Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: New treatment and treatment monitoring for iron overload in thalassaemia patients

1. Summary of the impact

The iron and red cell disorders group at UCL has worked for over 20 years on the pathophysiology of transfusion-dependent iron overload in thalassaemia patients, using models of iron uptake and overload and translating these into clinical practice. In collaboration with Novartis, a new treatment, deferasirox, was developed, which is now the treatment of choice for iron overload in the western world. In addition, a method for monitoring iron overload in the heart was developed in collaboration with Dr Pennell at the Brompton and pioneered in patients at UCL Hospital (UCLH) and the Whittington Hospital. This has become the standard approach worldwide.

2. Underpinning research

Around 7% of the global population carries an abnormal haemoglobin gene and between 300,000 and 500,000 children are born with clinically significant haemoglobin disorders annually, predominantly in developing countries. About 30% have thalassaemia syndromes, and for transfusion-dependent thalassaemia major (TM) an estimated 50-100,000 children die each year in low and middle income countries. This is mainly due to the effects of iron deposition in the liver, heart and endocrine system, originating from multiple blood transfusions. Ultimately this is fatal if the iron overload is not prevented. Iron initially accumulates in the liver but, if not controlled by chelation therapy, may spread to the heart causing heart failure from the second decade of life, which has been the commonest cause of death in TM. Until recently the only way to prevent iron overload was with the chelator desferrioxamine, which had to be given via a needle and by continuous infusion for 8-12 hours a day at least 5 days per week. The burden of such a regimen was enormous and compliance often poor.

From 1992 Professor John Porter advised Ciba-Geigy (now Novartis) about oral chelators at both the pre-clinical and clinical stages of development and an alternative chelating agent (deferasirox) was then developed by Novartis. Porter was involved in the planning and execution of pivotal registration trials (0107, 0108 **[1-4]** and 0109 **[5]**), which established the role of deferasirox in the treatment of liver and heart iron overload. Porter also played a central role in the design, recruitment and interpretation of the pivotal study that determined the place of deferasirox in patients aged 10 years and older who have chronic iron overload as a result of non-transfusion-dependent thalassaemia (NTDT) **[6]**.

UCL investigators also have a long-standing interest in monitoring the effects of iron chelators on heart failure in iron overload conditions **[7]** and in collaboration with cardiologists at Brompton Hospital and UCLH have been at the forefront of MRI developments for cardiac iron quantification. This has been key to evaluating the effects of chelators on iron mobilisation from the heart **[8]** and is now viewed as essential for optimal management of heavily transfused patients and determining the response to therapy. Patients in heart failure can be rescued as a late event when in heart failure with reversal of cardiomyopathy and good long-term survival **[7]**. Patients at UCLH and Whittington were the first cohort of patients to be studied, in collaboration with the MRI unit at the Brompton Hospital, using cardiac MRI. It is now clear that the highest risk patients can be identified by cardiac MRI and treatment intensified in those with high cardiac iron.

3. References to the research

[1] Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, Aydinok Y, Kattamis A, Kilinc Y, Porter J et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006;107:3455-62. http://dx.doi.org/10.1182/blood-

2005-08-3430

[2] Cappellini MD, Bejaoui M, Agaoglu L, Porter J et al. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine for iron overload in patients with beta-thalassemia. Clin Ther. 2007;29:909-17. http://dx.doi.org/10.1016/j.clinthera.2007.05.007

[3] Porter JB, Galanello R, Saglio G et al. Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. Eur J Haematol. 2008;80:168-176. http://dx.doi.org/10.1111/j.1600-0609.2007.00985.x

[4] Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood. 2008 Jan 15;111(2):583-7. http://dx.doi.org/10.1182/blood-2007-08-109306

[5] Vichinsky E, Onyekwere O, Porter JB et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Brit. J Haematol. 2007;136 501-508. http://dx.doi.org/10.1111/j.1365-2141.2006.06455.x

[6] Taher AT, Porter J, Viprakasit V, Kattamis A, Chuncharunee S, Sutcharitchan P, Siritanaratkul N, Galanello R, Karakas Z, Lawniczek T, Ros J, Zhang Y, Habr D, Cappellini MD. Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study. Blood. 2012 Aug 2;120(5):970-7. http://dx.doi.org/10.1182/blood-2012-02-412692.

[7] Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. Blood. 2004 Jul 1;104(1):263-9. http://dx.doi.org/10.1182/blood-2003-08-2841

[8] Pennell D, Porter JB, Cappellini MD et al. Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with beta-thalassemia major. Haematologica. 2012;97(6):842-8. http://dx.doi.org/10.3324/haematol.2011.049957

4. Details of the impact

Two key changes in practice have arisen from our research. Firstly, there have been improvements in chelation treatment for patients with transfusional and non-transfusional iron overload, particularly with the orally active chelator deferasirox. Secondly, there is improved monitoring of patients with transfusional iron overload. This has resulted in improved rates of survival from iron overload and better quality of life for patients. Over half the TM patients in the UK [390] are followed by the Joint Red Cell Unit of UCLH and the Whittington Hospital, led by Porter (the UK Registry). Recent analysis has shown that survival is improving progressively. The decade to 2009 saw an almost three-fold fall in the proportion of patients with myocardial iron overload. Mortality is substantially lower and cardiac iron overload is no longer the leading cause of mortality **[a]**.

