UNIT NO. 5

INFLAMMATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Clinical A/Prof K N Sin Fai Lam

ABSTRACT

There is usually a clear difference in the clinical presentation of asthma and COPD, although in some cases, the distinction may not be so obvious. Nevertheless, the response to corticosteroids in asthma is generally dramatic and sustained, whereas it is incomplete and imperfect in COPD. In both asthma and COPD, airway inflammation plays a pivotal role in the pathogenesis. However, the nature of inflammation is different. In asthma, the main inflammatory cells are eosiniphils, activated mast cells and CD4+ lymphocytes. In COPD, macrophages, neutrophils and CD8+ lymphocytes predominate. The inflammatory mediators are also different. COPD is a multicomponent disease, consisting of airway inflammation, mucociliary dysfunction, structural changes as well as a systemic component. There is evidence that treatment with corticosteroids reduces the inflammation in COPD and this is accompanied by functional improvement. The TORCH study is a large 3-year, multicentre, double blind, placebo-controlled study, which looked at all-cause mortality in patients with moderate to severe COPD treated with either SFC (salmeterol/fluticasone), salmeterol, fluticasone or placebo.

SFP2006; 32(4): 21-23

INTRODUCTION

The definition of inflammation is that it is the response of vascularised tissue to an insult leading to the perception of redness, pain, swelling and heat (rubor, dolor, tumor, calor). This is usually accompanied by loss of function of varying degree. The best example is that of an inflamed joint. However, we also talk about inflammation in the context of disease of the airways and we emphasise that asthma is a disease caused by inflammation of the airways; treatment of the inflammation leads to excellent improvement in symptoms. Treatment with inhaled corticosteroids has revolutionised the management of asthma, and the understanding of how corticosteroids reduce inflammation is well documented.

WHAT ARE THE CLINICAL DIFFERENCES BETWEEN ASTHMA AND COPD?

Most clinicians are able to tell the difference between asthma and COPD from the history and simple lung function tests. We know, for example, that asthma is usually an episodic disease, which often starts in childhood, does not progress inexorably, responds well to inhaled corticosteroids, and shows good reversibility to bronchodilators. On the other hand, COPD is a slowly progressive condition, mostly occurring in smokers, with patients diagnosed usually in their 60s, with little variability in symptoms, and limited response to bronchodilators or corticosteroids. There is however a good number of patients who fall in between these classical presentations. Some patients with asthma have poor reversibility and response to inhaled corticosteroids with chronicity of symptoms and a progressive course. On the other hand, patients who clearly have COPD may show a significant amount of reversibility. More than 40 years ago, *Orie* and his colleagues argued that all airway diseases, including asthma, emphysema and chronic bronchitis should be considered a single disease with common genetic origins. This became known as the *Dutch hypothesis* and led to a fierce debate across the continents for decades. Although the evidence now is not in favour of the *Dutch hypothesis*, there are circumstances when the distinction between asthma and COPD is not so clear.

HOW IS THE INFLAMMATION DIFFERENT BETWEEN ASTHMA AND COPD?

Although COPD is also a disease of the airways, the type of inflammation in COPD is less well understood. In COPD, response to corticosteroids, whether oral or inhaled, is not as dramatic or sustained as it is in bronchial asthma. The type, distribution and the pattern of inflammation in asthma and COPD are different. In asthma, there is typically an eosiniphilic infiltration of the airway wall and an increase in activated mast cells and CD4+ T lymphocytes. The inflammatory cells in COPD are mainly alveolar macrophages, neutrophils, CD8+ (suppressor/cytotoxic) T cells. The inflammatory mediators are also different. In asthma, they are mainly mediators which are bronchoconstrictor such as histamine, cysteinyl leukotreines, and prostaglandin D2, as well as cytokines derived from Th2 cells, such as interleukin(IL)-5 and IL-13. The mediators in COPD are neutrophil chemotactic such as leukotreine B4 (LTB4), TNF-alpha, Interferon-gamma, and IL-8. There are also differences in the structural changes in the airways in the two conditions. In asthma, there is shedding of the airway epithelial cells due to epithelial fragility and the presence of subepithelial fibrosis. In COPD there is squamous metaplasia of the airway epithelium. There is a lot more marked airway smooth muscle hypertrophy and increased bronchial vascularity in asthma. Most of the inflammation in asthma is in the central airways, whereas in COPD it is mainly in the small airways. Parenchymal involvement does not occur in asthma, but it is a major feature of COPD.

