**Institution:** King's College London

**Unit of Assessment:** 1- Clinical Medicine

**Title of case study:** Better treatment of anaemia and improved quality of life in patients with chronic kidney disease

## 1. Summary of the impact

King's College London (KCL) research has made a major contribution to improving the quality of life for patients who have anaemia linked with chronic kidney disease. Studies undertaken by KCL researchers established that intravenous iron supplementation was required in anaemic patients with advanced kidney disease, in whom oral iron therapy was ineffective, and defined the best regimes for administration of intravenous iron. Subsequent KCL work on drugs that stimulate production of red blood cells (erythropoiesis) defined the target levels of haemoglobin to aim for in chronic kidney disease patients. Most recently, KCL researchers made the key discovery that the novel drug peginesatide for the first time enables the rescue of patients who develop a rare and potentially fatal reaction against erythropoietin (which is the commonest treatment for anaemia in chronic kidney disease). These KCL research studies have had a significant impact by making a major contribution to national and international clinical guidelines, including UK NICE guidelines and the 2012 National Kidney Foundation KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease.

## 2. Underpinning research

**Anaemia in chronic kidney disease:** Chronic kidney disease is invariably accompanied by anaemia, as the kidneys are the source of erythropoietin, which stimulates red blood cell production in the bone marrow. Anaemia increases breathlessness and tiredness in these patients, increases their risk of infections and heart disease, and substantially worsens quality of life. It is therefore crucial to develop effective treatments to deal with this problem.

**KCL research to improve treatment of anaemia in chronic kidney disease:** The KCL team led by Professor Iain Macdougall has consistently tackled this problem over the last 20 years through multiple clinical trials and other studies to find the best way to treat anaemia. The overall focus of KCL research has been to define the best mode of iron supplementation and to use novel drugs (eythropoietin-stimulating agents) to stimulate red blood cell formation. An additional major achievement is research showing the effectiveness of the drug peginesatide to treat pure red cell aplasia, a rare and potentially fatal reaction that can develop to erythropoietin.

**Clinical trials establishing role of intravenous iron therapy:** A randomised controlled trial led by the KCL group provided evidence that iron taken orally is not effective in advanced chronic kidney disease, and that intravenous iron supplementation is required in this patient group (1). All the main anaemia guidelines refer to this seminal research. The safety of administering intravenous iron sucrose as a 2-minute push was also investigated in a subsequent study (2), and this practice has since been adopted in numerous kidney units worldwide. In addition, the largest study ever conducted in this field has established that the use of ferric carboxymaltose, a specific type of iron sucrose, reduces the need for erythropoiesis-stimulating agents or blood transfusion in patients who have chronic kidney disease that does not require dialysis and who suffer from iron deficiency anaemia (3). This study was conceived, designed and led by Professor Macdougall.

**Clinical trials studying target haemoglobin level:** It has been unclear how high a haemoglobin level should be aimed for in chronic kidney patients being treated for anaemia. KCL researchers contributed to several large randomised controlled trials showing that normalising the haemoglobin concentration in patients with chronic kidney disease potentially causes harm. Perhaps the most important study was the CREATE study published in the *New England Journal of Medicine* (4), for which Professor Macdougall was on the steering committee and involved in the design and running of the study. KCL researchers also contributed to a large Europe-wide study on the relation between variability in haemoglobin concentration and patient deaths (5), which showed that mortality is not predicted by modest fluctuations in haemoglobin levels. These studies have significantly influenced clinical guidelines for target haemoglobin levels in patients with chronic kidney disease.

**Comparing alternative epoietins:** KCL researchers have studied new epoietin drugs which mimic natural erythropoietin. Professor Macdougall was on the steering committee and was involved in the design, conduct and publication of the PATRONUS study, a large European multicentre randomised controlled trial that examined the efficiency of two such drugs in controlling anaemia if given at extended intervals compared to previous practice. This study showed that pegylated epoetin beta was more effective than darbepoetin alfa (6). This evidence contributes to better anaemia management and improved convenience for patients and is incorporated into clinical guidelines.

Pentoxifylline, which reduces blood viscosity and hence improves blood flow, was shown by the KCL group to affect the haemoglobin response in dialysis patients who did not respond to erythropoietin, and also to reduce inflammatory response (7). This finding became the basis for a large Australasian Kidney Network-funded study called the HERO trial, which is a randomised double-blind placebo-controlled study currently being conducted in centres throughout Australia (8).

**Pure red cell aplasia:** The rare condition of pure red cell aplasia is caused when the body generates antibodies when treated with erythropoietin. This is life-threatening, because the antibodies neutralise the erythropoietin being given to correct the anaemia. This worsens the impact of the lack of natural erythropoietin and frequent red cell transfusions are needed. KCL researchers initially collaborated with European investigators to identify the incidence and course of this serious complication and the response to therapies such as immunosuppression and kidney transplantation (9).

Subsequent KCL-led research studied the use of a novel peptide-based erythropoietin-receptor agonist, peginesatide, for the treatment of anaemia in chronic kidney disease patients who had developed pure red-cell aplasia due to antierythropoietin antibodies. In a key paper published in the *New England Journal of Medicine* (10), it was shown that peginesatide could mimic the effects of erythropoietin without the immunological reaction that some patients suffered in response to erythropoietin. Patients who developed pure red cell aplasia caused by antibodies against erythropoietin treatment could therefore be rescued with peginesatide therapy (10). As a result of this work, peginesatide was licensed for the treatment of red cell aplasia.

Additional large studies were also undertaken to assess the general use of peginesatide in chronic kidney disease patients with anaemia (i.e. those without red cell aplasia) and showed it to be effective in this setting (11,12).

## 3. References to the research

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epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial. *Nephrol Dial Transplant.* 2010;25:4009–17.

