

Impact case study (REF3)

Institution: University of Leicester		
Unit of Assessment: UoA5		
Title of case study: Development of mepolizumab (Nucala) as a new class of therapy for severe asthma		
Period when the underpinning research was undertaken: 2000-Present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
(1) Prof Andy Wardlaw	(1) Professor of Allergy and Respiratory Medicine	(1) 1992 - Present
(2) Prof Ian Pavord	(2) Professor of Respiratory Medicine	(2) 1994 - 2013
(3) Prof Peter Bradding	(3) Professor of Respiratory Medicine	(3) 1995 - Present
(4) Prof Chris Brightling	(4) Professor of Respiratory Medicine	(4) 1996 - Present
(5) Prof Ruth Green	(5) Professor of Respiratory Medicine	(5) 1996 - Present
(6) Dr Pranab Halder	(6) Associate Professor of Respiratory Medicine	(6) 2000 - Present
Period when the claimed impact occurred: August 2013–December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
<p>Asthma is a chronic inflammatory airway disease, affecting all ages. Asthma causes considerable morbidity and significant avoidable mortality. In the UK, 60,000 asthmatics are admitted to hospital annually, with over 1,000 dying. Globally, ~20% of children and ~5% of adults are affected, with 5% of cases having severe disease. Collaboration between the University of Leicester (UoL) and GlaxoSmithKline (GSK) resulted in the development, licensing, and widespread use of a first-in-kind monoclonal antibody, mepolizumab (Nucala™), which prevents severe exacerbations. Since its release in 2015, Nucala™ has been prescribed ~150,000 times globally, generating revenue of over GBP1,700,000,000, and transforming the lives of those asthmatics at risk of serious harm.</p>		
2. Underpinning research		
<p>Asthma is a chronic condition of the airways, which causes considerable morbidity and significant avoidable mortality globally. In the UK, 5,400,000 people receive treatment for asthma with 6,400,000 GP and nurse consultations annually. 60,000 asthmatics are hospitalised each year with >1,000 dying. Globally, the latter figure rises to >250,000 [E13]. Asthma costs the NHS >GBP1,000,000,000 per year. [E12].</p> <p>Generally, asthma is characterised by two patterns of disease presentation: episodic breathlessness primarily due to airway smooth muscle (ASM) contraction and exacerbations primarily due to airway inflammation. Standard treatment for ASM utilises beta2 agonists while inhaled corticosteroids are effective in preventing exacerbations, though oral administration is required in severe eosinophilic exacerbations. These exacerbations cause asthma deaths. The frequent need for continuous corticosteroid treatment is a risk factor for several conditions including diabetes, hypertension, obesity, and bone thinning. Asthmatics with inadequately controlled disease—estimated to be ~250,000 in the UK—suffer significant impairments in their quality of life, mental health, and employment.</p> <p>Prior to UoL research, there was a major unmet need for new therapies to help this group. Though the importance of eosinophils in asthma was known for several decades, by 2000 the widely accepted paradigm was that asthma resulted from eosinophilic inflammation, caused by allergen-activated T-cells synthesising the specific eosinophil growth factor interleukin 5 (IL-5).</p>		

The anti-IL-5 monoclonal antibody mepolizumab was developed by GSK to improve symptoms and lung function (FEV₁) by preventing IL-5 binding to the IL-5 receptor, thus neutralising it. However, allergen challenge models of asthma and clinical trials concluded that mepolizumab had no effect on either airway hyperresponsiveness (AHR) or FEV₁, despite marked reductions in blood eosinophils. These results had convinced GSK to halt mepolizumab development until intervention by the Leicester Institute for Lung Health (LILH), spearheaded by Wardlaw, Pavord, Brightling, and Bradding.

Based on their clinical and laboratory observations using innovative methods for investigating patient's sputum samples, LILH proposed a new model of asthma, deconstructing it to its component pathophysiological abnormalities [R1]. Examining airway tissue from their patients they found that eosinophils were only responsible for the exacerbation component of asthma, and not the ASM abnormalities which were responsible for day-to-day symptoms [R2]. LILH further demonstrated that active eosinophilic inflammation was not present in all asthmatics [R3] and proposed that only those with an increased sputum eosinophil count would respond to anti-eosinophil therapies [R4]. LILH proved this paradigm shift in a landmark paper that showed that if airway eosinophilia was effectively blocked by corticosteroids then exacerbations were almost completely prevented without major effects on day-to-day symptoms or lung function. The paper also demonstrated that only patients with active eosinophilic inflammation responded to corticosteroids [R5].

This ground-breaking research convinced GSK to commission and support LILH to undertake an investigator-designed and led, Phase-2, single-centre, double-blind, placebo-controlled clinical trial, of twelve months treatment with mepolizumab in patients with active eosinophilic airway inflammation (measured in sputum), using severe exacerbations as the primary outcome measure. This study demonstrated that mepolizumab prevented ~50% of exacerbations, without any discernible effect on day-to-day symptoms, AHR or FEV₁ [R6], showing that eosinophils were causal in exacerbations and suggesting that mepolizumab would be effective in severe asthma if targeted at those with eosinophilic, exacerbation-prone disease. GSK followed this trial with a multi-dose, multi-centre Phase-2 trial (DREAM) in collaboration with LILH, using the same design. This confirmed the original findings, additionally discovering that blood and sputum eosinophil counts were equally as effective in identifying treatment-responsive eosinophilic asthmatics [R7]. Subsequent Phase-3 studies (MENSA and SIRIUS) further verified LILH results.

