3, and the late differentiation factor IL-5 (Denburg 1999). In terms of their ontogeny they are closely related to the basophil rather than the neutrophil or monocyte. The selective recruitment of eosinophils into the airway is mediated by a multistep process directed by T_h2 cytokine-producing T cells (Wardlaw et al 1999). The first step is increased production and release of eosinophils from the bone marrow under the influence of the IL-5 and specific chemoattractants such as eotaxin. Second, the target organ vasculature has increased adhesiveness for eosinophils through the specific effects of locally generated IL-4 and IL-13. These cytokines induce expression of vascular cell adhesion molecule (VCAM)-1 on lung endothelial cells, which binds through eosinophil-expressed ligands VLA-4 and P-selectin, to which eosinophils bind with greater avidity than neutrophils (Symon et al 1996; Edwards et al 2000; Woltmann et al 2000). CC chemokines such as eotaxin released by cells in the airway wall activate the chemokine receptor CCR3 expressed by eosinophils and thus attract these cells into tissue. Here they survive for prolonged periods as a result of locally generated IL-5 and GM-CSF.

The eosinophil specific basic proteins, which are stored in the distinctive secondary granules, are major basic protein eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin. All of these proteins are toxic to bronchial epithelial cells. Eosinophils, with mast cells and basophils, are the most prominent source of cysteinyl-leukotrienes (Bozza et al 1997), and eosinophils also release a diverse range of cytokines. The physiological triggers in airway disease that lead to eosinophil mediator release remain uncertain but, importantly, eosinophils undergo piecemeal degranulation in most in vivo settings (Dvorak and Weller 2000).

Airway inflammation in COPD
Stable disease

For more than a decade, substantial effort has been made to define obstructive airways disease at an inflammatory cellular level with the aim to clarify mechanisms and improve treatment. Sputum and bronchoalveolar lavage
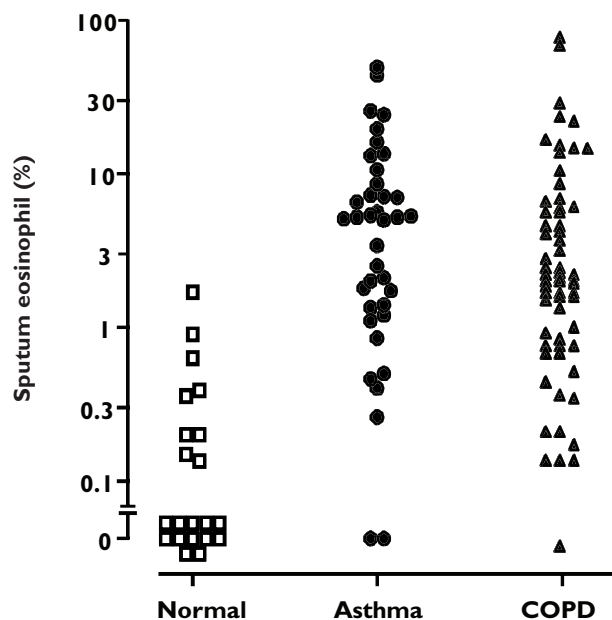
Figure 1 Sputum eosinophil count in subjects with corticosteroid-naïve asthma and COPD. Data derived from Brightling, Monteiro, et al (2000); Green, Brightling, Woltmann, et al (2002).

(BAL) have been used to identify inflammatory components of the large and small airways, respectively, whereas endobronchial biopsies and lung resection tissue have been used for analysis of the bronchial wall of the large and small airway and lung parenchyma. There are several difficulties facing researchers interested in measuring lower airway inflammation in COPD. First, the functionally important inflammatory response in the small airways and surrounding lung parenchyma is in the lung periphery and is therefore difficult to access. Second, the various techniques used to assess airway inflammation differ markedly in their properties and in the profile of inflammatory cells they measure, suggesting they are accessing different lung compartments (Keatings, Evans, et al 1997). Finally, when considering airway inflammation, the repeatability of such measures is not always known.

