Institution: University of Leicester

Unit of Assessment: UoA1 Clinical Medicine

Title of case study: Asthma and Chronic Obstructive Pulmonary Disease (COPD): characterising a new clinical syndrome and contributing to a new conceptual framework for developing drugs

1. Summary of the impact

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common, global diseases which cause considerable morbidity and mortality. Worldwide, around 235 million people suffer from asthma, while COPD accounts for 3 million, or 5% of all, global deaths, according to the World Health Organization (WHO). The relationship between inflammation and airway dysfunction is central to an understanding of their pathogenesis and treatment. The respiratory medicine group in the Department of Infection, Immunity and Inflammation has shown that optimal management of these conditions requires measurement of airway inflammation to stratify treatment regimes, an approach incorporated into national guidelines in 2012. In the late 1990s the group characterised a new clinical syndrome: 'eosinophilic bronchitis', which is one of the commonest causes of chronic cough. The group's work has helped to launch a new class of drugs for asthma and to change the conceptual framework by which anti-inflammatory drugs for asthma are being developed.

2. Underpinning research

Asthma and COPD comprise disordered airway function (a combination of variable and fixed airflow obstruction) associated with chronic airway inflammation. It had been assumed for at least two decades that the disordered airway function was secondary to the inflammation, which was regarded as being eosinophilic in nature and driven by a specific type of immune response directed by a subset of lymphocytes (Th2 cells) to inhaled allergens. However, these concepts were based on small numbers of mild asthmatics and animal models of allergen challenge. The group was one of the first to routinely measure airway inflammation in all types and severity of asthma and relate the degree and pattern of inflammation to the airway physiology. Using this approach the Leicester researchers made a number of important and novel observations.

In 'classic' eosinophilic asthma, the group has shown that:

- Eosinophilic inflammation is closely associated with severe exacerbations of asthma and yet can be clinically silent, hence sputum eosinophilia can provide an early-warning indicator of impending exacerbation (**3**.4).

- Treatment response to corticosteroids is closely associated with the presence of eosinophils in the sputum (**3**.1-**3**.7).

- Suppression of sputum eosinophilia, either with corticosteroids or drugs which specifically inhibit eosinophil production, prevents exacerbations of asthma, demonstrating for the first time that eosinophils are causal in the exacerbation process (**3**.6).

The research also indicated that about 20% of people with asthma do not have eosinophilic inflammation. The group was one of the first to recognise such non-eosinophilic asthma and to demonstrate that this phenotype did not respond well to treatment with corticosteroids (**3**.1, **3**.5).

Similar findings apply to COPD where stratification into eosinophilic (about 30%) and non-eosinophilic (infective) based on sputum analysis results in different patterns of treatment response to steroids and antibiotics (**3**.3).

The group showed that eosinophils were not sufficient to cause the variable airway obstruction and airway hyper-responsiveness (AHR) that characterises asthma (which appears to require additional processes such as mast cell infiltration), and that a distinct sub-set of patients with

eosinophilia have only chronic cough – hence defining a new condition of 'eosinophilic bronchitis' (**3**.2).

This work demonstrated the importance of measuring inflammation (inflammometry) in assessing asthma (and now into COPD), which has since been incorporated into a number of asthma guidelines. It has influenced the study design of clinical trials of anti-inflammatory medications which now focus on severe exacerbations as the primary outcome.

Key staff:
Professor Peter Bradding, Professor of Respiratory Medicine (Leicester 1998 – present)
Professor Chris Brightling, Professor of Respiratory Medicine (Leicester 1999 – present)
Dr Ruth Green, Consultant Respiratory Physician (Leicester 01/07/2005 – 30/05/2010)
Dr Pranab Haldar, Senior Lecturer in Respiratory Medicine (Leicester 01/08/2009 – present)
Professor Ian Pavord, Professor of Respiratory Medicine (Leicester 01/04/2005 – present)
Professor Andrew Wardlaw, Professor of Allergy and Respiratory Medicine (Leicester 31/12/2009 – present)

Notable grants are:

National Institute for Health Research: Leicester Respiratory Biomedical Research Unit (2012-2017) £4.5 million

AirProm: European Framework 7. PI Christopher Brightling (2011-2016) £1.44 million

GlaxoSmithKline: Wardlaw, Pavord and Brightling as PIs (2005-2011) £1.22 million

3. References to the research

1. **Pavord ID**; **Brightling CE**; Woltmann G, **Wardlaw AJ** Non-eosinophilic corticosteroid unresponsive asthma Lancet 1999; 353:2213-2214 (198 citations)
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4. **Brightling CE**, **Bradding P**, Symon FA, Holgate ST, **Wardlaw AJ**, **Pavord ID**. Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med. 2002 May 30;346(22):1699-705.(607)
5. **Green RH**, **Brightling CE**, McKenna S, Hargadon B, Parker D, **Bradding P**, **Wardlaw AJ**, **Pavord ID**. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002 Nov 30;360(9347):1715-21. (692)
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4) Details of the impact

The main impact of the group's work has been to change the paradigm of asthma from a hierarchical model in which Th2 mediated eosinophilic inflammation causes all aspects of the

disease, to a more complex model in which inflammation and lung function abnormalities are relatively independent of each other. In this model the heterogeneity of asthma, including different responses to treatment, is explained by the varying extent to which abnormalities such as lung function, lung damage and inflammation are expressed in any one individual. This conceptual framework is in harmony with the increasing emphasis on stratified medicine in which treatments are targeted at specific disease processes within a condition rather than necessarily all aspects of the disease. The group's work therefore has had important consequences for understanding disease pathogenesis, drug development and patient management.

