Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: The Introduction of a Successful Treatment of Pulmonary Arterial Hypertension in Adults

1. Summary of the impact (indicative maximum 100 words)

Pulmonary arterial hypertension (PAH) is a fatal disease that typically affects women in their childbearing years. Professor Wilkins led a research team at Imperial College that identified phosphodiesterase type 5 (PDE5) as a drug target in the lungs of patients with PAH. Imperial validated the target in cell and animal models and demonstrated proof in patients that Sildenafil, a PDE5 inhibitor, was an effective treatment for PAH. Professor Wilkins conducted a clinical study to compare the effect of oral Sildenafil with Bosentan, the only other available oral therapy for PAH at the time. This study was the first, and remains the only, head-to-head study of two treatments for PAH. Sildenafil demonstrated comparable efficacy, had a greater effect on reducing cardiac mass (an integrated measure of heart work) and was well tolerated.

Sildenafil is now the most commonly prescribed drug for PAH. It is the most cost-effective, as judged by a technology appraisal initiated by NICE. National and international guidelines recommend Sildenafil as a first line treatment for patients in functional classes II and III pulmonary hypertension. Worldwide sales of sildenafil (Revatio®) for the management of PAH were $500m in 2010. With the expiration of the patent the cost of treatment will fall further.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Martin Wilkins, Professor of Clinical Pharmacology (1990-present)
Dr John Wharton, Honorary Senior Lecturer (1984-present)

PAH, high blood pressure in the blood vessels of the lungs, is a devastating, fatal disease with few treatment options. In the UK, the likely prevalence of PAH has been estimated to be up to 50 cases per million population. It is characterised by structural remodelling of pulmonary arterioles, narrowing the vessel lumen and increasing resistance to blood flow. Patients die prematurely from right heart failure.

Imperial is a centre of excellence for research in pulmonary hypertension. Professor Wilkins has led a peer-reviewed funding programme that demonstrated:

(a) That the expression of phosphodiesterase type 5 (PDE5) is increased in the pulmonary remodelled vessels of patients with PAH (1)
(b) That inhibition of PDE5 with Sildenafil inhibited pulmonary vascular cell growth in culture (1)
(c) That oral Sildenafil attenuated pulmonary hypertension in rodent models of the disease (2, 3)
(d) That Sildenafil reduced pulmonary artery pressure in patients with high altitude pulmonary hypertension (3, 4).

These data led to a double-blind, randomised controlled single centre study based at Imperial, published in 2005 and funded by the British Heart Foundation, to compare the effects of Sildenafil and Bosentan in patients with PAH (5). Imperial examined the effects of the two drugs on right ventricular mass, together with exercise capacity, assessed by 6-minute walk distance, cardiac function, and circulating cardiac hormones. It was a landmark study, the first head-to-head comparison of two treatments (Sildenafil and Bosentan) in PAH, rather than the active ingredient vs. placebo. The data provided a scientific rational for a larger US phase 3 study (SUPER-1) which led to the licensing of Sildenafil as Revatio® for PAH in 2006.

3. References to the research (indicative maximum of six references)

(1) Wharton, J., Strange, J.W., Moller, G.M., Growcott, E.J., Ren, X., Franklyn, A.P., Phillips, S.C., Wilkins, M.R. (2005). Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. *American Journal of Respiratory and Critical Care Medicine*, 172, 105-113. DOI. Times cited: 168 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 11.04

(2) Sebkhi, A., Strange, J.W., Phillips, S.C., Wharton, J., Wilkins, M.R. (2003). Phosphodiesterase type 5 as a target for the treatment of hypoxia-induced pulmonary hypertension. *Circulation*, 107, 3230-3235. DOI. Times cited: 127 (as at 7th Novemebr 2013 on ISI Web of Science). Journal Impact Factor: 15.20

(3) Zhao, L., Mason, N.A., Morrell, N.W., Kojonazarov, B., Sadykov, A., Maripov, A., Mirrakhimov, M.M., Aldashev, A., et al. (2001). Sildenafil inhibits hypoxia-induced pulmonary hypertension. *Circulation*, 104, 424-428. DOI. Times cited: 267 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 15.20

