Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Clinical development and manufacture of a new drug, Chronocort®, for treatment of the rare orphan disease congenital adrenal hyperplasia

1. Summary of the impact

Research on Congenital Adrenal Hyperplasia (CAH) at the University of Sheffield has resulted in both health and commercial impacts. The research has led to a new drug treatment, Chronocort®, being developed for CAH. Chronocort® has been tested in CAH patients with the positive outcome of improved disease control.

Commercial impact arose from the creation of a spin-out company, Diurnal Ltd, in 2004 which has raised investment of £3.8M since 2008, including £0.4M from pharmaceutical industry sources, and (as an SME partner) a €5.6M Framework 7 grant to develop a paediatric treatment for CAH. Diurnal has created five new jobs and has contracts with six UK companies worth £2.7M.

2. Underpinning research

In 2000, Professor Richard Ross (University of Sheffield, 1995-date), led a UK audit, funded by the Endocrinology Trust, assessing the standard of care for adult patients with congenital adrenal hyperplasia (CAH). CAH is a condition in which the adrenal gland secretes insufficient amounts of the essential stress hormone, cortisol. The audit demonstrated that there was no consensus on patient care and that current treatment regimens were inadequate. Following presentation of the findings to the British Endocrine Society in 2001, the CaH Adult Study Executive (CaHASE), chaired by Ross, was formed to investigate the health of patients with CAH across 17 UK endocrine centres.

Between 2001 and 2010, CaHASE studied the world's largest cohort of adult CAH patients. The research highlighted that these patients have poor health outcomes including obesity, osteoporosis, an impaired quality of life, poor metabolic profile, and infertility, and that this was related to inadequate disease control through a lack of appropriate cortisol (hydrocortisone) replacement therapy (R1). The work demonstrated the unmet need for new drug treatments and was cited by the Endocrine Society (USA) as one of the most influential publications in adrenal disease (R2).

In 2001, recognising the need for new treatments, Ross examined the cortisol rhythm in healthy volunteers and the pharmacokinetics of current hydrocortisone therapy in patients with CAH. Cortisol levels in the body naturally follow a circadian (around the day) rhythm, rising overnight from about 3am to peak on waking and then falling during the day. Thus, the main rise in cortisol levels occurs whilst sleeping.

In 2004, Ross demonstrated that oral tablet hydrocortisone replacement therapy cannot replace the overnight rise in cortisol levels because of the short plasma half-life of hydrocortisone (R3). The failure of cortisol to rise overnight in patients with CAH is critical and the main cause of poor control of the disease. CAH results from an enzyme block in the production of cortisol from the adrenal gland, and without appropriate cortisol replacement at night, precursor hormones accumulate like water behind a dam. These precursor hormones are androgens (male hormones) and cause precocious puberty, infertility and virilisation of women. To try and prevent this overnight rise in androgens, clinicians often over-treat patients with potent steroids causing increased cardiovascular risk, obesity and osteoporosis.

In 2006, Ross addressed the failure of treatment in CAH, undertaking continuous intravenous infusion studies with hydrocortisone (R4) and demonstrating that it was possible to replicate the overnight cortisol rise and 24h circadian rhythm with infusions of hydrocortisone. This improved the disease control of CAH by preventing the inappropriate rise in precursor androgenic hormones without exposing patients to excess steroid. Based on this proof of concept work, Ross then developed an oral formulation of modified release hydrocortisone, called Chronocort®, to replace the normal physiological overnight rise in cortisol levels with the aim of improving treatment outcomes for patients with CAH (R5, R6).

The potential beneficiaries from Chronocort® include those patients with cortisol deficiency due to CAH (60-100 cases per million), Addison's disease (93-140 cases per million) and pituitary failure (150-280 cases per million). Treatment for cortisol deficiency was only introduced in the 1950s; prior to that date most patients died. With the introduction of treatment there is now a growing cohort of adult patients who require on-going therapy.

3. References to the research

University of Sheffield Authors are highlighted in bold.