The underpinning research described above, from preclinical to clinical stages of development, has resulted in deferasirox, a novel orally active chelating agent, becoming the first line treatment for transfusional iron overload in the developed world. It was licensed by the FDA in 2005 **[b]** and the EMA in 2006 **[c]**. Porter's contribution to the development of deferasirox was recognised by Novartis when he was asked to accept the Prix Galien prize at the House of Commons in 2008, awarded to Novartis for innovative research in development in orphan drugs **[d]**. Deferasirox is now recommended in guidelines issued by the Thalassaemia International Federation (TIF) **[e]**, by the UK Thalassaemia Society **[f]** in Canada **[g]** and in the US **[h]**. In excess of 65,000 patients have received deferasirox, a cumulative exposure of 163,350 patient years, with global sales exceeding $800m annually **[i]**. Use of this drug results in improved quality of life for patients, because they no longer need to endure treatment administered by prolonged infusion, but can take an orally active medication **[j]**. In 2012, the license for deferasirox was extended to include the new

indication of the treatment of iron overload in non-transfusion dependent thalassaemia. These patients become iron-overloaded because of excess iron absorption from the GI tract, and deferasirox is now indicated where alternative iron chelators are ineffective or poorly tolerated **[k]**.

Improved monitoring had been particularly advanced by the use of MRI to identify patients with the highest risk of cardiac disease from iron overload. Early identification of high-risk patients allows intervention with intensification of chelation therapy. This approach is now recommended worldwide, as described in a recent review of guidelines which said: "*All guidelines recommend cardiac siderosis assessment by cardiac T2* MRI*" **[l]**. In the UK, longitudinal monitoring by cardiac MRI has become standard practice **[m]**. This approach is increasingly impacting on survival and quality of lives of children and young adults with TM at risk of death each year in low and middle income countries.

5. Sources to corroborate the impact

[a] Thomas AS, Garbowski M, Ang AL, Shah FT, Walker MJ, Moon JC, Pennell DJ, Porter JB. A decade follow-up of a thalassemia major (TM) cohort monitored by cardiac magnetic resonance imaging (CMR): Significant reduction in patients with cardiac iron and in total mortality. Blood. 2010:116(21):Abstract 1011. https://ash.confex.com/ash/2010/webprogram/Paper29471.html

[b] http://www.drugs.com/nda/exjade_050929.html. *Article references the trials cited above in section 3.*

[c] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000670/human_med_000780.jsp&mid=WC0b01ac058001d124 *References [1-4 and 8].*

[d] Medical Research News. http://researchit.info/2011/07/novartis-once-daily-iron-chelator-exjader-deferasirox-awarded-prestigious-uk-prix-galien-medicines-prize/

[e] Thalassaemia International Federation. Guidelines for the clinical management of thalassaemia. 2nd edition. 2008. http://www.thalassaemia.org.cy/wp-content/uploads/pdf/educational-programmes/Publications/Guidelines%20%282008%29/Thalassaemia%20Guidelines%20ENGLISH.pdf *Porter is an author, and many of papers listed in section 2 are cited throughout the book.*

[f] United Kingdom Thalassaemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. (2008). Porter contributed directly to the writing of the first edition in 2005. References a number of papers. http://sct.screening.nhs.uk/getdata.php?id=10921

[g] Canadian guidelines. http://www.thalassemia.ca/wp-content/uploads/Thalassemia-Guidelines_LR.pdf The authors say: "These guidelines were inspired by the Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK."

[h] Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, Hoffman TM, Kiernan MS, Lerakis S, Piga A, Porter JB, Walker JM, Wood J; American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology and Council on Cardiovascular Radiology and Imaging. Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the American Heart Association. Circulation. 2013 Jul 16;128(3):281-308. http://dx.doi.org/10.1161/CIR.0b013e31829b2be6

[i] Deferasirox patient and sales data. http://www.novartis.com/investors/financial-results/product-sales.shtml Novartis Sales Data – $870m sales for Exjade in 2012. Also http://www.zacks.com/stock/news/91268/FDA-Approves-Novartis-Exjade "*First approved in 2005, Exjade is now approved in more than 100 countries, including the US, EU and Japan. We note that Exjade generated sales of $870 million in 2012, up 7% year over year, driven by*

growth in Europe, Latin America, Canada and Japan."

[j] Porter JB, Bowden DK, Economou M, et al. Health-related quality of life, treatment satisfaction, adherence and persistence in β-thalassemia and myelodysplastic syndrome patients with iron overload receiving Deferasirox: Results from the EPIC clinical trial. Anemia. 2012;2012:297641. http://dx.doi.org/10.1155/2012/297641

[k] European Medicines Agency 15 November 2012. Procedure No. EMEA/H/C/000670/II/0026. Committee for Medicinal Products for Human Use (CHMP) EMA/44672/2013. Available on request.

[l] Musallam KM, Angastiniotis M, Eleftheriou A, Porter JB. Cross-talk between available guidelines for the management of patients with beta-thalassemia major. Acta Haematologica. 2013;130(2):64-174. http://dx.doi.org/10.1159/000345734

[m] Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D, Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation. 2009 Nov 17;120(20):1961-8. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.874487 *This paper demonstrates how, by 2009, this approach was standard practice, and over 80% of UK patients had been monitored longitudinally by cardiac MRI.*