Optimal Treatment of Renal Anaemia (OPTA): improving the efficacy and efficiency of renal anaemia therapy in haemodialysis patients receiving intravenous epoetin

Co-chairs

Walter H. Hörl and Yves Vanrenterghem

Working group

Bernard Canaud, Johannes Mann, Ugo Teatini, Christoph Wanner and Björn Wikström

Abstract

The medical care of renal anaemia has received much attention over the past decade, as nephrologists have recognized the increased therapeutic value of erythropoiesis-stimulating agents. The European Best Practice Guidelines and the US National Kidney Foundation’s Kidney Disease Outcome Quality Initiative Guidelines have provided evidence-based advice on the optimal treatment of renal anaemia, and have recommended a target haemoglobin (Hb) level of 11 g/dl or 11–12 g/dl. Achieving this target Hb level has been shown to improve quality of life and reduce the rate of hospitalization; there is also good evidence to suggest that achieving adequate Hb levels reduces morbidity and mortality in patients with end-stage renal disease. In recent years, a number of factors have been identified that may counteract the positive action of epoetin therapy. These treatment-influencing factors include inadequate dialysis dose, absolute and functional iron deficiency, anticoagulant use, inflammation and infection. Each factor on its own may result in a substantial decrease in Hb levels, or an increase in epoetin requirements of up to 100%. Therefore, optimal and cost-effective treatment can only be achieved by adequately managing all of the factors that potentially can influence anaemia in patients with chronic kidney disease. Large-scale, cross-sectional surveys, such as the European Survey on Anaemia Management and the Dialysis Outcomes and Practice Patterns Study, have shown that there is still room for improving the efficacy and efficiency of anaemia therapy. The Optimal Treatment of Renal Anaemia (OPTA) initiative aims to help both physicians and nurses improve renal anaemia management by ‘translating’ the standards set in published guidelines into practical clinical advice.

Keywords: epoetin; haemodialysis; infection; inflammation; iron; renal anaemia

Introduction

The medical care of patients with renal anaemia has been the focus of much attention over the past decade as nephrologists have recognized the increasing therapeutic value of erythropoiesis-stimulating agents. The main goal of treatment is to reach the recommended target haemoglobin level of >11 g/dl [European Best Practice Guidelines (EBPG)] or target haemoglobin level of 11–12 g/dl [the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI)] while also increasing the effectiveness of therapy to optimize the cost:benefit ratio of anaemia therapy [1,2].

In recent years, a number of factors have been identified that may counteract the positive action of epoetin (recombinant human erythropoietin) therapy, such as inadequate dialysis dose, absolute and functional iron deficiency, or inflammation and infection. Each factor on its own could lead to a substantial
On anaemia treatment in haemodialysis patients.

Large-scale, cross-sectional surveys, such as the European Survey on Anaemia Management (ESAM) 1998 and ESAM 2003 and the Dialysis Outcomes and Practice Patterns Study (DOPPS), have indicated that there is still room for improving the efficacy and efficiency of anaemia therapy ([3,4] and Jacobs et al., this Supplement). ESAM 2003, for example, showed that 33.9% of the patients on dialysis did not reach the recommended target haemoglobin level of >11 g/dl (13.2% even had a haemoglobin level <10 g/dl). ESAM and DOPPS also demonstrate that major treatment-influencing factors that may counteract the efficiency of epoetin treatment, such as inadequate dialysis (30% \( Kt/V <1.2 \) according to DOPPS) [5], iron substitution (26.6% functional or absolute iron deficiency) [6], or infection and inflammation, should be focused on because every single factor has a substantial influence on the efficiency of the treatment for anaemia.

The Optimal Treatment of Renal Anaemia (OPTA) initiative aims to improve anaemia management through doctors and nurses in order to provide optimal anaemia treatment so recommended target haemoglobin levels of 11–12 g/dl can be achieved with the highest efficiency. In a first step, the OPTA working group summarizes recent recommendations on anaemia treatment in haemodialysis patients.

**Major treatment-influencing factors**

**Haemodialysis adequacy (haemodialysis quality/quantity: mode of dialysis)**

Uraemic toxins have a negative impact on anaemia treatment by reducing erythrocyte survival time, erythropoietin receptor affinity and transferrin binding capacity for iron. The published literature demonstrates that an increase in epoetin dosage of up to 54% is required in underdialysed patients [7].

Results from the DOPPS [5,6] show an obvious gap between daily practice and guideline recommendations. At present, only a minority of European dialysis centres perform dialysis dose measurements as recommended.