R1. Arlt, W., Willis, D.S., Wild, S.H., Krone, N., Doherty, E.J., Hahner, S., Han, T.S., Carroll, P.V., Conway, G.S., Rees, D.A., Stimson, R.H., Walker, B.R., Connell, J.M. & **Ross, R.J.** (2010) Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocr Metab. 95, 5110-5121. doi: 10.1210/jc.2010-0917

R2. Carey, R.M. Adrenal disease update (2011). J Clin Endocr Metab, 96, 3583-3591. doi: 10.1210/jc.2011-2162

R3. **Mah, P.M., Jenkins, R.C., Rostami-Hodjegan, A., Newell-Price, J., Doane, A., Ibbotson, V., Tucker, G.T. & Ross, R.J.** (2004) Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clinical Endocrinol. 61, 367-375. doi: 10.1111/j.1365-2265.2004.02106.x

R4. **Merza, Z., Rostami-Hodjegan, A., Memmott, A., Doane, A., Ibbotson, V., Newell-Price, J., Tucker, G.T. & Ross, R.J.** (2006) Circadian hydrocortisone infusions in patients with adrenal insufficiency and congenital adrenal hyperplasia. Clinical Endocrinol. 65, 45-50. doi: 10.1111/j.1365-2265.2006.02544.x

R5. **Newell-Price, J**., Whiteman, M., **Rostami-Hodjegan, A**., Darzy, K., Shalet, S., **Tucker, G.T. & Ross, R.J**. (2008) Modified-release hydrocortisone for circadian therapy: a proof-of-principle study in dexamethasone-suppressed normal volunteers. Clinical Endocrinol. 68, 130-135. doi: 10.1111/j.1365-2265.2007.03011.x

R6. **Debono, M., Ghobadi, C., Rostami-Hodjegan, A.,** Huatan, H., **Campbell, M.J., Newell-Price, J.,** Darzy, K., Merke, D.P., Arlt, W. & **Ross, R.J.** (2009) Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocr Metab. 94, 1548-1554. doi: 10.1210/jc.2008-2380

4. Details of the impact

Research at the University of Sheffield into the outcome of treatments for patients with congenital adrenal hyperplasia (CAH) has led to a new drug treatment being developed, trialled with patients and positive outcomes demonstrated. The research has also had commercial impact through the creation of a spin-out company, Diurnal Ltd, to commercialise the treatment, which has successfully raised investment from both venture capitalists and the pharmaceutical industry, and created new jobs and major industrial contracts.

Process to impact:

In 2005, following a meeting with Ross, the European Medicines Agency (EMA) agreed that there was an unmet need for patients with CAH and adrenal insufficiency and that Chronocort® could provide a significant improvement in treatment, and granted Ross Orphan drug designation for Chronocort® to treat CAH (S1) and adrenal insufficiency (S2). This designation is to encourage drug development when a condition is chronically debilitating, the prevalence is <5 in 10,000, and the medicine would be of significant benefit to those affected. This enabled Phase 1 trials of Chronocort® to go ahead. The EMA stated that if use of Chronocort® could demonstrate better control of the morning androgen precursor hormones this would constitute evidence of significant benefit and would be an appropriate primary outcome in clinical trials of patients (S3). This led to a Phase 2 clinical trial in CAH patients.

Following publication in 2010 by the EMA PaeDiatric COmmittee (PDCO) that there was no licensed preparation of hydrocortisone for neonates and infants with CAH and adrenal insufficiency, the University of Sheffield and Diurnal Ltd as an SME partner won a European Framework 7 grant of €5.6M to develop a neonatal and infant preparation of hydrocortisone, Infacort (S4). Diurnal Ltd then submitted a Paediatric Investigation Plan (PIP) to the EMA PDCO – a process usually delivered only by major pharmaceutical companies - for the use of Infacort® in neonates and infants. The PIP was approved in 2013 (S5), confirming the unmet need that Infacort can address and that the clinical development plan was appropriate to provide a Paediatric Use Market Authorisation (PUMA). This has enabled the manufacture of Infacort® to go ahead and Infacort is currently being evaluated in phase 1 clinical studies in healthy volunteers.