Despite these problems, a number of inflammatory cells have been shown consistently to be present in increased numbers in the airways in COPD and to relate to the severity of airflow obstruction, suggesting a causal role. The evidence is perhaps strongest for the CD8+ T lymphocyte and the neutrophil. Increased numbers of CD8+ T lymphocytes have been demonstrated at all levels of the lung (large and small airways and parenchyma) in relation to smoking and COPD (O'Shaughnessy et al 1997; Saetta et al 1999). The mechanism of CD8+ lymphocyte recruitment and its functional significance remain to be determined. Increased neutrophil numbers are particularly obvious in patients with established airflow obstruction. Bronchial biopsy and induced sputum studies have consistently shown a correlation between the severity of airflow obstruction and neutrophil counts, and in some studies the correlation has been close (Keatings et al 1996; Stanescu et al 1996; Di Stefano et al 1998). Furthermore, the protease-antiprotease hypothesis (Stockley 1995) offers a biologically plausible mechanism for the tissue destruction seen in COPD in association with neutrophilic airway inflammation.

Less attention has been paid to the presence of eosinophilic airway inflammation in stable COPD, although a sputum eosinophilia has been observed in 20%–40% of patients with COPD (Saetta et al 1994; Confalonieri et al 1998; Pizzichini et al 1998; Brightling, Monteiro, et al 2000; Brightling et al 2005). One bronchial biopsy study has reported an increased number of eosinophils in patients with chronic bronchitis and COPD but lower BAL concentrations of ECP than in asthmatics, suggesting that eosinophils are present but are less activated in COPD (Lacoste et al 1993). However, sputum ECP concentrations were increased to a greater level than seen with asthma in moderate to severe COPD (Gibson et al 1998; Brightling, Monteiro, et al 2000; Brightling, Ward, et al 2000; Brightling et al 2005), suggesting that eosinophils are activated in more severe disease.

The relationship between lung function decline and eosinophilic inflammation is unclear. A negative correlation between FEV_1 and the ratio of activated eosinophils to total eosinophils in endobronchial biopsies from subjects with COPD was demonstrated (Lams et al 2000), and a similar negative correlation between FEV_1 and sputum eosinophils and ECP was found (Balzano et al 1999). Conversely, in another study there was no relationship between small airway eosinophilia and severity of COPD defined by the GOLD criteria (Hogg et al 2004).

The origin of eosinophilic airway inflammation in COPD is unclear, although it is widely assumed that it indicates an asthmatic component to the fixed airways obstruction (Barnes 1998). This is unlikely to be the case, as most studies on patients with COPD rigorously exclude subjects with variable airflow obstruction and those with clinical features suggesting asthma. It is more likely that smoking and other mechanisms that recruit neutrophils into the airway mucosa in COPD may in turn cause a minor degree of eosinophil influx. However, it is difficult to explain the very high levels of sputum eosinophilia observed in some of our subjects. An alternative and intriguing possibility is that eosinophilic COPD starts as eosinophilic bronchitis. This is a common cause of chronic cough in middle age characterized by a sputum eosinophilia but no symptoms and functional evidence of variable airflow obstruction or airway hyperresponsiveness (Gibson et al 1989). Although characterized by normal spirometric values at the time of diagnosis, this has been associated with an accelerated decline in FEV_1 and the development of COPD (Brightling et al 1999; Birring et al 2002; Berry et al 2005).

Exacerbations

COPD exacerbations are associated with sputum and bronchoscopic bronchial biopsy evidence of eosinophilic inflammation (Lacoste et al 1993; Saetta et al 1994). Bronchial biopsies taken from patients during acute exacerbations and compared with stable COPD show a 30-fold increase in the total number of eosinophils and only a 3-fold increase in neutrophils (Saetta et al 1994). The presence of high concentrations of tumor necrosis factor (TNF)-α (a proinflammatory cytokine that activates adhesion molecules on endothelial cells influencing

eosinophil chemotaxis) and the eosinophil products ECP and EPO in induced sputum also supports a role for the eosinophil in COPD exacerbations (Pizzichini et al 1996; Gursel et al 1997; Keatings and Barnes 1997; Keatings, Evans, et al 1997).

