Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study:
Case Study 10. Improving lives and transforming services for Paroxysmal Nocturnal Haemoglobinuria (PNH), a life-threatening, disabling blood disorder.

1. Summary of the impact

Eculizumab has transformed quality of life and life expectancy for patients with PNH and led to major economic impacts with global drug sales of $1,134 million in 2012 and to Alexion Pharmaceuticals being worth over $19 billion. PNH is a disabling blood disorder that was previously fatal in 50% of patients but with eculizumab survival is comparable to the normal population as well as returning patients to having a normal quality of life. Research in Leeds led to the introduction of eculizumab in 2007. Eculizumab is now approved for clinical use in over 40 countries and for another life threatening disease, atypical haemolytic uraemic syndrome.

2. Underpinning research

Background: Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired haemolytic anaemia affecting approximately 5 people per million population, most frequently occurring in early adulthood, is associated with severe life-long symptoms and results in death in half of patients. Peter Hillmen qualified in Medicine from the University of Leeds in 1985 and was awarded a PhD for his research into PNH in 1995. **Hillmen** was appointed as a Consultant Haematologist in Leeds and Honorary Senior Lecturer with the University of Leeds in 1996. He became Honorary Professor in 2008 and the Chair of Experimental Haematology in 2013. In 1995 **Hillmen** published the "Natural History of PNH" demonstrating that approximately 50% of patients died of PNH.[1] In 1997 Alexion Pharmaceuticals developed eculizumab, an inhibitor of the complement component C5, and commenced trials in autoimmune disorders.

In the early 1990's **Hillmen** had confirmed the importance of complement, a system of proteins that form part of innate immunity, in the destruction of PNH blood cells leading to the features, complications and deaths in PNH. This made **Hillmen** realize that anti-complement therapy, such as eculizumab, should be extremely effective in PNH. **Hillmen** had continued PNH research after returning to Leeds in 1994, published several papers and developed a PNH clinic. In 1999 ***Hillmen*** approached Alexion to request eculizumab to perform a clinical trial in PNH. The initial approach to Alexion to run a clinical trial was rejected due to concern over patient numbers for this rare disease. However **Hillmen** continued persuading Alexion to permit him to perform the trial and towards the end of 2001 the initial Pilot study was approved.

Since 2002 **Hillmen** has supervised Leeds PhD students working on PNH and including Dr Anita Hill from 2003 to 2006 (awarded a PhD in 2009) and Dr Richard Kelly from 2007 to 2011 (PhD to be submitted 2013). Drs Hill and Kelly were important in the clinical trials of eculizumab in PNH and now both work within the PNH National Service led by **Hillmen** and based in Leeds.

In May 2002 the Pilot study of eculizumab in 11 patients with PNH (9 in Leeds) commenced with **Hillmen** as the Chief Investigator. The results were dramatic leading to publication in the New England Journal of Medicine in 2004.[2] There were two subsequent Registration trials of eculizumab in PNH (the TRIUMPH[3] and SHEPHERD trials) which **Hillmen** helped design, was the Chief Investigator for both and recruited the largest number of patients. In total 195 patients were recruited into the three Pivotal studies of eculizumab in PNH from 43 Centres worldwide and the Leeds contribution was 34 of these patients (over double the next largest Centre). These trials confirmed the impressive responses to eculizumab seen in the Pilot study leading to the approval of eculizumab for clinical use in 2007 by the Food and Drug Administration in the USA and the European Medicines Agency in Europe. Subsequently eculizumab has been approved in over 40 countries for PNH and was approved for atypical haemolytic uraemic syndrome (aHUS) by the

FDA and EMA in 2011. Eculizumab stopped the intravascular haemolysis in all PNH patients and **Hillmen** subsequently demonstrated that the complications of PNH, including thrombosis, renal failure and pulmonary hypertension, were successfully treated. Subsequent publications from the Leeds PNH group (**Kelly, Hill, Hillmen**) have demonstrated that the survival of patients with PNH is normalised by eculizumab and that patients can lead relatively normal lives.[6]

3. References to the research

[1] **Hillmen P**, Lewis SM, Bessler M, Luzzatto L and Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. (1995) *New England Journal of Medicine,* 333, 1253-1258. 343 citations
Defined for the first time the dismal outcome for patients with PNH

