Erythropoiesis-stimulating agents in kidney and cardiac disease

For the last 20 years, erythropoiesis-stimulating agents have transformed the lives of renal dialysis patients, and they are now being used to correct anaemia in chronic kidney disease and after renal transplantation. In future, these drugs may be used outside the renal clinic to improve outcomes in patients with chronic heart failure.

After dialysis and transplantation, treatment of anaemia with erythropoiesis-stimulating agents (ESAs) is the next great success story in the treatment of end-stage renal disease (ESRD). Since the introduction of the first formulation in the late 1980s, ESAs – commonly referred to as erythropoietin or EPO – have transformed the lives of dialysis patients. Nephrologists are now using ESAs to correct anaemia in renal transplant patients, while UK guidelines have recognized the benefits of introducing ESAs before the need for renal replacement therapy in patients with chronic kidney disease (Renal Association/Royal College of Physicians, 2005). This expanding role for ESAs has been largely driven by accumulating evidence of the interaction between anaemia, chronic kidney disease and cardiovascular risk, and in future these drugs may also be used to improve outcomes in patients with chronic heart failure.

Erythropoiesis-stimulating agents

Endogenous human erythropoietin is a glycoprotein hormone that regulates the production of erythrocytes by interacting with the erythropoietin receptor on erythroid progenitor cells in the bone marrow. Erythropoietin is produced primarily in the kidney in response to changes in tissue oxygenation and, because currently available dialysis technologies cannot restore normal kidney function, erythropoietin deficiency is the primary cause of anaemia in patients with chronic renal failure, although other potential causes should be excluded during diagnostic work-up (Locatelli et al, 2004). Anaemia was recognized as an important complication of ESRD after the introduction of dialysis in the 1960s. Even with the implementation of strategies such as optimal dialysis, minimization of blood loss, and supplementation with iron, folic acid or androgens, haemoglobin (Hb) in dialysis patients of that time averaged about 8 g/dl and approximately 10% of patients were dependent on regular blood transfusions (Winerls, 1995).

Advances in molecular biology enabled the production of recombinant erythropoietin in the 1980s, and three ESAs are now available in the UK (*Table 1*). Early clinical trials demonstrated that ESA treatment is highly effective, correcting anaemia in 90–95% of patients (Eschbach et al, 1989; Canadian Erythropoietin Study Group, 1990). Current clinical guidelines do not, however, recommend normalization of Hb in renal patients treated with ESAs (*Table 2*). This follows a prospective study comparing the results of partial anaemia correction (~11 g/dl) and normalization of Hb (≥13 g/dl) in haemodialysis patients, which was ended prematurely because of a trend towards higher mortality in the normalization group (Besarab et al, 1998). These investigators recruited patients with severe chronic heart failure and/or angina,

Table 1. Erythropoiesis-stimulating agents available in the UK

Product name (brand)	Description	Summary of licensed UK indications
Epoetin alfa (Eprex)	Recombinant human erythropoietin	Anaemia associated with chronic renal failure in paediatric and adult dialysis patients. Renal anaemia accompanied by clinical symptoms in adults with renal insufficiency not yet undergoing dialysis. Anaemia and reduction of transfusion requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion. Increase yield of autologous blood in patients with moderate anaemia in predonation programme. Before orthopaedic surgery reduce exposure to allogeneic blood transfusion in adult non-iron deficient patients at high risk of transfusion complications
Epoetin beta (NeoRecormon)	Recombinant human erythropoietin	Anaemia associated with chronic renal failure in dialysis patients. Symptomatic renal anaemia in patients not yet undergoing dialysis. Treatment of anaemia in adults with solid tumours and treated with platinum-based chemotherapy. Anaemia in adults with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia. Increasing yield of autologous blood in predonation programme
Darbepoetin alfa (Aranesp)	Hyperglycosylated derivative of epoetin	Anaemia associated with chronic renal failure in adults and children aged ≥ 11 years. Treatment of anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy

From Electronic Medicines Compendium (emc.medicines.org.uk) (accessed 15 July 2006)

Dr Richard Fluck *is Consultant Nephrologist in the Department of Renal Medicine, Derby City General Hospital, Derby DE22 3NE*

and other studies have indicated that the results may not be applicable to patients without severe cardiovascular disease (Furuland et al, 2003). Optimal Hb targets remain controversial and randomized controlled studies are needed to investigate the effects of normalization of Hb on outcome in subgroups of renal patients.