Effect of treatment on airway inflammation

Intervention studies examining the effects of treatment on airway inflammation in COPD have generally used induced sputum to assess airway inflammation and inhaled or oral corticosteroids as the putative antiinflammatory agent. These studies are summarized in Table 1.

There is a consistent lack of effect on eosinophilic inflammation in COPD by inhaled corticosteroids (Keatings, Jatakanon, et al 1997; Confalonieri et al 1998; Culpitt et al 1999; Loppow et al 2001; Gizycki et al 2002; Brightling et al 2005). Two studies have shown a small reduction in the sputum neutrophil count (Confalonieri et al 1998; Yildiz et al 2000) and one a reduction in submucosal mast cell numbers (Gizycki et al 2002). The lack of an antiinflammatory effect of inhaled corticosteroid therapy in COPD has led to the hypothesis that COPD is a corticosteroid-resistant disease. Low levels of histone deacetylase (HDAC) demonstrated in COPD macrophages and lung tissue may be responsible for corticosteroid resistance (Ito et al 2005). HDAC prevents acetylation of histone, which leads to unwinding of chromatin architecture, thereby promoting transcription of proinflammatory cytokines implicated in COPD. Reduced levels of HDAC in macrophages have been seen in response to cigarette smoke. Levels are negatively correlated with increased levels of metalloproteinases, IL-8, and TNFα and a reduction in the ability of dexamethasone to reduce these mediators (Barnes et al 2004). However, though studies show that COPD is relatively corticosteroid resistant compared with asthma, the response of airway inflammation in COPD to systemic corticosteroids suggests that certain aspects of the inflammatory profile in COPD are corticosteroid responsive (Table 1).

One small single-blind study has shown that following treatment with a short course of prednisolone there was no evidence of a treatment-associated change in the sputum neutrophil count or in the sputum supernatant concentration of myeloperoxidase or elastase (Pizzichini et al 1998). The authors observed that oral corticosteroid treatment is associated with a significant fall in the sputum eosinophil count and in the sputum supernatant concentration of ECP. Furthermore, the improvement in FEV_1 and quality-of-life scores with treatment was significantly greater in those with a significant sputum eosinophilia (>3%) (Pizzichini et al 1998). This beneficial effect of oral corticosteroid treatment was confirmed in a randomized placebo-controlled trial of 2 weeks of prednisolone 30 mg daily. This study found that the degree of baseline eosinophilic inflammation was related to improvements in lung function and health status (Figure 2) (Brightling, Monteiro, et al 2000). Fujimoto et al (1999) treated 24 emphysema subjects (defined by obstructive spirometry with demonstrable irreversibility and emphysema on CT scan) with oral prednisolone 20 mg daily for 2 weeks with analysis of sputum before and after treatment. Corticosteroids did not modulate neutrophilic inflammation, but reduction in eosinophils was observed,
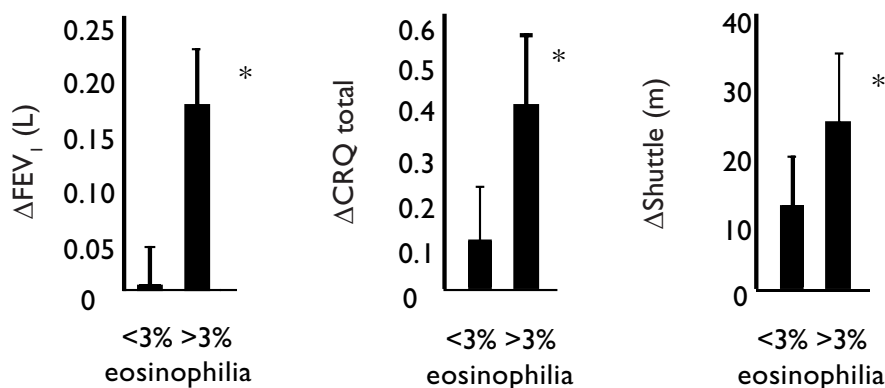
Figure 2 Improvement in post-bronchodilator FEV_1, health status (Chronic Respiratory Disease Questionnaire; CRQ), and shuttle walk distance in subjects with COPD with or without a sputum eosinophilia (>3% non-squamous cells). *p < 0.05; Δ represents change after prednisolone compared with placebo. Data derived from Brightling, Monteiro, et al (2000).