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8. Johnson DW, Hawley CM, Rosser B et al. Oxpentifylline versus placebo in the treatment of erythropoietin-resistant anaemia: a randomized controlled trial. *BMC Nephrol.* 2008;9:8

9. Verhelst D, Rossert J, Casadevall N, Krüger A, Eckardt KU, **Macdougall IC.** Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet.* 2004;363:1768–71.

10. **Macdougall IC,** Rossert J, Casadevall N, Stead RB, Duliege AM, Froissart M, Eckardt KU. A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med.* 2009;361:1848–55.

11. **Macdougall IC,** Provenzano R, Sharma A, Spinowitz BS, Schmidt RJ, Pergola PE, Zabaneh RI, Tong-Starksen S, Mayo MR, Tang H, Polu KR, Duliege AM, Fishbane S; PEARL Study Groups. Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis. *N Engl J Med.* 2013;368:320–32.

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**4. Details of the impact**

**Marked improvement in the management of anaemia in chronic kidney disease:** The research described above has significantly improved the management of anaemia in patients with chronic kidney disease worldwide, through its contribution to national and international guidelines.

**Contribution to UK NICE guidelines**: The 2011 clinical guidelines "CG114: Anaemia management in people with chronic kidney disease" (13) published by the UK National Institute for Health and Care Excellence (NICE) extensively incorporates the findings of KCL researchers. Seven pieces of original KCL research contribute to the guidelines, including the work on management of iron therapy and the use of a 2-minute push of intravenous iron sucrose (1,2), target haemoglobin levels in patients on erythropoietin therapy (4) and treatment of pure red cell aplasia (9).

**Global impact:** International clinical practice guidelines have also assimilated the scientific evidence base for the management of renal anaemia. The latest of these is the global KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (August 2012) (14). These guidelines extensively incorporate the findings of KCL researchers, which contributed 6 pieces of original research to the references cited in the guideline. These include the work on management of iron therapy (1,2), the work addressing normalisation of haemoglobin levels with erythropoietic therapy (4), work on the relevance of haemoglobin variability (5), research comparing pegylated epoetin with darbepoetin alfa (6), and studies on the management of antibody-mediated pure red cell aplasia (9).

**Iron supplementation:** Iron supplementation is important in the management of anaemia, but giving iron by oral tablet is ineffective in dialysis patients. Professor Macdougall's randomised controlled trial published in 1996 (1) was one of the first to show that oral iron was ineffective in these patients. These patients benefit from intravenous iron which corrects the iron deficiency and vastly improves patients' quality of life. The practice of administering intravenous iron sucrose (2) has been adopted in numerous kidney units worldwide. The recommendations within the KDIGO Anemia guideline (14 - Chapter 2) reinforce the benefit of this practice as evidenced by the KCL research and the international standing of the guideline ensures its impact worldwide. This relatively simple yet highly

effective intervention has had a major impact on patients' quality of life.

**Target haemoglobin level:** Although early studies suggested that variability in haemoglobin level might be harmful, other studies, including KCL research (4,5) suggested that this had little impact. The CREATE study (4) provided especially strong data for the evidence base supporting the inadvisability of aiming for haemoglobin concentrations above 13 g/dl in kidney patients. The KDIGO Anemia guideline states "In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). Evidence level 1A (ref 14 - Chapter 3). These quote extensively from the CREATE study.

**Comparing alternative epoietins:** Since recombinant human erythropoietin has become available, two longer-acting erythropoietin analogues – darbepoetin alfa and pegylated epoetin beta – have been investigated. International research to which KCL made a major contribution has shown that when used once-monthly, pegylated epoetin beta is superior to darbepoetin alfa (6). The practical benefit to patients is in the reduced frequency of injections that is now possible and this is also incorporated in the KDIGO Anemia guideline (ref 14 - Chapter 3).

**Pure red cell aplasia:** The finding that the severe condition of antibody-mediated pure red cell aplasia was transformed by peginesatide (10) opened a unique treatment option for patients who had developed antibodies against the conventional treatment, erythropoietin. It could therefore be used to rescue patients who had developed this condition. Before the peginesatide rescue study, there was uncertainty over the treatment of these patients. The KCL-led research on peginesatide forms the basis for the KDIGO global anemia guideline recommendation to consider peginesatide as the potential treatment of choice for pure red cell aplasia in patients with chronic kidney disease (ref 14 - Chapter 3).

The results of the studies that assessed the general use of peginesatide in chronic kidney disease patients with anaemia (i.e. those without red cell aplasia) (11,12) led to initial marketing authorisation for general use of this drug by the FDA in the USA (15). However, it has subsequently been withdrawn for this indication by the manufacturers because of cases of severe allergic reaction (16).

**5. Sources to corroborate the impact**

13. NICE Guideline 2011. CG114: Anaemia management in people with chronic kidney disease. http://guidance.nice.org.uk/CG114/Guidance/pdf/English

14. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int. Suppl.* 2012;2:279–335. http://www.kdigo.org/clinical_practice_guidelines/anemia.php.

Chapter 2: Use of iron to treat anemia in CKD references.
Recommendations on "Treatment with Iron agents" cite references 1 and 2.
Recommendations on "Cautions regarding Iron therapy" cite reference 2.

Chapter 3: Use of ESAs and other agents* to treat anemia in CKD.
Recommendations on "In initiating and maintaining ESA therapy..." and on "ESA Maintenance Therapy" extensively cite ref 4. Recommendations on "ESA Dosing" cite ref 5. Recommendations on "Type of ESA" cite ref 6. Recommendation on "Pure red cell aplasia" cite references 9 and 10.

15. FDA press release March 27, 2012.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm297464.htm

16. FDA press release February 23, 2013.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm340895.htm