Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
The Evidence-Based Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD)

1. Summary of the impact

COPD affects up to 3.5 million people in the UK and costs the NHS £700m pa. Over the last 15 years, research by Professor Calverley and colleagues at the University of Liverpool (UoL) has impacted significantly on the care of COPD patients. Specifically, this group showed that routine testing of COPD patients for the presence of bronchodilator reversibility was unreliable and did not predict clinical outcomes. This changed international guideline recommendations in 2007 and the Quality Outcomes Framework payments to GPs in 2009. They showed that oral corticosteroids accelerated recovery from exacerbations and that anti-inflammatory drugs, whether inhaled corticosteroids or PDEIV inhibitors, reduced exacerbations by 25% with a subsequent fall in the number and length of hospitalisations. This led to changed NICE guidance for corticosteroids in 2010 and drug registration with EMA and FDA for the PDEIV inhibitor treatment in 2011. Treatment in UK and Western Europe has changed as a result of this research.

2. Underpinning research

Historically, clinicians have used the short-term change in forced expiratory volume in 1 second (FEV_1) after inhaled bronchodilators to define COPD patients more responsive to treatment. This led treatment guidelines to recommend routine testing of all COPD patients to detect those who 'reversed' with treatment. The UoL Respiratory Group led by Professor Calverley undertook systematic investigation of reversibility testing and showed that it was influenced by baseline lung function, the number of drugs used to test for a response and the criteria adopted to define responder status [1].

In 2012 Paul Albert (Academic Fellow 2009-), analysing data from the large international prospective ECLIPSE cohort which Prof Calverley designed and direct, showed that the absolute change in lung function was normal in moderate/severe COPD and decreased rather than increased in very severe disease. They showed that physiological variation in airway calibre explained the between-test variation in reversibility response but did not predict clinical outcomes. COPD is characterised by persistent pulmonary inflammation that worsens during acute exacerbations which commonly lead to hospitalisation [2].

Work within The UoL Respiratory Group led by Dr Lisa Davies (Lecturer 1998/2002) tested whether anti-inflammatory treatment with oral corticosteroids could influence recovery from an exacerbation event. She conducted a technically demanding blinded randomised control trial of oral corticosteroids and showed that FEV_1 improved more rapidly and hospital stay was shorter with the active treatment [3]. The Liverpool data showed that these benefits could be achieved at lower doses than used in a similar trial, subsequently reported in the USA. Given that the duration of acute episodes could be shortened with treatment, it was reasonable to consider whether more patients could be managed successfully outside of hospital. In a further randomized controlled trial Davies and colleagues demonstrated that hospital-at-home nurse-led teams could safely manage patients in the community who would have previously been hospitalised without increasing their risk of readmission [4].

Determining whether regular anti-inflammatory treatment has a favourable risk/benefit profile in COPD involved much larger and long randomized multi-centre clinical trials. In the last decade, Professor Calverley has developed and led a series of international studies examining the effects of anti-inflammatory treatment of relevant outcomes like exacerbations, frequency, hospitalization, health status and mortality in COPD patients. The initial studies published in the Lancet in 2003 showed that inhaled steroids were effective alone and in combination with long-acting beta agonists findings confirmed in the 3 year multi-national TORCH study [5]. Calverley designed, analysed and reported this three year study involving 144 centres in 40 countries. It provided evidence that inhaled therapy decreased the rate of decline in FEV_1 during the study. The TORCH

trial and other subsequent studies involving Professor Calverley, showed for the first time that pneumonia occurred more often with inhaled corticosteroid treatment. Using an alternative approach of inhibiting of PDE4 pathways to reduce inflammation Calverley et al demonstrated that oral roflumilast treatment improved lung function and in patients with a history of exacerbations and chronic bronchitis decreased exacerbation frequency independently of background treatment [6].