[2] **Hillmen P**, Hall C, Marsh JCW, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF and Rother RP. Effect of eculizumab on hemolysis and transfusion requirements in paroxysmal nocturnal hemoglobinuria. (2004) *New England Journal of Medicine,* 350, 552-559. 176 citations
First description that targeted therapy with eculizumab was extremely effective in PNH

[3] **Hillmen P**, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, Roth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP and Luzzatto L. The Complement Inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. (2006) *New England Journal of Medicine,* 355, 1233-1243. 234 citations
Randomised trial proving that eculizumab is highly effective in PNH. Ensured the drug was accepted and funded in many countries

[4] **Hillmen P**, Muus P, Dührsen U, Risitano AM, Schubert J, Luzzatto L, Schrezenmeier H, Szer J, Brodsky RA, Hill A, Socié G, Bessler M, Rollins SA, Bell L, Rother RP, Young NS. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. (2007) *Blood*, 110, 4123-4128. 107 citations
First demonstration that the main cause of death and a major cause of illness in PNH, namely thrombosis, was effectively prevented and treated with eculizumab

[5] Risitano AM, Notaro R, Luzzatto L, Hill A, Kelly R, **Hillmen P**. Paroxysmal nocturnal hemoglobinuria--hemolysis before and after eculizumab. (2010) *New England Journal of Medicine,* 363, 2270-2272. 7 citations
Explanation for the continued transfusions for a minority of patient on eculizumab

[6] Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M, Mitchell LD, Cohen DR, Gregory WM, **Hillmen P**. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. (2011) *Blood*, 117, 6786-6792. 29 citations
First convincing evidence that survival in PNH was normalized by eculizumab. This led to it's approval and funding in many countries worldwide

Results of the eculizumab trials have been published in very high impact journals and presented at numerous International Conferences including the American Society of Hematology 2002 to 2012, the European Haematology Association 2004 to 2011 and other conferences such as the Japanese Society of Hematology, Brazilian Society of Hematology and the British Society of Haematology by Hillmen.

4. Details of the impact

Leeds research has led to the introduction of a highly effective drug, eculizumab, for PNH which has transformed patients lives, returned their survival to normal, radically reconfigured care services and generated a huge new pharmaceutical activity. Eculizumab is the only approved

agent for PNH in Europe, US, Canada, Japan and over 40 other countries and research in Leeds played a critical role leading to these approvals [A]. Eculizumab was awarded the 2008 Prix Galien USA Award for Best Biotechnology Product with broad implications for future biomedical research and the 2009 Prix Galien France Award for Drugs for Rare Diseases. Research led by Hillmen from Leeds has reached all patients with this condition in the developed world and has demonstrated normalization of overall survival for patients with PNH [A]. The impact on patients' lives is highly significant and impacts the areas of (i) health and welfare, (ii) commerce changing PNH from a disease that destroyed the quality of life of patients, often young adults, leading to the death of half of patients to one that is effectively managed with most patients returning to a normal life.

Health outcomes

PNH is a serious blood disorder found in 5 per million population with a huge impact on quality of life with severe disabling lethargy, severe intermittent abdominal pain, difficulty swallowing, erectile failure and life-threatening thrombosis with half dying due to PNH. 3 per million are severely affected requiring regular transfusions and usually being unable to work and/or are dependent. Eculizumab immediately reverses the symptoms and complications of PNH meaning that patients are able to return to work and stop supportive therapies, such as transfusions and pain-killers. Pregnancy is associated with very high maternal mortality (10% to 20%) meaning that many patients wouldn't risk pregnancy. We have demonstrated that eculizumab is safe in pregnancy and markedly reduces the risks with many women having now had successful pregnancies. Eculizumab prevents the complications of PNH meaning that patients can lead near normal lives including working and contributing to society (6) [B, C, D, E]. This was demonstrated in 195 patients from the clinical trials, 153 UK patients managed by Hillmen and colleagues and through the Global PNH Registry (currently over 2000 patients) and is Chaired by Peter Hillmen. Approximately 3000 patients have received eculizumab since its initial approval in 2007 including all eligible patients in the UK and global sales suggest that this pattern is similar in all developed healthcare systems.

Eculizumab has a clear, well-documented impact on survival in PNH as demonstrated by Hillmen's group (Kelly *et al.*, 2012[6]). Previously half of patients with PNH died within 10 years of diagnosis with only 25% of patients surviving 25 years which, given the disease is often diagnosed in early adulthood, has a profound impact. However eculizumab normalizes survival in PNH (PNH registry data [F]) compared to a 5 year mortality of approximately 35%.[6] The spectre of PNH for patients with virtually no quality of life and a high risk of early death has now been lifted by the use of eculizumab [B-E] which has a high public profile [G].