Pathogenesis

By showing that the lung function abnormalities, inflammatory processes and lung damage which characterise asthma and COPD can occur independently, the Leicester team's model emphasises the need to carefully phenotype patients according to those disease processes if sense is to be made of genetic data and analysis of diseased tissue.

Drug development

Drug development depends first and foremost on identifying a biological target which, when blocked by a drug, will ameliorate a disease process. It is fundamentally important that the target is closely linked to a specific outcome which is relevant to disease control and can be measured when evaluating the drug. Drug development in asthma, particularly involving inhibitors of the Th2 pathway which has been the main focus of the pharmaceutical industry in recent decades, has been hampered by a failure to select patients with eosinophilic disease for clinical trials and the choice of forced expiratory volume in one second (FEV_1,) which is not necessarily affected by inflammation, as the main outcome measure. Based on its observations the group hypothesised that blocking the Th2 pathway would have a relatively narrow effect, preventing severe exacerbations in patients with active Th2 (eosinophilic) inflammation, but would not have any effect on other aspects of asthma such as variable airflow obstruction or non-eosinophilic disease.

To support this hypothesis the group undertook a single-centre, investigator-led study of a biological therapy developed by GlaxoSmithKline called mepolizumab which neutralises the specific eosinophil growth factor IL-5 and ameliorates eosinophilic inflammation. This drug had been studied in unselected asthma patients using lung function as a primary outcome and had been regarded as ineffective, almost causing it to be dropped by the company. The Leicester researchers demonstrated that it was effective at preventing exacerbations in patients with active eosinophilic inflammation, findings which have been replicated in a large multi-centre trial (**5**.4). A phase 3 trial will report in 2014 and the group is confident it will be licensed and will be a life-changing treatment for tens of thousands of people at risk of dying from asthma or whose lives are blighted by the side effects of corticosteroids (**5**.5, **5**.6). The group's work has also blazed a trail for two more anti-eosinophil therapies which are in late stages of development and has explained the findings with other anti-Th2 therapies which have also been shown to prevent exacerbations in eosinophilic patients with relatively little effect on non-eosinophilic patients or lung function. While the life-changing impacts on patient care through new drugs are still potential, the research has already had a significant impact on the business decisions and strategic direction of drug development companies. It has also already had an impact on patient care through a change in the way asthma patients are managed: -

Patient management.

Perhaps the most important impact of our observations has been on patient management. Asthma comprises in large part two components: inflammation and disordered lung function. Traditionally asthma management has been based on measuring lung function but not inflammation. In the sub-set of patients in which lung function and inflammation are most clearly dissociated (i.e. adult onset, eosinophilic inflammation predominant asthma and non-eosinophilic asthma), the group has shown that measurement of inflammation (by analysing sputum), allows targeted use of corticosteroids leading to both reduced side effects and a lower risk of exacerbations.

In 2003 the group established a difficult asthma clinic, which more than 1,000 patients have since attended, based on the idea of routinely measuring airway inflammation. An internal audit showed

a 50% reduction in severe exacerbations; in addition, the group is expecting the Royal College of Physicians' national audit of asthma deaths, which will report in 2014, to show that Leicestershire has a very low rate of asthma deaths in adults – the group is aware of only two over the last decade, neither of which could easily have been prevented. The importance of measuring inflammation, particularly in more severe disease, has now been widely incorporated into asthma guidelines in the UK and internationally (**5**.1, **5**.2, **5**.3) and is embedded in the practice of the members of the British Thoracic Society (BTS) severe asthma network.

5. Sources to corroborate the impact

1. BTS-SIGN Asthma Guidelines Updated 2012: Section 7.3.5 Monitoring airway response in difficult asthma.

2. American Thoracic Society-European Respiratory Society Guidelines on severe asthma. In press

3. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926-38. Epub 2010/10/12

4. **Pavord ID**, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012 Aug 18;380(9842):651-9

5. Leicester Mercury: Breakthrough for asthma patients. 17 August 2012. http://www.leicestermercury.co.uk/Breakthrough-asthma-patients/story-16726460-detail/story.html

6. The Telegraph. New asthma drug can cut hospital admissions by half: study. 17 August 2012. http://www.telegraph.co.uk/health/healthnews/9480016/New-asthma-drug-can-cut-hospital-admissions-by-half-study.html