The most obvious benefits of anaemia correction with ESAs are avoidance of blood transfusions (Eschbach et al, 1989) and improvement in patients' quality of life (Evans et al, 1990), but studies have also demonstrated positive effects on dialysis patients' exercise capacity (Barany et al, 1993), improved cardiac function and regression of left ventricular hypertrophy (Low-Friedrich et al, 1991; Pascual et al, 1991). Subsequent studies have also shown a positive correlation between survival and increased Hb concentration in dialysis patients treated with ESAs (Ma et al, 1999; Mocks, 2000).

Anaemia and cardiovascular disease

Patients on dialysis have an excess of morbidity and mortality. Even after stratification for age, gender, race and the presence of diabetes, the risk of death in dialysis patients is 10–20 times higher than in the general population (Foley et al, 1998). Much of this is related to cardiovascular disease but in addition to standard risk factors in the dialysis population, significant anaemia is an important risk. The overall risk develops before the need for renal replacement therapy, since it is estimated that coronary artery disease is present in 40%, left ventricular hypertrophy in 75% and chronic heart failure in 40% of prevalent dialysis patients (Foley et al, 1998). Excess cardiovascular risk becomes apparent when the glomerular filtration rate (GFR) falls below 60 ml/min (Sarnak et al, 2003) and Hb levels fall linearly with GFR (Hsu et al, 2002). Anaemia induces left ventricular hypertrophy and limits oxygen delivery (Levin, 2002), and is associated with increased cardiovascular risk in all patients with progressive kidney disease, including dialysis patients, people with chronic kidney disease and renal transplant recipients with impaired graft function (Foley et al, 1998; Vanrenterghem, 2003).

Table 2. Current recommendations on anaemia correction in renal patients

UK recommendations	Chronic renal failure patients should achieve Hb of 10 g/dl within 6 months of being seen by a nephrologist unless there is a specific reason
	It is unclear as yet how ESAs should be used optimally in patients before dialysis becomes necessary and whether normalization of Hb gives further benefit
	Evaluate anaemia in chronic renal failure when Hb <12 g/dl (adults males and postmenopausal females)/11 g/dl (premenopausal females)
	Anaemia may be considered the result of uraemia if GFR is <30 ml/min (<45 ml/min in diabetics) and no other cause (e.g. blood loss, folate or vitamin B_{12} deficiency) is identified
European recommendations	Patients with chronic kidney disease should in general maintain a target Hb of >11 g/dl or reach this target within 4 months of starting treatment, regardless of age, gender or ethnicity
	Exact target Hb concentrations >11 g/dl should be defined for individual patients, taking into account gender, age, ethnicity, activity and comorbid conditions. In haemodialysis patients, pre-dialysis Hb >14 g/dl is not desirable because of the risks associated with post-dialysis haemoconcentration
	Hb concentrations >12 g/dl are not recommended for patients with severe cardiovascular disease unless continuing severe symptoms dictate otherwise
	Unit data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to >12 g/dl in patients with diabetes especially with concurrent peripheral vascular disease
	Patients with chronic hypoxaemic pulmonary disease may benefit from a higher Hb target

ESAs = erythropoiesis-stimulating agents; GFR = glomerular filtration rate; Hb = haemoglobin. From Locatelli et al (2004); Renal Association/Royal College of Physicians (2005)

Chronic kidney disease

ESAs are now being used to correct anaemia in people with chronic kidney disease who do not yet need dialysis (pre-dialysis patients) and in renal transplant recipients, because of the association between renal dysfunction, anaemia and increased cardiovascular risk. In chronic kidney disease patients there is no evidence that treatment of anaemia accelerates the progression of renal failure or has a deleterious effect on blood pressure; indeed, some studies have indicated that EPO may slow disease progression (Jungers et al, 2001). There is also prospective epidemiological evidence that earlier correction of anaemia reduces the risk of mortality during the first year on dialysis (Xue et al, 2002). While UK guidelines acknowledge the importance of anaemia correction in people with chronic kidney disease (Renal Association/Royal College of Physicians, 2005), there are no formal recommendations in the UK concerning anaemia targets in renal transplant recipients; in the absence of randomized studies it is reasonable to follow guidelines for other renal patients with anaemia.

At present 43% of patients in the UK start dialysis with Hb below the Renal Association target of 10 g/dl (Ansell et al, 2003). Anaemia is unavoidable when patients present as emergencies, but a UK study suggests that earlier referral might be possible in half of the 30–50% of chronic kidney disease patients in the UK who start renal replacement therapy within a few months of referral (John et al, 2004). While a minority of patients with chronic kidney disease go on to need dialysis or transplantation, earlier recognition of renal dysfunction would allow the possibility of initiating measures to slow or halt disease progression and to reduce their risk of cardiovascular disease.