Table I Studies monitoring effect of corticosteroids (inhaled and oral) on airway inflammation and lung function

Reference	Number of patients	Design of trial	Severity of COPD	Inflammatory cell outcome	Lung function outcome
Barnes et al 2005 Qui et al 2005 Zhu et al 2005	140	Randomized, double-blind; 12 weeks of inhaled combined salmeterol/ fluticasone therapy	FEV$_1$ 59%	Reduction in sputum neutrophils and eosinophils and nonsignificant reduction in submucosal mast cells from EBB. Also reduction in TNFα and IFNγ +ve cells in subepithelium	Increase in FEV$_1$ (0.17 L) in treatment group. Reduction in exacerbations (treatment 16% vs 33% placebo)
Brightling et al 2005	60	Randomized, double-blind, crossover; 6 weeks of inhaled mometasone or placebo 800 μg daily	FEV$_1$ 44%	No change in sputum cell counts	No significant overall increase. Post BD FEV$_1$ increase improved with increasing tertile of sputum eosinophil count
Gizycki et al 2002	24	Randomized, double-blind; 3 months of fluticasone 1000 μg daily	FEV$_1$ 50%	No change in inflammatory cells in EBB except for submucosal mast cells. Increase in neutrophils in EBB	No change in lung function
Hattotuwa et al 2002	30	Randomized, double-blind; 3 months of fluticasone 1000 μg daily	FEV$_1$ 45%	No significant change in CD8+, macrophages, neutrophils, and eosinophils in EBB. Reduction in submucosal mast cells	No change in lung function
Loppow et al 2001	19	Randomized, double-blind, crossover; 4 weeks of fluticasone or placebo 1000 μg daily in chronic bronchitis $\pm$ mild obstruction	FEV$_1$ 83% FEV$_1$/VC 68%	Decrease in total number of cells in sputum in fluticasone group but not when compared against placebo. No change in differential counts, IL-8, ECP, and NPE. No change in lung function and exhaled NO	No change in lung function
Balbi et al 2000	8	Open clinical study; 6 weeks of inhaled BDP 1.5 mg daily	FEV$_1$ 70%	Reduction in IL-8, MPO, total cell numbers, neutrophils (59.7% vs 31.5% mean) in BAL	No change in lung function
Yildiz et al 2000	18	Randomized, double-blind; 1500 μg fluticasone, in subgroup theophylline also added (not stated to which patients)	FEV$_1$ 42%	Reduction in total cell count and neutrophils with fluticasone with increase of neutrophils after washout period; no change in eosinophil count	No change in lung function
Culpitt et al 1999	13	Randomized, double-blind, crossover; 4 weeks of fluticasone or placebo 1000 μg daily	FEV$_1$ 50%	No change in sputum cell counts or IL-8, MMP-1, -9, SLPI, and TIMP-1.	No clinical benefit with lung function or symptom scores
Confalonieri et al 1998	34	Randomized, double-blind: 2 months of BDP 1500 μg daily	FEV$_1$ 60%	Reduction of total cell count and neutrophils in sputum (–42% and –27%, respectively). No change in eosinophils	No change in lung function
Keatings, Jatakanon, et al 1997	13	Open study with 2 weeks of budesonide 1600 μg with analysis of induced sputum followed by 2-week course of prednisolone 30 mg daily, compared against 10 atopic asthma subjects	FEV$_1$ 35%	No reduction in ECP, EPO, MPO, TNFα, and IL-8 in sputum with inhaled corticosteroids. Sputum eosinophil numbers, ECP, EPO reduced in asthma but not in COPD subjects with oral prednisolone	No change in lung function

