Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Targeting endothelin in systemic sclerosis – improved survival in pulmonary arterial hypertension (PAH) in systemic sclerosis and licensing of the first drug specifically for digital ulcers in systemic sclerosis

1. Summary of the impact

The research described below has made a major contribution to the clinical and preclinical development of endothelin receptor antagonists (ERAs) for the treatment of systemic sclerosis (SSc). As a result, ERAs are now standard management for pulmonary arterial hypertension related to connective tissue disease and specifically complicating SSc. This work has also led to the licensing of bosentan (one of the ERAs) for digital ulcer disease, a major non-lethal complication of SSc that impacts on quality of life, employment status and the major economic cost of SSc management. By 2012, more than 16,000 patients with SSc had been treated worldwide with these therapies, with numbers increasing every year.

2. Underpinning research

Research conducted by the Centre for Rheumatology & Connective Tissue Disease, UCL Division of Medicine, has underpinned the development of endothelin receptor antagonists (ERA) as treatment for systemic sclerosis (SSc). In 1993 we made the key observation that endothelin-1 (ET-1) in the plasma was increased in SSc. Over the following years we published a number of seminal papers in the field that delineated the association between ET-1 and vasculopathy and fibrosis in SSc **[1]**.

As a result of this early work, a number of studies took place in different centres, building on our original observations, and these led to licensing of the first ERA (bosentan) for pulmonary hypertension in connective tissue disease. This was founded upon the observation that pulmonary arterial hypertension (PAH) in SSc was very similar to idiopathic and familial forms of PAH and this led to the inclusion of PAH cases associated with connective tissue disease, especially SSc, in trials for licensing purposes. The first study, led from North America, looked at non-scleroderma associated PAH and was so successful that a further clinical trial – BREATHE-1 – was fast-tracked. UCL researchers played an instrumental role in this study. Leading on from this, we undertook a sub-group analysis of both trials, which showed that the scleroderma patients had responded as well as others to the treatments – an observation which provided an impetus to develop these therapies for scleroderma patients **[2]**. Following licensing of the drugs, we were the first to show that this treatment improved survival **[3]**.

The second phase of research in this area refined and extended our early work, demonstrating the class effect of several drugs, and defining the differences between them. Our patients with PAH have been enrolled into major studies of bosentan and other ERAs (e.g. ambrisentan, sitaxentan) and we have explored differences between these agents in ways that would not be possible in commercial trials. We have led the largest recent study of SSc-PAH that explored long-term benefit of bosentan on quality of life **[4]**. We defined mortality benefit of ERA therapy using data from our cohort and also developed new and better assessment for PAH including the first study of the biomarker NT-pro-BNP in PAH-SSc that included robust haemodynamics and longitudinal sampling **[5]**.

Our centre has led on research to extend the use of bosentan for digital ulcer disease, another complication of SSc for which there were previously no treatments available, or scientific rationale for treatments. Our observation that patients taking part in clinical trials seemed to have fewer digital ulcers led to a pivotal trial (RAPIDS-1) being set up, which we led **[6]**. Along with a further trial (RAPIDS-2), to which we made a significant contribution, this led to the licensing of bosentan for digital ulcers – the first ever drug for the condition, and in fact the first ever specific therapy for

SSc.

We have provided academic leadership to the Digital Ulcers Outcome (DUO) register of cases recruited across Europe with digital ulcer disease in SSc and this is providing a unique resource for academic study of this important complication that contributes major morbidity. A positive outcome of this work has been better care for digital ulcers in SSc and harmonisation of good practice across many major centres in Europe.

3. References to the research

[1] Abraham DJ, Vancheeswaran R, Dashwood MR, Rajkumar VS, Pantelides P, Xu SW, du Bois RM, Black CM. Increased levels of endothelin-1 and differential endothelin type A and B receptor expression in scleroderma-associated fibrotic lung disease. Am J Pathol. 1997 Sep;151(3):831-41. http://europepmc.org/abstract/MED/9284832

[2] Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Ann Rheum Dis. 2006 Oct;65(10):1336-40. http://dx.doi.org/10.1136/ard.2005.048967

[3] Williams MH, Das C, Handler CE, Akram MR, Davar J, Denton CP, Smith CJ, Black CM, Coghlan JG. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart. 2006 Jul;92(7):926-32. http://dx.doi.org/10.1136/hrt.2005.069484