Inadequate screening of at-risk groups and failure to recognize the possible implications of an abnormal serum creatinine have been important barriers against timely referral. Current evidence does not support

population screening, and UK chronic kidney disease guidelines recommend surveillance of at-risk groups using urinalysis and a formula-based estimation of GFR (eGFR) based on serum creatinine concentration, age, sex and, in African-Caribbean people only, ethnic origin (Renal Association/Royal College of Physicians, 2005). eGFR is a linear variable, akin to percentage kidney function, and is a more accurate assessment of renal function than creatinine alone since the latter varies according to age, body mass and ethnic origin. Much of this surveillance will fall to GPs – especially as chronic kidney disease is now included in the Quality and Outcomes Framework (QoF) of the General Medical Services contract – but secondary-care clinicians should also be aware of the possibility and adverse consequences of renal impairment in the patient groups listed in *Table 3*.

Since an estimated 6% of adults may be in stages 1–2 and a further 4% may be in stage 3 chronic kidney disease (Coresh et al, 2003) (*Table 4*), it is impossible for nephrologists to manage every patient with renal impairment. Identification and management of most patients in stages 1–3 is best performed in primary care, especially as much of the QoF is specifically designed to optimize management of cardiovascular risk factors. Care pathways for diabetes, coronary heart disease and chronic kidney disease share common features and require integration. The National Service Framework for Renal Services advises that primary care trusts and renal networks should collaborate to set local priorities and actions based on the quality requirements and markers of good practice in the document (Department of Health, 2005). This process is clearly a priority and must include the formulation of referral guidelines, which should apply across primary and secondary care to reduce the risk of inappropriate referral, but also offer optimal treatment to patients with chronic kidney disease.

Diabetes

Use of eGFR to assess renal function will undoubtedly identify more chronic kidney disease patients who might benefit from treatment with ESAs. A high proportion will have diabetic nephropathy since this is now the primary cause of ESRD in the UK and other industrialized countries (Ansell et al, 2003). The cardiovascular risks seen in non-diabetic ESRD patients are even greater in diabetic patients, who are more likely to have clinically defined ischaemic heart disease, chronic heart failure and left ventricular hypertrophy at the start of dialysis (Foley et al, 1997).

Diabetic chronic kidney disease patients require intensive management of cardiovascular risk factors, including classical risk factors such as hyperglycaemia, dyslipidaemia, hypertension, smoking cessation and central obesity, and novel risk factors such as anaemia. It is possible to overlook the presence of anaemia in diabetes patients since this complication develops early in diabetic nephropathy (Bosman et al, 2001), and Hb levels should be monitored regularly, especially in patients with proteinuria. Treatment with ESAs appears to help to delay the need for dialysis and improve survival after the start of renal replacement therapy in diabetic patients (Fink et al, 2001; Jungers et al, 2001), although concerns about high blood and plasma viscosity associated with diabetes have led current guidelines to advise that Hb concentrations should be raised slowly to levels no higher than 12 g/dl (Locatelli et al, 2004).

Chronic heart failure

Anaemia is also common in chronic heart failure, where it is associated with increased disease severity and poor outcomes including high rates of hospitalization and mortality. In one study, for every 1 g/dl reduction in Hb concentration, the risk of death rose by ≈16% and the risk of mortality or hospitalization by 14.2%. This association between a higher risk of morbidity and mortality

Table 3. UK chronic kidney disease guidelines: recommendation for assessment of renal function

Serum creatinine concentration should be measured, allowing concentration of estimated GFR at initial assessment and then at least annually in all adult patients with:	
Previously diagnosed chronic kidney disease including	Polycystic kidney disease
	Reflux nephropathy
	Biopsy proven chronic glomerulonephritis
	Persistent proteinuria
	Urologically unexplained persistent haematuria
Conditions associated with a high risk of obstructive nephropathy including	Known or suspected bladder outflow obstruction
	Neurogenic bladder caused by spina bifida or spinal cord injury
	Urinary diversion surgery
	Urinary stone disease
Conditions known to be associated with a high risk of developing silent chronic kidney disease including	Hypertension
	Diabetes
	Heart failure
	Atherosclerotic coronary, cerebral or peripheral vascular disease
Conditions requiring long-term treatment with potentially nephrotoxic drugs including	ACE inhibitors and angiotensin receptor blockers
	Non-steroidal anti-inflammatory drugs
	Lithium carbonate
	Mesalazine and other 5-aminosalicylic acid drugs
	Calcineurin inhibitors (cyclosporin, tacrolimus)
Multisystem diseases that may involve the kidney including	Systemic lupus erythematosus
	Vasculitis
	Myeloma
	Rheumatoid arthritis
A first-degree relative with stage 5 chronic kidney disease (*Table 4*)	