Table 1 *continued*

Reference	Number of patients	Design of trial	Severity of COPD	Inflammatory cell outcome	Lung function outcome
Brightling, Monteiro, et al 2000	67	Randomized, double-blind, crossover; 2 weeks of prednisolone 30 mg daily	FEV$_1$ 42%	Reduction in sputum eosinophil counts	No significant overall increase. Post BD FEV$_1$ increase improved with increasing tertile of sputum eosinophil count. Increase in CRQ score
Fujimoto et al 1999	24	Open study of 2 weeks with prednisolone 20 mg daily	FEV$_1$ 41%	Sputum measurements of cell counts, ECP, NPE-PI complex, and IL-8. Reduction in ECP and eosinophils	Baseline eosinophil count correlated with post-treatment FEV$_1$ increase
Pizzichini et al 1998	18	Randomized, double-blind; 2 weeks of oral prednisolone 30 mg daily	FEV$_1$ 29%	Reduction in sputum eosinophil and ECP count	Eosinophilia indicated reduction in dyspnea and small increase in FEV$_1$ of 0.11 L
Chanez et al 1997	25	Open study with 15 days of prednisolone 1.5 mg/kg daily; eosinophilic inflammation characterized by peripheral blood, BAL, and EBB	FEV$_1$ 51%	Increased levels of eosinophils and ECP in BAL seen in steroid responders	12/25 subjects showed increase of FEV$_1$ >12% and 200 mL

Abbreviations: BAL, bronchoalveolar lavage; BD, bronchodilator; BDP, beclomethasone dipropionate; CRQ, Chronic Respiratory Disease Questionnaire; EBB, endobronchial biopsies; ECP, eosinophil cationic protein; EPO, eosinophil peroxidase; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NPE, neutrophil elastase; NPE PI, neutrophil elastase-α-protease inhibitor; NO, nitric oxide; SLPI, secretory leukocyte proteinase inhibitor; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor.

as were predicted improvements in FEV$_1$. In another study, administration of 15 days of prednisolone (1.5 mg/kg daily) to 25 COPD subjects showed FEV$_1$ improvements greater than 12% and 200 mL above baseline in 12 subjects; this subgroup exhibited raised levels of eosinophilic inflammation in BAL specimens compared with nonresponders (Chanez et al 1997). Hence, reversibility can be predicted from evidence of tissue eosinophilia at baseline. Recently, a large placebo-controlled study using combination inhaler therapy (fluticasone and salmeterol) has shown reduction in sputum eosinophils and neutrophils over a 12-week period when compared with placebo, with an associated improvement in lung function and reported exacerbations (Barnes et al 2005; Qui et al 2005; Zhu et al 2005). Comparison between combination and single-agent inhaled therapy is required to clarify the antiinflammatory benefit of combined corticosteroid and long-acting β-agonists in COPD.

These observations suggest that systemic and inhaled corticosteroids have differential effects on airway inflammation in COPD. The differences between the effects of oral versus inhaled corticosteroids may reflect differences in dose or perhaps the site of action. Systemic corticosteroids are likely to exert more of an effect on small airway inflammation, which is less accessible to inhaled therapy, and systemic corticosteroids also suppress eosinophil production by the bone marrow.

Sputum inflammatory cell counts can be influenced to some extent by smoking status. A cross-sectional study showed COPD subjects who had given up smoking by 12 months had a lower percentage of eosinophils than smokers, though sputum eosinophil levels were still high in both groups (smokers 8% vs 4% ex-smokers) (Domagala-Kulawik et al 2003). There was no difference in the response to oral corticosteroids between current smokers and ex-smokers (Brightling, Monteiro, et al 2000). These findings are in contrast to those in smokers with asthma, who have reduced sputum eosinophil counts compared with non-smokers and were less corticosteroid responsive (Chalmers et al 2001; Tomlinson et al 2005).

There has been little exploration into the effects of other antiinflammatory treatments on COPD-related airway inflammation. Cilomilast, an oral phosphodiesterase D4 inhibitor, has been used in a randomized, double-blind 12-

week trial; there was no demonstrable difference in sputum counts or FEV_1 after 12 weeks, but bronchial biopsies at 10 weeks showed reductions in macrophages and CD8+ T lymphocytes compared with baseline in the cilomilast treatment arm (Gamble et al 2003).

Role of measuring inflammation in management of disease

One important question is whether measuring airway inflammation in COPD can influence the management of this disease. This is particularly difficult in a disease that is largely resistant to current therapy.