[4] Denton CP, Pope JE, Peter HH, Gabrielli A, Boonstra A, van den Hoogen FH, Riemekasten G, De Vita S, Morganti A, Dölberg M, Berkani O, Guillevin L; TRacleer Use in PAH associated with Scleroderma and Connective Tissue Diseases (TRUST) Investigators. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheum Dis. 2008 Sep;67(9):1222-8. http://dx.doi.org/10.1136/ard.2007.079921

[5] Williams MH, Handler CE, Akram R, Smith CJ, Das C, Smee J, Nair D, Denton CP, Black CM, Coghlan JG. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J. 2006 Jun;27(12):1485-94. http://dx.doi.org/10.1093/eurheartj/ehi891

[6] Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, Rich E, Carpentier P, Molitor J, Seibold JR, Hsu V, Guillevin L, Chatterjee S, Peter HH, Coppock J, Herrick A, Merkel PA, Simms R, Denton CP, Furst D, Nguyen N, Gaitonde M, Black C. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004 Dec;50(12):3985-93. http://dx.doi.org/10.1002/art.20676

4. Details of the impact

Our ongoing programme of basic science, translational and clinical research has underpinned substantial advances in understanding vascular complications of SSc and has directly informed the development of new effective therapies. The best example for this is the targeting of endothelin receptors. ET-1 is a vasoconstrictor peptide implicated in SSc pathogenesis and ERAs have been developed that are now licensed therapies for PAH in SSc and also for digital ulcer disease. The latter represents the first ever SSc-specific licensing indication.

Use of ERAs for PAH in SSc

PAH is a complication that affects about 10% of SSc patients. As a result of the research described above, use of ERAs has become standard practice in the management of PAH related to connective tissue disease (specifically complicating SSc) **[a]**. Our work specifically defined tolerability and efficacy in SSc cases with PAH. The FDA and EMA approvals of Bosentan in 2002 were dependent on the BREATHE-1 study to which we contributed **[b, c]**. The use of Bosentan is now recommended in European guidelines **[d]** and our studies provided key evidence used in

guideline development.

Worldwide, many thousands of patients have now benefitted from treatment with bosentan for PAH. Actelion (the company that markets bosentan) reported that in one year alone (2012) 44,000 patients were currently receiving the therapy. It is estimated that around a quarter of PAH patients have connective tissue disease (see Badesch et al. 2010), so we can assume that around 11,000 of these treatments were for SSc patients **[e]**.

Endothelin antagonism with bosentan in SSc patients with PAH reduces death rate by 30%. Thus the average survival for pulmonary arterial hypertension in SSc has improved from less than two years to more than five years from diagnosis **[f]**. This can be estimated to have saved around 30 lives a year in our cohort of SSc cases and perhaps 150 lives per year in the UK **[g]**. Furthermore, there is an important benefit in terms of quality of life and symptom burden as most patients with PAH treatment improve their functional class to grade II, representing minor breathlessness that allows them to participate in normal activities. This benefit was demonstrated by the improvement in the heath transition domain of the SF-36 heath status measure in the TRUST clinical trial that our centre led **[see reference 4 above]**. This has been possible due to the pivotal work that our centre undertook in defining a role for ET-1 in pathogenesis and also in defining benefit in terms of mortality and efficacy of ERA.

Licensing of bosentan for digital ulcer disease

Digital ulcers are a significant complication of SSc. They are painful, and may take between three and 15 months to heal. Secondary infections may occur in 50% of cases, and recurring ulcers can be a major source of disability, interfering with the patient's daily activities and capacity to work. Digital ulcers can also lead to the chronic use of analgesics and antibiotics, and sometimes to hospitalisation and surgery (including digital amputation) **[h]**. In May 2007, Bosentan was licensed by the European Medicines Agency (EMA) as a preventative treatment to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. As well as the research provided above, Black and Denton made the presentation to the EMA on the clinical impact of digital ulcer disease that underpinned the approval **[i]**.

Our work defined the patients most likely to benefit from this high cost therapy, in order to facilitate targeting of appropriate cases where clinical impact and economic considerations are favourable. This treatment is now recommended in consensus guidelines issued by the UK Scleroderma working group **[j]**.