AIRFLOW LIMITATION IN ASTHMA AND COPD

Airway narrowing in asthma results mainly from smooth muscle contraction due to the action of bronchoconstrictor mediators, although mucosal wall oedema and mucus production also play an important part. The airflow limitation in COPD is

K N SIN FAI LAM, Senior Consultant & Head, Department of Medicine, Alexandra Hospital

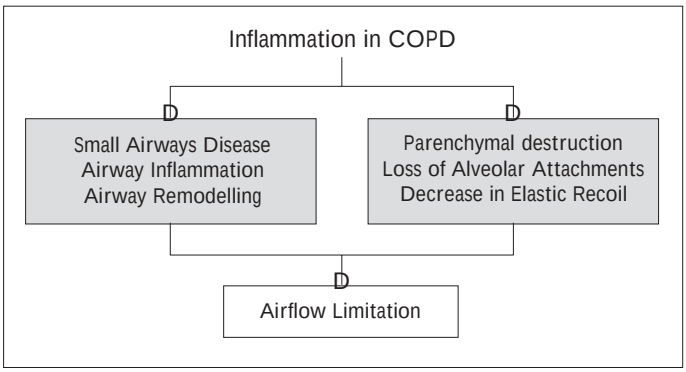

Fig 1: Effects of inflammation in COPD

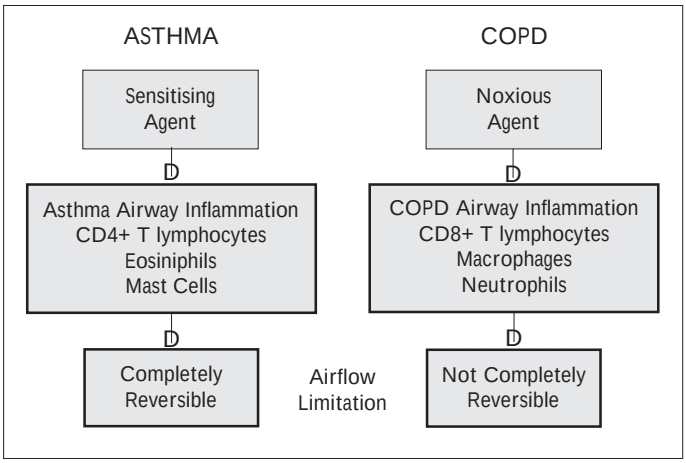

Fig 2: Comparison between Asthma and COPD

contributed mostly by the structural changes resulting from the development of emphysema. There is closure of the small airways as well as loss of lung recoil leading to air trapping, hyperinflation and the increase sensation of dyspnoea. As a result of emphysema, and loss of diffusion area, the gas exchange in COPD is markedly impaired, with low levels of carbon monoxide gas transfer (DLCO and KCO). This does not happen in asthma. The DLCO and KCO are normal or high in asthma.