**Recommendations**

- Haemodialysis should be performed at least three times per week.
- The duration of dialysis should be not less than 4 h per session if dialysis is performed three times per week.

- Haemodialysis dose should be quantified every 3 months using equilibrated \( Kt/V \).

Quantification of the dialysis dose improves outcome and reduces the costs related to anaemia. According to EBPG and NKF-K/DOQI, the minimum delivered dialysis dose per session for a thrice-weekly schedule should be urea-equilibrated \( Kt/V \geq 1.2 \) (Daugirdas II), corresponding approximately to a urea reduction rate of \( >65\% \) [8,9]. The duration of dialysis should be not less than 4 h per session, even if the standards of adequacy are reached [8]. The Hemodialysis (HEMO) Study and observational trials suggest a so-called plateau of dialysis efficacy that may be overcome by long-term dialysis (3 \( \times \) 8 h/week), short daily dialysis (6 \( \times \) 2–3 h/week) or daily dialysis overnight [8,10].

Adequate dialysis appears to be of major importance for the correction of anaemia, possibly by removing uraemic toxins that are suspected to inhibit erythropoiesis [11]. Middle and high molecular weight inhibitors are removed exclusively by highly permeable membranes and convective treatment modalities. Some studies suggest that high- and super-flux membranes, including albumin-leaking membranes, could reduce epoetin requirements and therefore improve outcome [12–14]. The use of ultra-pure dialysate has been shown to result in a reduction of serum C-reactive protein (CRP) concentration, and some data suggest a reduction in epoetin dosage [15,16].

**Recommendations**

- Bioincompatible dialyser membranes that activate inflammatory cells should be avoided.
- High-flux biocompatible dialyser may be preferred.
- The use of ultra-pure water is recommended in order to minimize epoetin consumption.
- Haemolysis during dialysis can be prevented by avoiding shear stress.

Bioincompatible dialyser membranes can induce oxidative damage to red blood cells [17]. Because middle and high molecular weight inhibitors of erythropoiesis can only be removed by highly permeable large-pore membranes, it has been suggested that the regular use of such high-flux membranes may improve outcome with respect to haemoglobin levels [12,13]. In the dialyser circuit, solid fragment (plastic) spallation or soluble fragment (plasticizer) release can induce inflammatory reactions and enhance blood cell destruction, but may be prevented by the use of adequate circuitry [18,19]. Adequate pre-rinsing of ethylene oxide-free dialysers is mandatory. Shear stress-related problems can be avoided by correct positioning of large needles (14/15 gauge) in the access system, by preventing excessive pressure on tubing in roller pumps, and by preventing high negative
arterial pressure (>300 mmHg) and minimizing re-circulation [20].

Iron

Absolute or functional iron deficiency is the most common cause of a suboptimal response to anaemia therapy, and it develops in all haemodialysis patients not receiving continuous iron supplementation. Optimal management of iron deficiency leads to a substantial reduction in epoetin dosage (20–70%) and to a reduction in the number of low responders to anaemia therapy.

Absolute iron deficiency, a deficit of total body iron store, is defined as a serum ferritin concentration <100 µg/l [21].

Functional iron deficiency (ferritin >100 µg/l, transferrin saturation <20%) is the failure of iron to reach proliferating erythroblasts, despite sufficient iron stores.

Iron deficiency develops primarily during the correction phase of anaemia (150 mg of iron is necessary for an increase of 1 g/dl in haemoglobin level), during states of inflammation or if blood losses are not adequately taken into account.

Recommendations

- Absolute iron deficiency should be distinguished from functional iron deficiency (i.e. inflammation).
- Diagnosis of iron deficiency and guidance of iron supplementation should be done in stable patients by ferritin and transferrin saturation measurements at 3 month intervals. Ideally, the percentage of hypochromic red blood cells should be determined whenever possible.

Iron requirements (Table 1)

To compensate for the unavoidable blood loss in haemodialysis patients, intravenous administration of iron is mandatory for the majority of these patients and is the treatment of choice. Oral iron supplementation is often not sufficient due to relatively low bioavailability and poor intestinal absorption.

When calculating the total amount of iron required, it should be taken into account that each millilitre of blood contains 0.5 mg of iron. Annual blood losses can be as high as 41 of blood, equivalent to 2 g of iron [22–25]. Young women require more iron than men.