(4) Aldashev, A.A., Kojonazarov, B.K., Amatov, T.A., Sooronbaev, T.M., Mirrakhimov, M.M., Morrell, N.W., Wharton, J., Wilkins, M.R. (2005). Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax*, 60 (8), 683-687. DOI. Times cited: 36 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 8.37

(5) Wilkins, M.R., Paul, G.A., Strange, J.W., Tunariu, N., Gin-Sing, W., Banya, W., Westwood, M.A., Stefanidis, A., Ng, L.L., Pennell, D.J., Mohiaddin, R.H., Nihoyannopoulos, P., Gibbs, J.S. (2005). Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. *American Journal of Respiratory and Critical Care Medicine*, 171, 1292-1297. DOI. Times cited: 163 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 11.04

Key funding:

- British Heart Foundation (BHF) (2000-2003; £144,897), Principal Investigator, M. Wilkins, Pharmacological manipulation of cyclic GMP in pulmonary hypertension.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, public policy and services, commercial
Main beneficiaries include: patients, NICE, European Society of Cardiology, industry

Until 2001, the only treatment available for PAH was intravenous epoprostanol, an expensive (£>80K per patient, per annum) drug with an extremely short half-life, given directly into the pulmonary circulation. Bosentan, an endothelin antagonist, was the first orally active drug approved for PAH (costing £30K per patient per annum). Sildenafil, which works by a different mechanism, was the second; originally licensed for erectile dysfunction (as Viagra®). Professor Wilkins and his team at Imperial explored its off label use in PAH from bench-to-bedside and collated a persuasive data set that argued its efficacy, and so offering a cheaper alternative (£9k per patient per annum). Sildenafil was approved for PAH internationally in 2006. Pfizer launched the drug as Revatio® to distinguish it from Viagra® but it is the same drug. Sildenafil was adopted and recommended as a first line treatment for PAH by international societies (British Thoracic Society [2008], European Cardiac Society/European Respiratory Society [2009]) [1, 2]. Subsequent meta-analyses which cite the Wilkins study (among others since then) confirm the efficacy of Sildenafil in PAH [3].

Sildenafil is now the most commonly prescribed drug for PAH and it is the most cost-effective, as judged by a technology appraisal initiated by NICE [4]. Equally important, it is available, as Viagra®, and affordable in the developing world. Worldwide sales of sildenafil (Revatio®) for the management of PAH were $500m in 2010, up from $95m in 2006, $201m in 2007 and $336m in 2008 [5]. Revatio® was the first drug with this mode of action to be approved worldwide for

patients with PAH. In 2013, the Pfizer patent expired leading to reports that the cost of the drug will fall further as new generic drugs enter the market making the treatment significantly more cost effective [6].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] European Society of Cardiology/European Respiratory Society guidelines 2009 http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-ph-ft.pdf. Archived on 7th November 2013.

[2] Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in UK and Ireland (Thorax 2008). http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pulmonary%20hypertension/PulmHyper_ThoraxMarch08.pdf. Archived on 7th November 2013.

[3] Meta-analyses of clinical findings:
Macchia, A., Marcholi, R., Tognoni, G., Scarano, M., Marfisi, R-M., Tavazzi, L., Rich, S. (2010). Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *American Heart Journal*, 159 (2), 245-257. DOI

[4] NICE - Pulmonary arterial hypertension (adults) - drugs: appraisal consultation document. http://www.nice.org.uk/guidance/index.jsp?action=article&o=39688 (archived on 7th November 2013)

[5] Worldwide sales of Sildenafil (Revatio ®) http://www.evaluategroup.com/Universal/View.aspx?type=Entity&entityType=Product&lType=modData&id=19784&componentID=1002. Archived on 7th November 2013

(6) Sildenafil patent expires and drug price set to fall
http://www.bbc.co.uk/news/health-22990247 (archived on 7th November 2013)
http://www.pharmatimes.com/Article/13-06-24/Generic_firms_poised_as_Viagra_goes_off-patent_in_Europe.aspx (archived on 7th November 2013)
http://www.marketingweek.co.uk/opinion/how-pfizer-can-sustain-growth-after-viagra/4007129.article (archived on 7th November 2013)