COPD IS A MULTI-COMPONENT DISEASE

COPD is a multi-component disease. It consists of airway inflammation, mucociliary dysfunction, structural changes, and a systemic component, all of which contribute to airflow limitation. However, the pathogenesis of COPD rests mainly on the central role of airway inflammation. The traditional definition of COPD includes 2 terms, *chronic bronchitis* and *emphysema*, of which only *chronic bronchitis* suggests the presence of any inflammation. It is only recently with the advent of fiberoptic bronchoscopy and less invasive methods of sampling, that it was realised that inflammation is a major feature of the disease. Inflammation in the acute form is protective to the subject, but in the chronic form, when there is repeated insult, which may be severe, such as chronic smoking or high-dose environmental pollutants, the inflammatory response changes to a predominantly mononuclear cell type and becomes persistent and harmful. The inflammation of COPD is predominantly of the small airways (<2 mm) and of the parenchyma. Only 15-20% of smokers will develop symptomatic COPD. There must therefore be a genetic predisposition for the disease. Individuals who develop incompletely reversible airflow obstruction demonstrate *"an abnormal inflammatory response of the lungs to noxious particles or gases"*. The inflammatory response in COPD is variable and depends on several factors, including individual variability, stage of disease severity, whether the subject is still smoking, and whether there is an exacerbation present. T cells have a central role in the chronic inflammatory response leading to airflow obstruction. T cells, once activated, can induce diverse responses downstream which lead to many of the other inflammatory effects which are pathogenic in COPD, leading to fibro proliferation and lung remodeling. These adaptive responses are ongoing and persist even after the subject stops smoking.

The natural history of COPD is a steady decline of FEV1 over time. Cessation of smoking leads to a slower decline in the fall of FEV1. However, if COPD is a disease of inflammation, we do not fully understand the relationship between this inflammation and the accelerated decline in lung function or even how exactly any treatment of COPD affects the inflammation.

Hogg et al (2004) examined the evolution of the pathological effects of airway obstruction in patients with COPD. The small airways were assessed in surgically resected lung tissue from 159 patients with different stages of severity of COPD according to the GOLD classification. These lungs were resected either during surgical treatment of small peripheral tumours, or from patients participating in the National Emphysema Treatment Trial (NETT). The results show that progression of COPD is associated with an increase in the volume of tissue in the wall and the accumulation of inflammatory exudates in the lumen of small airways. There was also an increase in the percentages of the airways that contained polymorphonuclear neutrophils, macrophages, CD4 cells, CD8 cells, B cells and lymphoid aggregates containing follicles, as well as the absolute volume of B cells and CD8 cells. The inflammatory responses are coupled to a repair or remodeling process that thickens the wall of the airways.

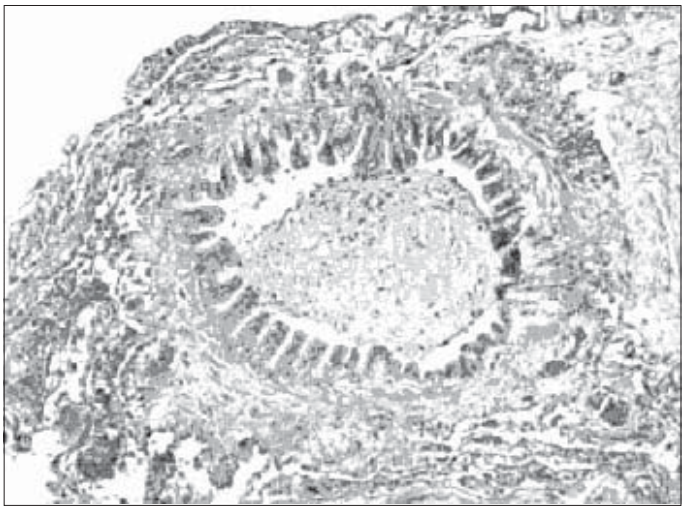

Fig 3: Peripheral airway wall thickening and increased peripheral luminal mucous occlusion in GOLD Stage 4 COPD
Source: Hogg JC et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. Nengl J Med 2004;350:2646-53.

DOES TREATMENT OF COPD REDUCE INFLAMMATION?