3. References to the research

1. **Calverley PM**, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003 August;58(8):659-64. Citations: 244 Impact Factor: 8.376

2. **Albert P**, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. Thorax 2012 August; 67(8):701-8. Citations: 11 Impact Factor: 8.376

3. **Davies L**, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: A prospective randomised controlled trial. Lancet 1999;354 (9177):456-60. Citations: 344 Impact Factor: 39.060

4. **Davies L**, Wilkinson M, Bonner S, **Calverley PMA**, Angus RM. "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. BMJ 2000 November 18;321 (7271):1265-8. Citations: 115 Impact Factor: 17.215

5. **Calverley PM**, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007 February 22;356 (8):775-89. Citations: 1428 Impact Factor: 51.658

6. **Calverley PM**, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009 August 29;374 (9691):685-94. Citations: 281 Impact Factor: 39.060

Key Grants

2000-2003. **GlaxoSmithKline**. Genetic basis of COPD, **PMA Calverley**, £350k

2003-2007 GlaxoSmithKline: Towards a Revolution in COPD Health, **PMA Calverley. £200k**

2006-2008. **British Lung Foundation**. Chest wall movement and tidal flow limitation in COPD, **PMA Calverley**, £105k

2008-2011. **GlaxoSmithKline**. Evaluation of Clinical variables to Identify Prospective Surrogate Endpoints (ECLIPSE), **PMA Calverley**, £440k

2011-2014. **MRC/ABPI COPD consortium**, Phenotyping COPD in the UK, **PMA Calverley** (co-applicant), £6.3m

2010-2015. **NIHR Programme Grant**. Innovative use of antibiotics in the prevention of COPD exacerbations, **PMA Calverley** (jointly with JA Wedzicha), £2.0m

2012-2015. **FP7 Innovation for Health**. Clinical trials for elderly patients with multiple diseases, **PMA Calverley** (jointly with R Dellaca, Politecnico di Milano University) €2.2m

4. Details of the impact

The Liverpool studies of bronchodilator responsiveness in COPD have changed the respiratory community's view of the optimal management of COPD. Before our studies, guidance from the American and European Respiratory Societies and the Global initiative for COPD recommended that bronchodilator testing should be a routine part of diagnostic evaluation in COPD [8,9]. The publication of the data by Calverley et al led to a change in the approach adopted in the first NICE guidelines in 2005 and then in the revised GOLD guidance in 2007 [10]. These issues have recently been reviewed by Albert et al in Lancet Respiratory Medicine. The preliminary presentation of data by Albert et al in 2010 led the Department of Health to revise their quality outcome points allocation by removing routine reversibility testing from the points allocated to GPs assessing COPD patients [11], Instead points were awarded for undertaking better quality spirometry and recording symptom intensity which we have shown to be better markers of disease severity. In this regard the Chief scientist in the Department of Health said 'The work of Professor Calverley and his colleagues in Liverpool has had a direct effect on the recommendations for assessment of the COPD patient' [12].

The paper by Davis et al on oral corticosteroids in exacerbations [3] has been cited 344 times as of November 2013 and has been quoted in many COPD guidelines documents [8-10] and in the NICE evidence review about the management of COPD exacerbations [7]. Subsequent work from Canada published in the NEJM confirmed Liverpool's findings and showed that corticosteroid treatment reduced re-admission rates. Recent data from clinical trials indicate that upwards of 80% of exacerbations are now managed using oral corticosteroids, a considerable change when the previous practice, where antibiotics were the first line of treatment. After the UoL RCT of hospital-at home-care, multiple NHS Trusts have set up outreach teams based on the model the UoL developed and this has now been taken up across the UK from 2008 onwards. Dr Davies has spoken extensively nationally and internationally on this topic and members of the UoL team have helped developed the British Thoracic Society Guidelines on Hospital at Home Care [13] which accelerated the adoption of research into wider practice. A Spanish trial reported that these protocols reduced COPD treatment costs by 62%, reduced hospitalisation from 4.2 to 1.7 days and increased patient satisfaction [18].