Iron therapy

Intravenous treatment strategies depend on the availability of iron products in the respective countries (see recommendations). Haemodialysis patients should receive at least one dose of iron every 2 weeks [1]. Intravenous iron therapy may cause acute and long-term complications. Anaphylactic reactions are related to iron dextran [26–29]; and high-dose iron therapy may result in neutrophil inhibition [30–32], oxidative stress [33] and atherosclerosis [34]. A recent multicentre phase IV clinical trial documented the safety of intravenous iron sucrose for the treatment of iron deficiency and for the maintenance of iron sufficiency in haemodialysis patients [35].

Recommendations: iron dosage and administration frequency

- Absolute iron deficiency:
  - 30–50 mg/haemodialysis or 1000 mg in 6–10 weeks
- Maintenance phase:
  - Fe-sucrose 10–25 mg/haemodialysis or 1–3 x Fe-glucionate 20 mg/week
  - 1 x Fe-glucionate 62.5 mg/week
  - 1 x Fe-sucrose 100 mg/1–2 weeks
  - 1 x Fe-dextran (low molecular weight) 100 mg/1–2 weeks
- Haemoglobin (Hb) correction phase:
  - 150 mg of iron/Hb increase of 1 g/dl

Blood loss

Although the amount of iatrogenic blood loss has been reduced through technical advances, some centres have increased the frequency of blood sampling for routine laboratory parameters from once every 6 weeks to once every 4 weeks. Remember that routine clinical chemistry can usually be done with <1 ml of serum. Potential blood losses include:

- residual blood in extracorporeal circuits (dialysers and tubing)
- continuous monitoring and routine laboratory tests
- the use of catheters
- occult gastrointestinal blood losses.

Recommendations

- The amount of blood wasted during dialysis should be minimized (i.e. during disconnection).
- The amount of blood drawn for diagnostic tests and routine clinical chemistry should be adapted to the parameters selected.
- Patients with anaemia that is unresponsive to usual doses of epoetin should be checked for gastrointestinal bleeding, blood loss during dialysis and blood loss for routine laboratory tests.

**Prevention of bleeding and clotting during anticoagulation**

Few studies have demonstrated that patients treated with low molecular weight heparin needed fewer blood transfusions [36,37]. The use of epoetin and its consequent increase in haemoglobin and haematocrit levels results in a higher heparin dose (up to 25%) to avoid clotting in the dialyser [38–43].

**Recommendation**

- When patients are started on haemodialysis with low haemoglobin levels, care should be taken to adjust the heparin dosage to achieve appropriate anticoagulation.

**Inflammation**

Apart from uraemia, chronic inflammation is associated with anaemia (anaemia of chronic disease). Inflammation and the acute-phase response interact with the haematopoietic system at several levels, resulting in reduced erythrocyte stem cell proliferation, suppressed erythropoiesis and endogenous erythropoietin production, accelerated destruction of erythrocytes and blunting of the reactive increase in erythropoietin in response to reduced haemoglobin levels. Epoetin resistance has been linked with inflammation, associated with functional iron deficiency. Acute or chronic inflammation and infections not only suppress erythropoiesis, but also inhibit mobilization of stored iron and may cause gastrointestinal blood loss. The process is driven by release of pro-inflammatory cytokines [interleukin (IL)-1, IL-6, tumour necrosis factor-α and interferon-γ] resulting in an increase in CRP. CRP concentration measured years before an acute event predicts future all-cause and cardiovascular mortality [44–47] as well as hospitalizations [48]. The causes for elevated CRP are multifactorial and derive from endogenous or exogenous stimuli. Patients with a past history of systemic disease causing renal failure are at risk of recurrence or exacerbation of the disease. Occasionally, a flare-up of the underlying primary renal disease, such as systemic lupus erythematosus or Wegener’s granulomatosis, may occur.

There may be a continuum from (micro-)inflammation to clinically evident inflammation to infection, but no clear-cut CRP value is helpful in clinical practice to distinguish between these stages. In the absence of overt infection, inflammation is defined as a CRP concentration in the range 5–20 mg/l. At concentrations >50 mg/l, an underlying infectious cause is likely.

**Recommendations**

- CRP testing should be included in the routine evaluation at least every 3 months [49].
- In patients with elevated CRP (>5 mg/l), biocompatibility of dialyser membrane and haemodialysis fluid quality should be checked.
- If chronic inflammation persists, ensure optimization of the dialysis protocol and dialysis dose.
- In patients with a continuous increase in CRP and a past history of systemic disease causing renal failure, recurrence of the disease should be excluded.
- In the presence of both a high Ca × PO₄ product and high serum CRP concentration, patients should be screened and treated for calciphylaxis.
- Patients returning from transplantation should be monitored carefully, because rejected grafts may be a source of inflammation.
- In patients with a failed renal allograft still in place or in patients with intravenous catheters, a higher dose of epoetin may be needed to correct anaemia.