Treatment of COPD has until recently been aimed at controlling the symptoms, increasing exercise tolerance, reducing exacerbations and improving health status. The only measures which have been shown to prolong survival was Long Term Oxygen Treatment (LTOT), and smoking cessation. More recent studies have shown that the use of high dose inhaled steroids in patients with moderate or severe COPD with frequent exacerbations, especially in combination with long acting beta2-agonists is more effective in improving lung function and symptoms and reducing exacerbations. However, none of these studies had looked at the effect on inflammation.

Barnes et al (2006) tested the hypothesis that the combination therapy of a long-acting beta2-agonist (salmeterol) and corticosteroid (fluticasone propionate) will reduce inflammation. Bronchial Biopsies and induced sputum were taken from 140 current and former smokers with moderate to severe COPD and the subjects were randomized to a 13-week double blind study to receive placebo or salmeterol/fluticasone. Biopsies were repeated at 12 weeks and sputa repeated at weeks 8 and 13. The results showed that the combination therapy led to a reduction in biopsy CD8+ cells of 36% over placebo. There was also a progressive reduction of sputum differential but not total neutrophils and at 13 weeks, significantly with combination treatment. The anti-inflammatory effects were accompanied by a significant improvement in pre-bronchodilator FEV1. This might suggest that the combination treatment has a beneficial effect on the inflammation in COPD, which may contribute to its efficacy.

DOES TREATMENT OF COPD AFFECT MORTALITY?

DD Sin et al (2005) carried out a pooled analysis, based on intention to treat, of individual patient data from seven randomised trials involving 5,085 patients. The effects of inhaled corticosteroids and placebo were compared over at least 12 months in patients with stable COPD. The end point was all-cause mortality. The mean follow-up was 26 months, and 4% of the participants died. Inhaled corticosteroids reduced all-cause mortality by about 25% relative to placebo. The beneficial effects were especially noticeable in women and former smokers.

THE TORCH (TOWARDS A REVOLUTION IN COPD HEALTH) STUDY

The TORCH study is the only multicentre, randomized, double blind, parallel-group, placebo-controlled study designed to look at all-cause mortality in patients with moderate to severe COPD randomly assigned to treatment with either SFC (salmeterol/fluticasone) 50/500 mcg bd, fluticasone 500 mcg bd, salmeterol 50 mcg bd or placebo for 3 years. The first patient was recruited in September 2000 and the study has just been completed with results announced at the European Respiratory Society (ERS) scientific meeting in Munich. 6,000 participants from 42 countries including Singapore were enrolled and followed for 3 years.

The findings of the TORCH study was that SFC reduced the risk of dying at any time in the three years by 17.5%. SFC is the first intervention since O2 and smoking cessation to improve survival in COPD.

In addition, the mortality benefit was accompanied by significant improvements in health status, lung function, and number of exacerbations. The SPC combination was also found to have a good safety profile with no increase in adverse events.

If inflammation is the major factor in the pathogenesis of COPD, it would be logical that any treatment which can suppress this inflammation would lead to clinical benefits. The studies by Neil Barnes have demonstrated that the combination treatment SFC has a significant effect on the inflammation. The TORCH study now seems to have demonstrated that the clinical benefits of SFC are seen in the improvement of the quality of life, reduction of exacerbations, improvement in lung function, and a clear survival benefit.

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LEARNING POINTS

- **Asthma and COPD are distinctly separate diseases, with different clinical presentations.**
- **Inflammation plays a pivotal role in the pathogenesis of both asthma and COPD, but the type of inflammation, pattern and distribution, as well as the inflammatory mediators are different.**
- **COPD is a multi-component disease consisting of airway inflammation, mucociliary dysfunction, structural changes, as well as a systemic component.**
- **Progression of COPD is associated with histological evidence of increased degree of inflammation.**
- **Treatment of COPD with inhaled corticosteroids has been shown to reduce inflammation in biopsy and sputum specimens and improve lung function.**
- **The TORCH study has demonstrated clinical benefits of combination treatment salmeterol/fluticason on the quality of life, lung function, number of exacerbations and survival.**