ACE = angiotensin-converting enzyme; GFR = glomerular filtration rate.
From Renal Association/Royal College of Physicians (2005)

Table 4. Classification of chronic kidney disease*

Stage	GFR (ml/min)	Description	Prevalence
1	≥ 90	Normal or ↑ GFR, with other evidence of kidney damage*	3.3%
2	60–89	Slight ↓ GFR, with other evidence of kidney damage†	3.0%
3	30–59	Moderate ↓ in GFR, with or without other evidence of kidney damage	4.3%
4	15–29	Severe ↓ in GFR, with or without other evidence of kidney damage	0.2%
5	<15	Established renal failure	0.2%

*Defined as either kidney damage or GFR < 60 ml/min for > 3 months; †Demonstrated by abnormal urinalysis or renal imaging. GFR = glomerular filtration rate. From Coresh et al (2003); Department of Health (2005)

and lower Hb concentrations was independent of New York Heart Association functional classification (Anand et al, 2004).

In randomized studies (n = 32; n = 26), correction of anaemia with ESAs reduced chronic heart failure symptoms and hospitalization, and improved exercise capacity and quality of life (Silverberg et al, 2001; Mancini et al, 2003). Anaemia correction has not yet been shown to improve survival in chronic heart failure , although this may be demonstrated by larger outcome studies. Other outstanding issues include the optimal Hb target in chronic heart failure patients, and the importance of individualizing the management of anaemia in chronic heart failure. There are many potential underlying causes of anaemia in chronic heart failure, including the anaemia of chronic disease, renal impairment, haematinic deficiencies, haemodilution, and medications such as aspirin, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) that are commonly used to treat chronic heart failure.

However, a survey of Scottish chronic heart failure patients with anaemia found that most had anaemia of chronic disease and would benefit from treatment with ESAs (Crombie et al, 2002). The cost of such treatment could be significant although it would depend on the dosage of ESA needed in chronic heart failure patients.

KEY POINTS

- Anaemia is a complication of several chronic diseases including progressive renal failure and chronic heart failure.
- Anaemia reduces renal patients' quality of life and is associated with poor outcomes.
- Correction of anaemia with erythropoiesis-stimulating agents substantially reduces the need for blood transfusion and improves haemoglobin in most renal patients.
- Anaemia correction with erythropoiesis-stimulating agents also improves renal patients' wellbeing and is associated with improved outcomes.
- In future, erythropoiesis-stimulating agents may be included in a treatment regimen designed to optimize outcomes in chronic heart failure.

However, despite optimal use of conventional medical therapy, many patients with chronic heart failure remain symptomatic and generally their outlook is poor, with a worse 5-year survival than many common malignancies (Stewart et al, 2001). ESAs would be an especially attractive addition to the treatment of appropriate chronic heart failure patients if they could reduce the risk of hospitalization, which accounts for most of the costs associated with the condition.

Regular blood transfusion is an alternative to ESAs, but this is also costly (estimated at £635 per adult red cell transfusion in 2000–2001) (Varney and Guest, 2003). In addition, transfusion is associated with risks such as infection, graft *vs* host disease and transfusion error, and does not result in long-term improvement in Hb – all important considerations especially in an environment of declining blood donations and a potential risk of shortages (Chief Medical Officer, 2003).

Conclusions

Since their introduction over 20 years ago, ESAs have improved quality of life and have been associated with reduced cardiovascular risk in renal dialysis patients. UK guidelines are likely to accelerate the existing trend to use ESAs to correct anaemia in people with chronic kidney disease as well as in transplant recipients. While large randomized studies are needed to define their role, ESAs may also in future help to reduce the high rates of morbidity and mortality still seen in patients with chronic heart failure. BJHM

Conflict of interest: Dr Fluck has received funding for educational meetings, lecturers and has provided consultancy work for AMGEN, Roche, Ortho Biotec, Baxter and Gambro Hospital.