Commercial impact

The spin-out company, Diurnal Ltd, was founded in 2004 with Professor Ross as a founding director and subsequently Chief Scientific Officer. Diurnal Ltd was created to develop and commercialise the new drug Chronocort® based on the research and patents filed by the University of Sheffield. Diurnal Ltd licensed the original patent from the University of Sheffield and has 15 pending patent applications and 5 granted patents all filed since 2001. Since 2008, Diurnal Ltd has successfully raised over £3.8M investment for development of its drug product portfolio from a venture capital consortium including a £461K investment from a global pharmaceutical company, through an option to licence Chronocort® from Diurnal Ltd (S6). Diurnal Ltd has a Cooperative Research and Development Agreement (CRADA) with the National Institute of Health (NIH), USA for the development of Chronocort (S7). CRADAs signify recognition by NIH of the importance of the drug development programme to patients, with NIH agreeing to fund all components of the clinical trials performed at NIH. Diurnal Ltd has undertaken its drug development and manufacture through both manufacture (Penn Ltd, Quay Pharmaceuticals Ltd, GLATT GmbH) and clinical (Simbec Research Ltd) research organisations with contracts worth over £2.7M, bringing new work and employment to these companies. Diurnal Ltd employs 5 staff and since 2008 has spent £288K on consultant contracts to help bring Chronocort® to market (S6).

Health impact

The research has led to the development and manufacture of two new drugs for cortisol deficiency: Chronocort® for adults and a neonatal and infant formulation, Infacort®. In 2008, oral formulations of hydrocortisone, Chronocort®, were generated with a delayed and sustained release profile and trialled in 6 healthy volunteers (S8). The results demonstrated that it was possible to replace the overnight rise in cortisol with Chronocort. In 2009, further phase 1 clinical trials were carried out in 28 healthy volunteers and these demonstrated that Chronocort® could reproducibly replace overnight circadian cortisol levels (S9). In 2010, a 3 month phase 2 trial of Chronocort® in 14 adult patients with CAH demonstrated improved overnight disease control, using the primary outcome

recommended by the EMA (S10). Since 2010 Diurnal has moved its manufacture to a facility that can optimise the formulation and supply phase 3 clinical trial material.

Public understanding

The public awareness of the problems for patients with CAH has been stimulated by media publicity surrounding the CaH Adult Study Executive (CaHASE) publications of poor health outcomes in CAH patients. Patient group awareness has been increased through presentations by Ross to patient groups including American CAH patient group CARES (5000 Community Members), New York 2009; UK CAH patient group, Manchester 2011; and UK Addison's Disease Self-Help Group (1400 members), London, 2012. In the USA CARES are promoting clinical trials with Chronocort®, and Ross has been appointed an Advisor to the American CAH patient support group.

5. Sources to corroborate the impact

S1. Orphan Designation of Chronocort for CAH (http://tinyurl.com/ornrmoh).

S2. Orphan Designation of Chronocort for Adrenal insufficiency (http://tinyurl.com/q3jr5nt).

S3. Report from EMA meeting on Chronocort on file.

S4. Treatment of Adrenal Insufficiency in Neonates (TAIN) funded by EU FP-7 Grant: http://www.tain-project.org/ and http://cordis.europa.eu/projects/rcn/102053_en.html

S5. Paediatric Investigation Plan for Infacort programme approved by the EMA (http://tinyurl.com/mdlmxf7).

S6. Letter from Diurnal Ltd to University of Sheffield confirming investment and spend since 2008.

S7. Diurnal press release "Diurnal enters into a Cooperative Research and Development Agreement with the National Institute of Health" (http://tinyurl.com/kn64c3w).

S8. Newell-Price, J., Whiteman, M., Rostami-Hodjegan, A., Darzy, K., Shalet, S., Tucker, G.T. & Ross, R.J. (2008) Modified-release hydrocortisone for circadian therapy: a proof-of-principle study in dexamethasone-suppressed normal volunteers. *Clinical Endocrinology* **68**, 130-135. doi: 10.1111/j.1365-2265.2007.03011.x

S9. Debono, M., Ghobadi, C., Rostami-Hodjegan, A., Huatan, H., Campbell, M.J., Newell-Price, J., Darzy, K., Merke, D.P., Arlt, W. & Ross, R.J. (2009) Modified-release hydrocortisone to provide circadian cortisol profiles. *The Journal of clinical endocrinology and metabolism* **94**, 1548-1554. doi: 10.1210/jc.2008-2380

S10. Verma, S., Vanryzin, C., Sinaii, N., Kim, M.S., Nieman, L.K., Ravindran, S., Calis, K.A., Arlt, W., Ross, R.J. & Merke, D.P. (2010) A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort) vs. conventional hydrocortisone (Cortef) in the treatment of congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)* **72**, 441-447. doi: 10.1111/j.1365-2265.2009.03636.x