**Infection**

Bacterial infections are a paradigmatic inflammatory state and rank second behind cardiovascular disease as a major cause of death. Inflammation or infections lead to higher epoetin dosages [50–52]. Patients with a CRP concentration >50 mg/l need ~30% higher epoetin doses than do patients with a CRP concentration <50 mg/l [50]. Inhibited iron mobilization is found in infection and states of high CRP concentration (>20 mg/l), and functional iron deficiency is likely.

Withdrawing any suspected prosthetic or unused material (polytetrafluoroethylene product or catheter) should be considered as the best way of correcting the infection and restoring epoetin responsiveness in the dialysis patient. Cases of persisting subclinical infection require careful examination and oriented investigation to determine the site of origin. In contrast to this, however, hepatitis C reduces epoetin requirements.

**Recommendations**

- Iron supplementation should be stopped during documented infection, because intravenous iron may also enhance bacterial growth.
- Patients with CRP concentration >20 mg/l should be screened for silent infection of haemodialysis access grafts (visual control), periodontal disease or any low-grade infection (diabetic foot ulceration).
• Elderly patients should be screened for urinary tract infection when epoetin requirements increase.

**Malnutrition**
Malnutrition rarely occurs without concomitant inflammation or infection. Elements of the malnutrition–inflammation complex syndrome may blunt the responsiveness to epoetin [53]. If malnutrition is present without inflammation, it is treatable, and it can be avoided by increasing the dialysis dose and by providing adequate protein and caloric intake. The combination with specific drugs [e.g. growth hormone (GH)] may potentiate the success of the modified treatment modalities, particularly in male patients above 50 years of age who need nutritional support. Nutritional support (supplementation with nutritional products) should also be given if the body mass index decreases constantly or somatic proteins (albumin and pre-albumin) and cholesterol decline over time.

**Recommendation**
• Haemodialysis patients with an elevated CRP concentration, unresponsive to epoetin therapy, with a decreasing body mass index and a total serum cholesterol level <150 mg/dl should be considered for nutritional support (evidence level C, opinion).

**Minor treatment-influencing factors**

**Secondary hyperparathyroidism**
Secondary hyperparathyroidism is usually associated with a diminished response to epoetin. Most probably, a high serum concentration of parathyroid hormone (PTH) results in toxic effects on erythropoietin synthesis, on erythroid stem cells in the bone marrow, and on bone marrow fibrosis by interfering with normal bone calcium metabolism and increasing erythrocyte fragility and haemolysis [54]. In contrast to this, vitamin D increases the number of erythropoietin receptors in erythropoietic progenitor cells [55], explaining the additive effects of epoetin and calcitriol even in the absence of PTH reduction.

**Recommendation**
• PTH levels should be controlled 2–4 times a year.

**Non-iron adjuvants**
Intravenous vitamin C supplementation is recommended when otherwise unexplained epoetin resistance is documented and ferritin levels are elevated [56,57]. The optimal vitamin C dose, however, is unclear. Recommendations include post-haemodialysis intravenous vitamin C 300 mg [57] or 500 mg [58]. Whether oral vitamin C supplementation is similarly effective is currently unknown; vitamin C 1.0–1.5 g/week should be given orally. Secondary oxalosis should be avoided [59,60]. Smokers undergoing regular haemodialysis or, in particular, haemodiafiltration have low serum vitamin C levels [61]. However, plasma vitamin C levels only weakly correlate with haemoglobin or response to epoetin [62].

Folic acid and vitamins B12 and B6 apparently have no major effects on anaemia, except in those rare cases with severe deficiencies of folic acid, vitamin B12 and/or vitamin B6.

Supplementation of vitamin E—or the use of vitamin E-substituted cellulose dialyser membranes—may allow preservation of blood antioxidative capacity [63,64], but has not been shown to ameliorate anaemia or to reduce epoetin doses. In children, the combination of vitamin E with epoetin increased haemoglobin levels significantly [65].

l-Carnitine may increase blood haemoglobin levels in haemodialysis patients without epoetin therapy, and may decrease epoetin dose in haemodialysis patients receiving combined treatment with l-carnitine and epoetin. