Individualizing anaemia treatment: a discussion of case histories

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Abstract
Current guidelines give evidence-based advice on how best to manage anaemia in patients with renal disease, but these guidelines do not consider individual patient needs, so tailoring anaemia management to each patient still remains a challenge for the treating physician. Two case studies are described that illustrate some of the key factors that need to be considered. The first case emphasizes that haemoglobin (Hb) targets recommended in current guidelines may not suit all patients. The patient had been stably maintained on subcutaneous epoetin therapy with an average Hb concentration of > 13.0 g/dl because he developed angina symptoms when his Hb level fell to 12.2 g/dl. Iron deficiency was identified as the likely cause of falling Hb in this patient. After the patient’s iron supplementation was increased, his Hb level was normalized back to > 13.0 g/dl without increasing the epoetin dose, and the angina symptoms were resolved. The second case involved a pre-dialysis patient with diabetes, who required a higher dose of epoetin after beginning concomitant antihypertensive treatment with an angiotensin-converting enzyme inhibitor. Previously, the treatment of renal anaemia in pre-dialysis patients has not been the focus of attention. Two ongoing randomized controlled trials have been designed to study early initiation of epoetin treatment in pre-dialysis patients and will provide much needed information in this area.

Keywords: anaemia; cardiovascular; epoetin; haematocrit; haemoglobin; pre-dialysis; target

Introduction
Recombinant human erythropoietin (rhEPO; epoetin) has been used for more than a decade in the treatment of renal anaemia, yet the optimum haemoglobin (Hb) target remains a controversial topic. Current practice is to aim for only a partial correction of anaemia in some patient groups, in line with treatment guidelines. European Best Practice Guidelines recommend that haemodialysis (HD) patients should have a Hb concentration of >11.0 g/dl [haematocrit (Hct) >33%], and US guidelines from the National Kidney Foundation suggest a Hb target level of 11.0–12.0 g/dl [1,2]. Despite these recommendations, it is generally accepted that normal Hb concentrations are 13.0–15.0 g/dl for women and 14.0–16.0 g/dl for men. Furthermore, there is ongoing debate as to whether the same target Hb levels should be maintained in all patients with renal anaemia, and at all times.

In recent Hb normalization studies, higher Hb levels were associated with clinical benefits and minimal adverse effects [3–5], but normalization of Hb levels was associated with an increase in the risk of adverse events in patients with cardiac disease participating in the US Normal Hematocrit Study [6]. The benefits and risks of epoetin therapy should therefore be weighed against each other when selecting the most appropriate Hb target level for individual patients. For example, a young, physically active dialysis patient with anaemia could experience significantly improved quality of life at a higher Hb level, but may also be at increased risk of adverse events such as vascular access failure. Target Hb levels should be individualized to balance the potential risks of higher Hb against the potential benefits of effective anaemia management. This article presents the case histories of two contrasting patients, to enable discussion of some of the key issues for individualizing epoetin treatment, and how this relates to daily clinical practice.

Case history 1: a HD patient with a history of angina

Case details
A 58-year-old man with renal failure, secondary to chronic glomerulonephritis, was referred from a peripheral dialysis centre to a specialist renal unit.
He had been on HD for 5 years and had received epoetin 3000 IU twice weekly (~85 IU/kg) for >2 years, but otherwise had no other significant clinical problems. His interdialytic weight gain was 2–3 kg and his weekly delivered dialysis dose (Kt/V, 1.55) and serum albumin (37 g/l) were within acceptable parameters.

The patient had a history of hypertension and coronary heart disease and was taking a low dose of metoprolol (25 mg twice daily). His pre-dialysis blood pressure (BP) control had been good, fluctuating between 120 and 130 mmHg (systolic) and 70 to 80 mmHg (diastolic). However, during the previous 3 months, the patient’s Hb levels had decreased from 13.8 to 12.2 g/dl and he had complained of worsening chest pain, which followed the fall in his Hb level. Further examination of the patient’s medical records revealed a history of angina dating back 6 years before the onset of renal failure. The patient had been free from angina while on dialysis, and during this time his Hb levels had been maintained at >13.0 g/dl with epoetin treatment. Notably, the patient was insistent that his epoetin dose should be increased to ensure his Hb level was >13.0 g/dl, because he felt that this would relieve his anaemia-related symptoms of angina.

**Case outcome and discussion**

Further evaluation of the patient’s decreasing Hb levels revealed that, although most of his laboratory parameters were within accepted normal limits (Table 1), his transferrin saturation level was below the accepted normal of 20%, suggesting that iron deficiency was the likely cause of the fall in Hb.

The patient had initially been receiving intravenous iron dextran 100 mg every 6 weeks and this was increased to once every 2 weeks to correct the iron deficiency, but his epoetin dose was not changed. After 3 months’ treatment, his Hb had stabilized at 13.5 g/dl and transferrin saturation was 25% (Table 1). All symptoms of angina had resolved as a consequence of the improved Hb level and the addition of low-dose transdermal nitroglycerine.

It is tempting in such a patient simply to increase the epoetin dose to restore Hb to previous levels. In this case, to do so would have been a mistake. Loss of prior responsiveness to epoetin, as in this patient, should always raise the suspicion of acquired iron deficiency. Iron deficiency is the most common cause of inadequate response to erythropoietin [7,8]. Increasing the epoetin dose in the presence of iron deficiency will not correct anaemia because, although epoetin stimulates red blood cell production, erythropoiesis is a dynamic process that requires 30–40 mg of iron each day [9]. The logical option for this patient is therefore to evaluate the cause of the recent decline in Hb and to treat the angina symptoms as a separate issue.

This case illustrates several important points. First, patients with cardiovascular disease (CVD) should not necessarily be constrained by an arbitrary Hb target of 11.0–12.0 g/dl. Secondly, determination of a target Hb level should be carried out on a patient-by-patient basis. Thirdly, in ‘stable’ patients on long-term epoetin treatment for known renal anaemia, investigation of the potential causes of anaemia is occasionally required.

In recent studies, higher Hb levels produced significant clinical benefits in patients with cardiomyopathy [3] as well as in healthier patient groups [4,5,10]. In the Canadian normalization study, the Hb levels of HD patients with left ventricular hypertrophy (LVH) or LV dilatation were either partially corrected to 10.0 g/dl or normalized to 13.5 g/dl with epoetin [3]. Although there was no obvious benefit in normalizing Hb in patients with overt LV dilatation, such treatment

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**Table 1. Key laboratory parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit 1</th>
<th>Visit 2</th>
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<tbody>
<tr>
<td><strong>Case 1</strong></td>
<td></td>
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<tr>
<td><strong>Below normal limits</strong>:</td>
<td></td>
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</tr>
<tr>
<td>Transferrin saturation</td>
<td>17%a</td>
<td>Transferrin saturation</td>
</tr>
<tr>
<td>Serum parathyroid hormone</td>
<td>11.3 nmol/l</td>
<td>25%</td>
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<tr>
<td>Ferritin 153 ng/ml</td>
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<tr>
<td>Aluminium 187 nmol/l</td>
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<tr>
<td>C-reactive protein 2.6 mg/l</td>
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<td>Negative fecal occult blood tests</td>
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<tr>
<td><strong>Above normal limits</strong>:</td>
<td>Serum albumin 2.9 g/dl</td>
<td>Serum creatinine 3.0 mg/dl</td>
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<tr>
<td>Serum creatinine</td>
<td>5.1 mmol/l</td>
<td>Urinary protein 1.73 g/l</td>
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<tr>
<td>Urinary protein excretion</td>
<td>4.63 g/24 h</td>
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</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.47 ml/s</td>
<td>Total serum cholesterol</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>6.2 mmol/l</td>
<td>5.1 mmol/l</td>
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<tr>
<td>HDL cholesterol 1.1 mmol/l</td>
<td></td>
<td>LDL cholesterol 3.3 mmol/l</td>
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<td>LDL cholesterol 4.83 mmol/l</td>
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aWhere normal is 20%.
bWhere normal is <6.1 nmol/l, but in this case levels were not sufficiently raised to induce a reduction in sensitivity to epoetin. Measured over 24 h.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
appeared to slow progression in patients with less severe disease (Figure 1). Studies in HD patients without significant co-morbidities also support the beneficial effect of normalizing Hb. The Australian and Spanish normalization studies showed significant improvements in echocardiographic parameters, quality of life, exercise performance and hospitalization rates in these patients [4,5,10]. Notably, the earlier US Normal Hematocrit study contradicts the findings of other normalization studies. This study compared epoetin correction to normal Hct levels (42%) with low Hct levels (30%) in HD patients with established cardiac disease [6]. Although patients in the higher Hct group had an improved quality of life and were less likely to need a blood transfusion, they were also at higher risk (risk ratio 1.3) for death or non-fatal myocardial infarction (MI) than those in the lower Hct group (Figure 2), and the study was terminated early. However, the authors acknowledge that these results apply to a specific patient group, namely HD patients with established cardiac disease. These patients were older and had more co-morbidity than would be expected in the general population of dialysis patients. Overall, the data from these normalization studies suggest that some patients will have additional benefit when their Hb is raised, and the case discussed here supports this idea.

**Case history 2: a pre-dialysis patient with diabetes**

**Case details**

A 65-year-old woman with chronic renal failure was referred to a specialist renal unit by her family practitioner. The patient had a 10 year history of type 2 diabetes mellitus that was originally controlled by diet, but which had required the administration of oral hypoglycaemic agents for the previous 6 years. She also had a 15 year history of hypertension and had been treated with a variety of antihypertensive agents during this time. The patient had evidence of end-organ damage as a result of her diabetes and had previously received photocoagulation therapy for her retinopathy. There was no other significant medical history apart from a cholecystectomy and mild symptoms of gastroparesis.

The patient consulted her family practitioner regarding progressive ankle swelling that had developed during the previous 3 months, and she also reported mild effort dyspnoea (but no other cardio-respiratory symptoms). However, the patient also stated that her glycaemic control was somewhat variable. Following tests requested by her family physician, the patient’s urinalysis was positive for protein and her serum creatinine level was 3.03 mg/dl.

At the initial visit to the renal unit, the patient was clinically obese with a body mass index of 31.1 (weight 84.8 kg, height 1.65 m), a BP of 160/98 mmHg and a Hb level of 11.2 g/dl. Oedema of the lower limbs and bibasilar lung crackles were also present, but otherwise her physical examination was normal. Laboratory tests showed that serum creatinine was elevated and serum albumin was slightly depressed (Table 1). Other laboratory test findings were not notable. However, an electrocardiogram (ECG) showed voltage criteria for LVH and suggested a possible prior inferior wall MI of indeterminate age.

The patient’s treatment regimen was amended following consultation (Table 2). The objectives of treatment were to achieve a target BP below 125/75 mmHg (systolic/diastolic) and to reduce urinary protein excretion as much as possible, while maintaining renal function and controlling both diabetes and hypercholesterolaemia in an attempt to minimize the patient’s cardiovascular risk. Cessation of metformin was advised.
Case outcome and discussion

Two months later, a review showed that the patient’s BP had decreased to 128/72 mmHg (systolic/diastolic) and that glycaemic control had improved. Cholesterol levels and renal function had also improved (Table 1). However, the Hb level had decreased by 1.4 g/dl to 9.8 g/dl. There were no symptoms to suggest active blood loss: iron stores, vitamin B12, folate and CRP levels were normal, ruling out nutrient deficiency or inflammation as a causative factor; and stools were negative for occult blood.

Medication change, specifically the initiation of ramipril, was the likely reason for the fall in Hb levels in this patient. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists have been reported to induce a predictable 1.0–2.0 g/dl decline in Hb levels during chronic therapy [11]. Indeed, the ACE inhibitor captopril has been found to increase plasma levels of a stem cell regulator (Ac-SDKP) that inhibits differentiation of stem cells and early progenitors [14]. ACE inhibitors also appear to reduce production of insulin-like growth factor-1 (IGF-1) and interleukin-12 (IL-12), both of which are involved in erythropoietic activity [15,16]. Whatever the mechanism by which ACE inhibitors and angiotensin II receptor antagonists lower Hb, patients receiving these agents may require higher epoetin doses [11].

Thus the Hb level of 9.8 g/dl recorded at the patient’s second visit indicated a need to initiate epoetin therapy, which was begun at an initial dose of 4000 IU weekly by the subcutaneous route. Stopping ACE inhibitor therapy in this patient was not considered appropriate, as these agents are of prognostic importance in reducing cardiovascular risk. The logical management strategy was to initiate epoetin on an out-patient basis and work with the patient to provide an individualized approach to the dose schedule since patients on ACE inhibitors are, for the reason given above, known to need somewhat higher doses of epoetin.

This patient was at considerable cardiovascular risk since her initial ECG suggested the presence of LVH and a possible prior MI, despite the absence of coronary ischaemia symptoms. On referral, her Hb level of 11.2 g/dl may not have indicated the need for correction with epoetin, however, evidence suggests that anaemia is an important determinant in the development of LVH in renal failure. In turn, LVH is known to be an independent risk factor for cardiovascular morbidity and mortality in patients with end-stage renal disease (ESRD) [17]. Several studies have suggested that early intervention with epoetin can

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**Table 2.** A pre-dialysis patient with diabetes: treatment modification

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Revised treatment</th>
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<tbody>
<tr>
<td>Glibenclamide 10 mg (bid)</td>
<td>Insulin&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metformin 750 mg (tid)</td>
<td>Ramipril 10 mg/day</td>
</tr>
<tr>
<td>Amlodipine 10 mg/day</td>
<td>Diltiazem 24 mg/day</td>
</tr>
<tr>
<td>Doxazosin 4 mg/day</td>
<td>Furosemide 20 mg (bid)</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg/day</td>
<td>Domperidone 10 mg (qid)</td>
</tr>
<tr>
<td>Domperidone 10 mg (qid)</td>
<td>Pravastatin 10 mg/day</td>
</tr>
</tbody>
</table>

<sup>c</sup>If diet plus glibenclamide unsuccessful
bid = twice a day; tid = three times a day; qid = four times a day.

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**Fig. 2.** Kaplan–Meier estimates of the probability of death or a first non-fatal MI in the US Normal Hematocrit Study (adapted from Besarab <i>et al.</i> [11] with permission.)
prevent the development or progression of LVH and might, therefore, be expected to reduce the severity of later CVD [18–20]. Furthermore, in the Canadian normalization study, for every 1 g/dl decrease in mean Hb level there was a 46% increase in the risk of developing LV dilatation, a 28% increase in de novo heart failure, a 20% increase in recurrent heart failure and a 14% increase in death [21]. Findings such as these have led Silverberg and colleagues to suggest a model for a ‘vicious circle’ (the Cardio-Renal Anaemia syndrome) in which anaemia, chronic kidney disease (CKD) and congestive heart failure are interrelated and cause each other to worsen [20].

**Tailoring treatment to the individual**

Currently, renal anaemia is managed according to evidence-based advice in existing guidelines, but this does not always take into account individual patient needs. The two cases described here illustrate that a single Hb target will not achieve maximum clinical benefit for all patients. Achieving higher Hb targets may have significant benefits in renal anaemia, including reduced cardiac disease and improved quality of life and exercise tolerance; however, low Hb levels alone should not be an indication to initiate epoetin therapy. Rather it should prompt an evaluation of the relationship between Hb levels, clinical symptoms and the expected benefit of anaemia correction for that patient. Co-morbidity, concomitant medication, response to anaemia correction and patient expectation should all be taken into account, as shown by the cases presented herein. Other factors to consider include the age of the patient and his/her level of physical activity, the duration of CKD and the mode of dialysis [22,23].

CVD mortality rates in ESRD patients are ~20–40 times higher than those in the general population [24], and only ~15% of these renal patients have normal LV structure and function at dialysis initiation [25]. Since anaemia usually develops early in the course of CKD [26], there is a need for early treatment to help reduce cardiac morbidity and mortality. There is room for improvement in the care of pre-dialysis patients with CKD and anaemia [27]. A retrospective analysis conducted in the USA (1995–1997) showed that few patients receive regular treatment with epoetin before the initiation of dialysis [28]. A total of 89 193 elderly incident dialysis patients were surveyed: only 15.6% of patients had previously received epoetin and even fewer had received epoetin consistently (4.6%). A more recent retrospective analysis of 4333 pre-dialysis patients found that, on beginning dialysis, the Hb level of most (68%) patients was ≤11.0 g/dl (i.e. below the European Best Practice Target recommendations) [29].

Two ongoing studies will provide much needed information on the benefits of early treatment in pre-dialysis patients, and they should assist the development of an individualized approach. The Anaemia CORrection in Diabetes (ACORD) and Cardiovascular Reduction Early Anaemia Treatment Epoetin β (CREATE) studies have been designed to provide information on optimal anaemia management in pre-dialysis patients. Both studies have an open-label, randomized design and will compare the effect of early intervention with epoetin-β (Hb target of 13.0–15.0 g/dl) with standard epoetin-β intervention (epoetin initiated when Hb falls below 10.5 g/dl, to a target of 10.5–11.5 g/dl) (Figure 3). Subcutaneous epoetin-β will be self-administered by patients once weekly at an initial dose of 2000 IU.

The ACORD study was designed to recruit 160 pre-dialysis patients with early diabetic nephropathy. The primary efficacy variable is the change in LV mass index, and secondary variables include LV volume, the proportion of patients with stable Hb and the mean weekly epoetin-β dose. CREATE involves a broader population of pre-dialysis patients with
poorer initial renal function than patients eligible for ACORD (Figure 3). The first primary end-point is the change from baseline in LV mass index within 1 year. If there is a difference between treatment groups in the first primary end-point after a year, the study will proceed to assess the second primary variable of time to first cardiovascular event. Secondary outcomes include progression of CKD and effects on quality of life. Baseline data for ~600 patients enrolled in CREATE show that the two treatment groups are well matched and that, overall, a large burden of CVD is present [30]. The results of ACORD and CREATE are awaited with interest.

Conclusions

The cases presented here clearly demonstrate that a single Hb target will not achieve maximum clinical benefit for all patients. In addition, low Hb in itself is not an indication for EPO therapy, but demands a full investigation of the potential causes of anaemia, as recommended by current best practice guidelines. In many patients, evaluation of the relationship between clinical symptoms and Hb might be used to determine individual target Hb levels. The challenge for physicians is, therefore, to identify the best target Hb level for each patient, taking into account any co-morbid conditions, concomitant medications and the patient’s own expectations of therapy. Optimizing the management of renal anaemia, particularly in early disease, should be a priority and will require greater collaboration between all physicians involved in the care of patients with chronic renal anaemia.

Conflict of interest statement. None declared.

References