This research collaboration with LILH led to GSK obtaining a global license in 2015 for the use of mepolizumab in adults and children, marketed as Nucala™. GSK continues to adapt Nucala for the treatment of rare conditions related to severe asthma including eosinophilic granulomatosis with polyangitis (EGPA; formerly Churg-Strauss) and hypereosinophilic syndrome with **Wardlaw** a co-author.

The study designs established by LILH for mepolizumab, stemming from their concepts of asthma based on their laboratory and clinical studies, have been used successfully to develop several other anti-T2 biologicals including reslizumab (also anti-IL-5), benralizumab (anti-IL-5 receptor), and dupilumab (anti-IL-4/13).

3. References to the research

R1. Wardlaw AJ, Brightling CE, Green R, Woltmann G, Bradding P, Pavord ID. *New insights into the relationship between airway inflammation and asthma.* Clinical Science. 2002.103: 201-211.

R2. 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. 346: 1699-705.

R3. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. *Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids.* Thorax. 2002. 57: 875-9.

R4. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. *Cluster analysis and clinical asthma phenotypes.* Am J Respir Crit Care Med. 2008. 178:218-224.

R5. 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. 360:1715-21.

R6. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. *Mepolizumab and exacerbations of refractory eosinophilic asthma.* N Engl J Med. 2009. 360:973-84.

R7. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. *Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.* Lancet. 2012. 380:651-9.

Supporting Grants

G1. Immunohistochemistry of Bronchial Biopsies, Wardlaw (PI), Pavord (COI), Brightling (COI), 2005 – 2011, GlaxoSmithKline, GBP1,220,000.

G2. Mepolizumab at time of admission to hospital for severe exacerbation of COPD, Brightling (PI), 2019-2022, GlaxoSmithKline, GBP2,461,119.

4. Details of the impact

Through highly original reverse translational research and innovative laboratory methodologies, LILH were integral to the development of mepolizumab – a new class of highly effective treatment therapies for severe asthma. First licensed in 2015, the drug is prescribed worldwide, providing substantial economic benefits and significant patient outcome improvements.

Using novel targeting of distinct pathophysiological traits identified through innovative laboratory approaches by the team, with a classical precision medicine approach, LILH have trail-blazed therapy development for asthma and related diseases, achieving global impact in three main areas.

Economic Impact

Prior to LILH intervention, GSK intended to cease mepolizumab development. Leicester research prevented this and opened new markets enabling global release of mepolizumab (Nucala™), now a key pillar of GSK's continued success. Nucala™ was first licensed in 2015 [E1] and has grown exponentially, with sales revenue rising from GBP1,000,000 in 2015 to GBP768,000,000 in 2019. To date, Nucala™ has generated GSK revenue of ~GBP1,800,000,000 [E2].

Significantly, Nucala™ is the fastest growing respiratory product within the GSK portfolio and, despite its relatively recent market introduction, has compensated for the general decline of sales within the GSK pharmaceuticals area. The 2019 Annual Report states that “respiratory sales were up 18% AER, 15% CER to [GBP]3,081 million, on growth of Trelegy, Elipta and Nucala”. Of the drugs listed as continuing successes, Nucala™ is the highest selling drug class [E2].

Beyond GSK, mepolizumab's benefits are widespread within the healthcare sector. Of the GBP1,100,000,000 annual NHS cost of asthma treatment, GBP137,000,000 results from patient hospitalisation [E11]. Studies into mepolizumab's efficacy demonstrate that its use provides a 73% reduction in hospitalisation, thereby saving the NHS an estimated ~GBP19,000,000 annually [E8].

Changing Clinical Practice

In 2016, a joint committee of the British Thoracic Society and the Scottish Intercollegiate Guideline Network, on which Brightling provided expert advice, produced their 'British Guideline on the Management of Asthma'. This guideline, for the first time, recommended the use of mepolizumab as a treatment option for severe asthma based on LILH research. The guideline also extensively utilised LILH research to inform and underpin best-practice recommendations for eosinophilic disease detection. These recommendations were adopted and included in guidelines issued the same year by the British Society for Haematology, European Academy of Allergy and Clinical Immunology, and American Academy of Allergy, Asthma and Immunology [E4].

National clinical standards in the UK are defined by NICE whose recommendations are implemented as standard procedure within all NHS hospitals and represent the gold standard globally. Following the BTS-SIGN guideline, NICE began consultation on the use of mepolizumab as a treatment for severe asthma, resulting in the 2017 guideline 'Mepolizumab for treating severe refractory eosinophilic asthma'. This codified the drug as a treatment option in the NHS for the first time, noting that prior to its creation "*there was a need for alternative treatments for people with severe refractory eosinophilic asthma*" [E3].

Since 2016, as a result of ground-breaking LILH research, mepolizumab is recommended for use in treatment of severe eosinophilic asthma in clinical practice guidelines worldwide including Japan, the EU, Canada, Australia, New Zealand, and Saudi Arabia [E4].

The Global Initiative for Asthma (GINA) is the leading international medical guidelines organisation covering asthma prevalence, morbidity, and mortality. Each year, GINA publish evidence-based guidelines titled 'Global Strategy for Asthma Management and Prevention', used by clinicians worldwide. In each iteration since 2017, mepolizumab is a recommended treatment option. This demonstrates the paradigm shift driven and enabled by LILH [E5].

Improving Patient Health Outcomes

Following NICE approval, a statement was released by the Director of the NICE Centre for Health Technology Evaluation, Professor Carole Longson, in which the novelty and efficacy of Mepolizumab was foregrounded. Longson stated that the 100,000 adults in England and Wales with severe, uncontrolled asthma previously "*had limited treatment options*" with many using inhaled corticosteroids for prolonged periods causing further complications such as diabetes and high blood pressure; "*as the first biologic treatment to target immune cells called eosinophils. These cells are responsible for symptoms in thousands of asthma patients*". Mepolizumab would enable significant treatment and quality of life improvements for sufferers [E6].

By 2019, there were an estimated 17,507 UK patients eligible for mepolizumab, with 3,258 receiving the treatment [E11]. Global adoption of mepolizumab immediately provided significant patient health improvements. The French mepolizumab early-access programme demonstrated 86% reduction in severe exacerbations with 65% of patients stopping continuous corticosteroid treatment [E7], while the Australian Mepolizumab Registry showed 60% reduction in severe exacerbations. Follow-up studies demonstrated a 73% reduction in hospitalisations in patients receiving the drug between 2015 and 2017 [E8].

The real-world benefits of mepolizumab were confirmed by the US Institute for Clinical and Economic Review which concluded that use of the drug was associated with a 53% reduction in asthma exacerbations with similar reductions demonstrated in the annual per-patient rates of emergency department visits (61% reduction) and hospitalisations generally (69% reduction)

[E9]. To date, an estimated 150,000 people worldwide have been treated with mepolizumab since 2015 [E10].

Without the expert intervention of LILH, mepolizumab would have been abandoned, falsely regarded as ineffective based on an incorrect understanding of asthma pathophysiology. Instead, thousands of patients globally now benefit from new treatment options and drastically improved life quality. Drug discovery methods have been revolutionised and avenues for novel, effective treatments have been opened, ensuring continued progress in the global battle against asthma.

5. Sources to corroborate the impact

E1. GSK Press Release 2015. <http://globalpharmaupdate.com/fda-approves-glaxosmithklines-nucala-drug-for-severe-asthma/>

E2. GSK Annual Reports 2015-2019.

E3. NICE 'Mepolizumab for treating severe refractory eosinophilic asthma' 2017.

E4. National and International Clinical Practice Guidelines

- 'British guideline on the management of asthma' 2016.

- Japanese Ministry of Health, Labour and Welfare panel deliberation report.

- British Society for Haematology 'Guideline for the investigation and management of eosinophilia' 2016.

- Joint consensus statement of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology (PRACTALL).

- Canadian Thoracic Society position statement.

- Polish Agency for Assessment of Medical Technologies.

- National Asthma Council Australia 'National asthma strategy 2018'.

- The Saudi Initiative for Asthma 'Guidelines for the diagnosis and management of asthma in adults and children: Update' 2019.

- European Respiratory Society/American Thoracic Society guideline 'Management of severe asthma' 2020.

- National Asthma Council Australia 'Australian Asthma Handbook' 2020.

E5. Global Initiative for Asthma 'Global Strategy for Asthma Management and Prevention' 2017-2019.

E6. NICE Press Release, 2016. <https://www.nice.org.uk/news/article/nice-recommends-first-of-its-kind-asthma-treatment-mepolizumab>

E7. Gruber A et al. *Real-life experience with mepolizumab in the French early access program for severe eosinophilic asthma*. European Respiratory Journal 2019 54 (suppl 63); PA1654.

E8. Harvey E et al. *Clinical response to mepolizumab in patients with severe eosinophilic asthma*. European Respiratory Journal 2019. 54 (suppl 63); PA 541.

E9. US Institute for Clinical and Economic Review 'Mepolizumab (Nucala), GlaxoSmithKline plc.) for the treatment of Severe Asthma with Eosinophilia' 2016.

E10. Testimonial: PBR Report GSK.

E11. Asthma UK report 'Living in Limbo: The Scale of Unmet Need in Difficult and Severe Asthma' 2019.

E12. *Asthma UK* article 2019. <https://www.asthma.org.uk/about/media/news/asthma-uk-study-1.1bn/>

E13. European Medicines Agency 'Summary of the Risk Management Plan for Nucala (Mepolizumab) 2015. https://www.ema.europa.eu/en/documents/rmp-summary/nucala-epar-risk-management-plan-summary_en.pdf