Several recent large, placebo-controlled studies have clarified the role of long-term treatment with inhaled corticosteroids. Regular treatment with inhaled corticosteroids in stable COPD does not alter the long-term decline in lung function (Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000; The Lung Health Study Research Group 2000), and there is conflicting evidence whether inhaled corticosteroids alter mortality (Soriano et al 2002; Fan et al 2003). However, they do reduce the number of exacerbations and improve health status in individuals with severe COPD (Burge et al 2000; Mahler et al 2002; Jones et al 2003; Szafranski et al 2003). Intriguingly, subjects who had an improvement in FEV_1 of >20% following short-term treatment with prednisolone had a more significant reduction in exacerbation frequency with longer-term treatment with inhaled fluticasone than those without (Burge et al 2003; Pavord et al 2004). This suggests that the benefit from corticosteroid therapy in COPD is more marked in a subgroup of patients. Likewise in an earlier uncontrolled study, COPD subjects treated with oral corticosteroids had reduced decline in their lung function (Postma et al 1988). Thus, one important question is whether these relatively minor long-term benefits are confined to a definable subgroup of patients.

Since sputum eosinophilia was also associated with an improvement in lung function after a short course of prednisolone, it is possible that the identification of eosinophilic airway inflammation might still allow corticosteroid therapy to be targeted to a population who would particularly benefit in the long term, in terms of both exacerbation rate and lung function decline. This approach has been applied to asthma, whereby in a management strategy aimed at normalizing the sputum eosinophil count there was a striking reduction in severe exacerbations (Green, Brightling, McKenna, et al 2002). We have recently applied this approach to a group of 80 subjects with COPD.

Over a 12-month period, we have shown that a management approach with the additional aim of reducing the sputum eosinophil count below 3% using corticosteroids was associated with a 62% reduction in severe exacerbations of COPD requiring hospitalization when compared with traditional symptom-based management (Siva et al 2005). This benefit was largely achieved by the targeted use of oral corticosteroid in the eosinophilic group. Therefore, the measurement of a sputum eosinophil count can be used to identify COPD patients with corticosteroid-responsive disease and to guide treatment.

Future treatments for eosinophilic inflammation

COPD therapies have limited efficacy. It is likely that identification of specific inflammatory phenotypes may reveal subgroups of patients who are particularly susceptible to targeted therapy. New treatments specifically aimed at modifying eosinophilic inflammation may have benefit in some patients with COPD. The best documented of these is mepolizumab, an anti-IL-5 antibody. In clinical trials, reduction of peripheral blood and bone marrow eosinophils was seen after administration but with little clinical benefit observed. This was possibly due to poor penetration of bronchial tissue, the site of activity for eosinophils in asthma (Flood-Page et al 2003). In murine models, overexpression of IL-13 leads to pulmonary emphysema; potentially, treatment against IL-13 may have therapeutic benefit, though overall IL-13 levels in human emphysematous tissue are low (Boutten et al 2004). A neutralizing antibody against eotaxin (which promotes eosinophil recruitment as well) has reduced lung eosinophilia in mice (Gonzalo et al 1996), and early clinical trials are ongoing with antibodies against receptor CCR3 on the eosinophil cell surface (Erin et al 2002). Whether these new therapies will be effective in COPD is unknown, and further clinical trials are required.

Summary

The mechanistic pathways behind airway inflammation in COPD are complex, and clearly there is no one inflammatory cell that is responsible for the spectrum of this disease. However, the argument is strong for a specific role of eosinophilic inflammation in COPD. Eosinophilic airway inflammation is linked to exacerbations, which contribute to both lung function and health decline. Airway eosinophilia is not evident in all COPD patients but a large subgroup can be clearly defined by simple, non-invasive sampling of sputum. This subgroup exhibits improvement in lung

function and health status to systemic, but not inhaled corticosteroids. Specific targeting of eosinophilic inflammation may be effective in some patients with COPD, and validation of long-term systemic corticosteroids and new treatment regimens is warranted in COPD patients who exhibit an airway eosinophilia.

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