Guidelines and Governmental Approvals

PNH has now been nationally funded in many countries worldwide including the Netherlands, France, Australia, Canada, and Japan as well as being available in the US, Germany, etc. Since 2011 eculizumab has been approved in the US, Europe and Canada for atypical Haemolytic Uraemic Syndrome (aHUS), previously an untreatable condition leading to renal failure and premature death. This approval would not have happened without the PNH trials [A, B, C].

Changes in service configurations and disease regulation

As a result of our research PNH is designated as a highly specialised service in England and funded as a National Service through the Advisory Group for National Specialised Services (AGNSS) [H]. This covers the cost of the Service (in excess of £1million/year) and the cost of eculizumab for PNH (approximately £25million/year). The National PNH Service employs 15 people and contracts homecare nurses to deliver 4000 doses of eculizumab by intravenous infusion in patients' homes each year.

The approval of eculizumab led to the establishment of the PNH Global Registry (http://www.pnhsource.com/pnh-registry) which has enrolled over 2000 patients with PNH. Hillmen chairs the Executive Committee of the PNH Registry and Leeds has recruited over 250 patients being the largest Centre globally.

Commercial impacts

The approval of eculizumab for PNH has been an economic success for Alexion Pharmaceuticals as their only approved drug [I]. The sales of eculizumab in 2012 were $1.134 billion. This was highlighted in the September 2012 edition of Forbes magazine in an article entitled: "How A $440,000 Drug Is Turning Alexion Into Biotech's New Innovation Powerhouse" [G]. The current estimated market capitalisation for Alexion is $19billion making Alexion and the development of eculizumab one of the most impressive economic successes in the last 10 years [J].

5. Sources to corroborate the impact

A) Regulatory approval of eculizumab for the treatment of PNH in the U.S, E.U., Japan and other countries.

B) Australian Government Department of Health and Aging report entitled: "Guidelines for the treatment of Paroxysmal Noctunrnal Haemoglobinuria (PNH) through the Life Saving Drugs Program" published in December 2010 recommending the funding of eculizumab for PNH Nationally in Australia and widely referencing researchers from Leeds including **Hillmen, Hill and Kelly**.

C) All Wales Medicines Strategy Group Final Appraisal Report entitled: "Eculizumab (Soliris) for the treatment of paroxysmal nocturnal haemoglobinuria" was published in April 2009 with extensive references to the work of Leeds researchers (**Hillmen, Hill, Kelly**). It recommended that: "Eculizumab (Soliris®) is recommended for restricted use within NHS Wales according to agreed guidelines for the treatment of paroxysmal nocturnal haemoglobinuria."

D) Letters of support from leading international PNH clinicians confirming the impact the research on PNH in Leeds led by **Hillmen** has had on the lives of patients with PNH globally.

E) Letter of support from patients with PNH (one from UK and one from Canada) confirming the dramatic impact eculizumab has had on their lives.

F) Changes in outcome in national figures for PNH documented from the National Registry. Currently over 150 patients with PNH are on treatment with eculizumab in the United Kingdom.

G) Extensive coverage in the national and international media (print, electronic, radio and television; file available) involving Hillmen. This includes the recent article in the Forbes magazine describes the impact of eculizumab and Alexion Pharmaceuticals which extensively acknowledges the central role of **Hillmen.** (http://www.forbes.com/sites/matthewherper/2012/09/05/how-a-440000-drug-is-turning-alexion-into-biotechs-new-innovation-powerhouse/3/).

H) Service Specification and Standards 2012/13 - Paroxysmal Nocturnal Haemoglobinuria Service. National Specialised Commissioning Team (NSCT).
http://www.specialisedservices.nhs.uk/document/10383

I) Sales figures for eculizumab are available online (http://www.cnbc.com/id/49531010/Alexion_Reports_Third_Quarter_2012_Results_Soliris_R_eculizumab_Net_Product_Sales_Increased_44_to_294_1_Million)

J) Letter of support from Dr Leonard Bell, Chief Executive Officer, Alexion Pharmaceuticals Inc. confirming the central role **Hillmen** played in the development of eculizumab for PNH.

(http://www.specialisedservices.nhs.uk/service/paroxysmal-noctural-haemoglobunuria/)