Professor Calverley has given invited lectures to all the UK medical Royal Colleges, all the international respiratory societies (ATS, ERS, APSR, ELAT) and in many other countries on the subject of inhaled corticosteroids and long acting inhaled bronchodilators and related topics. The TORCH study provided the pivotal evidence which led the FDA to license the combination of an inhaled corticosteroid and a bronchodilator in the prevention of COPD exacerbations, the first time the Agency had accepted exacerbation prevention as an indication for COPD treatment [8]. The data the Liverpool group generated played an important role in the evidence–based evaluation of drug therapy in COPD conducted by NICE and now published as revised guidance [7]. Similar recommendations were made by the international GOLD guidelines [9,10] The new drug roflumilast, which the UoL investigated in several large clinical trials, has been reviewed by both the European Medicines Agency and the Federal Drugs Administration and in each case our data, together with expert witness input from Prof Calverley, played an important role in the licensing of this therapy as well as identifying areas for future research [16]. This led the sponsor's Medical Director to say, *'(Prof Calverley's) advice has significantly helped our company to bring Roflumilast to the market and provide the severe ill COPD patients an additional treatment option...*' – global sales were £19m in 2012, >200% increase over 2011 [17].

The large clinical studies have involved a range of collaborators in other UK centres and across Europe and North America. This has led to on-going collaborations such as the NIHR HTA grant held with Prof Wedzicha at UCL and the jointly managed EU FP7 grant recently awarded to UoL and colleagues in the Politecnico di Milano to study the early identification of exacerbations in COPD patients with co-morbidity monitored at home. Professor Calverley has been able to translate the findings into practical effect, having served from 2000-2011 on the GOLD Executive Committee and as Chair of both the Science and Dissemination Committees. He helped develop the joint ATS/ERS COPD guidelines and the UK NICE Guidelines. He chaired the Department of

Health External Reference Group which produced the Clinical Strategy for COPD Care published in 2011 [15] and presently chairs the NIHR Respiratory Speciality Group charged with delivering high quality clinical trials of the type the Calverley group has conducted for the last decade.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact). Specifically sources 8-12 relate to the work on reversibility testing cited above, source 13 to the hospital at home management programme and sources 7, 10, 14, 16, 17 and 18 to the studies of anti-inflammatory therapy.

7. O'Reilly J, Jones MM, Parnham J, Lovibond K, Rudolf M. Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. BMJ 2010 June 25;340:c3134. doi: 10.1136/bmj.c3134.:c3134.

8. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 February;59 Suppl 1:1-232.

9. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004 June;23(6):932-46.

10. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, **Calverley P** et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007 September 15;176(6):532-55.

11. The percentage of all patients with COPD diagnosed after 1st April 2009 in whom the diagnosis has been confirmed by post bronchodilator spirometry https://mqi.ic.nhs.uk/IndicatorDefaultView.aspx?ref=1.09.03.01

12. Letter from Department of Health - provided

13. Intermediate care--Hospital-at-Home in chronic obstructive pulmonary disease: British Thoracic Society guideline. Thorax 2007 March;62(3):200-10.

14. GSK's Advair Diskus approved for COPD exacerbations by US FDA 05/05/2008. http://www.thepharmaletter.com/article/gsk-s-advair-diskus-approved-for-copd-exacerbations-by-us-fda

15. An Outcomes Strategy for Chronic Obstructive Pulmonary Disease (COPD) and Asthma Department of Health/Medical Directorate/Respiratory Team July 2011 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216139/dh_128428.pdf.

16. Committee for medicinal products for human use (CHMP) European Medicines Agency summary of opinion Daliresp-Roflumilast. EMA/CHMP/825394/2010 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002398/WC500099959.pdf

17. E-mail from Takeda Phamaceuticals (N.B. Takeda Pharmaceuticals annual reports states 2012 roflumilast sales were ¥3b (£19m) and ¥1.3b in 2011).

18. Hernandez C *et al*. Home Hospitlaization of exacerbated chronic obstructive pulmonary disease patients. Eur Respir J 2003; 21: 58-67. DOI 10.1183/09031936.03.00015603.