European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research Group (EUSTAR) recommend: "*Bosentan has confirmed efficacy in two high-quality randomised controlled trials to prevent digital ulcers in diffuse systemic sclerosis patients, in particular those with multiple digital ulcers. Bosentan should be considered in diffuse systemic sclerosis with multiple digital ulcers after failure of calcium antagonists and, usually, prostanoid therapy*" **[d]**. In 2012, Actelion (manufacturers of Bosentan) reported that over 5,000 DU patients were currently on this therapy **[k]**.

Trial results showed that the use of bosentan for digital ulcers reduced the incidence in SSc patients by 50% **[l]**. A 50% reduction in new digital ulcer formation is a tangible impact on a non-lethal burden of SSc that affects up to 50% of cases. It has been shown in recent work from the DUO register that ulcer number correlates with inability to undertake employed work and also the need for paid help, specifically that having more than two digital ulcers is associated with reduced work participation **[m]**.

Reduction in need for hospital admission for intravenous prostcyclin has been a specific benefit of the availability of oral therapies for severe digital ulcers in SSc. This is exemplified by the approved algorithm for ulcer use that defines the need for three or more annual admissions for inpatient treatment as a threshold for funding application for ERA. This is based upon predicted per patient annual saving of around £3,600. Thus, with around 30 cases per year in our centre fulfilling this

standard, that has now been adopted by UK Scleroderma Study Group (chaired by Denton) as part of their "best practice recommendations" in 2012, would save the NHS in our hospital an estimated £100,000 and nationally a predicted £500,000 per year.

5. Sources to corroborate the impact

[a] Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol. 2009 Jun 30;54(1 Suppl):S78-84. http://dx.doi.org/10.1016/j.jacc.2009.04.017.

[b] FDA approval: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-290_Tracleer.cfm (see approval letters - 2nd page of PDF document)

[c] EMA approval: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000401/human_med_001100.jsp&mid=WC0b01ac058001d124

[d] Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, Clements P, Denton C, Farge D, Fligelstone K, Földvari I, Furst DE, Müller-Ladner U, Seibold J, Silver RM, Takehara K, Toth BG, Tyndall A, Valentini G, van den Hoogen F, Wigley F, Zulian F, Matucci-Cerinic M; EUSTAR Co-Authors. **EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR)**. Ann Rheum Dis. 2009 May;68(5):620-8. http://dx.doi.org/10.1136/ard.2008.096677

[e] Actelion annual report 2012 states that 44,000 patients on Tracleer (bosentan) at that time (all PAH) http://annualreport2012.actelion.com/en/ar2012/business-strategy-and-operations/our-products.html US registry study reports that 25% of patients with PAH associated with connective tissue diseases: Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD.Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010 Feb;137(2):376-87. http://dx.doi.org/10.1378/chest.09-1140

[f] Galia N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J. 2009 Feb;30(4):394-403. http://dx.doi.org/10.1093/eurheartj/ehp022

[g] Patient data used to make calculation available from UK National PH audit online at http://www.hscic.gov.uk/ph

[h] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000401/WC500041601.pdf See page 3

[i] http://www.medicines.org.uk/emc/medicine/20423/SPC/Tracleer+%28bosentan%29+125mg+film-coated+tablets See section 5.1

[j] http://www.rheumatology.org.uk/includes/documents/cm_docs/2012/0/0945_complications_of_scleroderma_vasculopathy_raynauds_phenomenon_digital_ulcers_and_critical_digital.pdf

[k] Actelion 2012 annual report: http://annualreport2012.actelion.com/en/ar2012/business-strategy-and-operations/our-products.html

[l] Dhillon S. Bosentan: a review of its use in the management of digital ulcers associated with systemic sclerosis. Drugs. 2009 Oct 1;69(14):2005-24. http://doi.org/bv65w3

[m] Guillevin L, Hunsche E, Denton CP, Krieg T, Schwierin B, Rosenberg D, Matucci-Cerinic M; DUO Registry Group. Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry. Clin Exp Rheumatol. 2013 Mar-Apr;31(2 Suppl 76):71-80. http://www.clinexprheumatol.org/pubmed/find-pii.asp?pii=23910613