Anand I, McMurray JJ, Whitmore J et al (2004) Anemia and its relationship to clinical outcomes in heart failure. *Circulation* **110:** 149–54

Ansell D, Feest T, Byrne C, Ahmad A (2003) *The Sixth Annual Report.* The Renal Association. UK Renal Registry, Bristol (www.renalreg.com, accessed 31 March 2006)

Barany P, Freyschuss U, Pettersson E, Bergstrom J (1993) Treatment of anaemia in haemodialysis patients with erythropoietin: long-term effects on exercise capacity. *Clin Sci (Lond)* **84:** 441–7

Besarab A, Bolton WK, Browne JK et al (1998) The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* **339:** 584–90

Bosman DR, Winker AS, Marsden JT, Macdougall IC, Watkins PJ (2001) Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care* **24:** 495–9

Canadian Erythropoietin Study Group (1990) Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *BMJ* **300:** 573–8

Chief Medical Officer (2003) *Health check on the state of the public health.* Annual report of the Chief Medical Officer. Department of Health, London

Coresh J, Astor BC, Green T, Eknoyan G, Levey AS (2003) Prevalence of chronic kidney disease and decreased kidney functions in the adult US population. Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* **41:** 1–12

Crombie N, Lee C, Struthers AD (2002) Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes? *Heart* **87:** 377–8

Department of Health (2005) *National Service Framework for Renal Services – Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care.* Department of Health, London

Eschbach JW, Abdulhadi MH, Browne JK et al (1989) Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. *Ann Intern Med* **111:** 992–1000

Evans RW, Rader B, Mannien DL, the cooperative Multicenter EPO Clinical Trial Group (1990) The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. *JAMA* **263:** 825–30

Fink JC, Blahut S, Reddy M, Light P (2001) Use of erythropoietin before initiation of dialysis and its impact on mortality. *Am J Kidney Dis* **37:** 348–55

Foley RN, Culleton BF, Parfrey PS et al (1997) Cardiac disease in diabetic end-stage renal disease. *Diabetologia* **40:** 1307–12

Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kid Dis* **32**(Suppl 3): S112–19

Furuland H, Linde T, Ahlmen J et al (2003) A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* **18:** 353–61

Hsu C-Y, McCulloch CE, Curham GC (2002) Epidemiology of anemia associated with chronic renal insufficient among adults in the United states: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* **13:** 504–10

John R, Webb M, Young A, Stevens PE (2004) Unreferred chronic kidney disease: a longitudinal study. *Am J Kid Dis* **43:** 825–35

Jungers P, Choukroun G, Oualim Z, Robino C, Nguyen AT, Man NK (2001) Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol Dial Transplant* **16:** 307–12

Levin A (2002) The role of anaemia in the genesis of cardiac abnormalities in patients with chronic kidney disease. *Nephrol Dial Transplant* **17:** 207–10

Locatelli F, Aljama P, Barany P et al (2004) Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* **19**(Suppl 2): ii1–47

Low-Friedrich I, Gruzmacher PO, Marz W, Bermann M, Schoeppe W (1991) Therapy with recombinant human erythropoietin reduces cardiac size and improves heart function in chronic hemodialysis patients. *Am J Nephrol* **11:** 54–60

Ma JZ, Ebben J, Xia H, Collins AJ (1999) Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* **10:** 610–19

Mancini DM, Katz SD, Lang CC et al (2003) Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* **107:** 294–9

Mocks J (2000) Cardiovascular mortality in haemodialysis patients treated with epoetin beta—a retrospective study. *Nephron* **86:** 455–62

Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M, Ortuno J (1991) Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol* **35:** 280–7

Renal Assocation/Royal College of Physicians (2005) Chronic kidney disease in adults: UK guidelines for identification, management and referral. The Renal Association, London (http://www.renal.org/CKDguide/ckd.html, accessed 31 March 2006)

Sarnak MJ, Levey AS, Schoolwerth AC et al (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* **108:** 2154–69

Silverberg DS, Wexler D, Sheps D et al (2001) The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* **37**: 1775–80

Stewart S, MacIntyre K, Hole DJ et al (2001) More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* **3:** 315–22

Vanrenterghem Y, Ponticelli C, Morales JM et al (2003) Prevalence and management of anemia in renal transplant recipients: a European survey. *Am J Transplant* **3:** 835–45

Varney SJ, Guest JF (2003) The annual cost of blood transfusions in the UK. *Transfus Med* **13:** 205–18

Winerls CG (1995) Historical review of the use of recombinant human erythropoietin in chronic renal failure. *Nephrol Dial Transplant* **10**(Suppl 2): 3–9

Xue JL, St Peter WL, Ebben JP, Everson SE, Collins AJ (2002) Anemia treatment in the pre-ESRD period and associated mortality in elderly patients. *Am J Kidney Dis* **40:** 1153–61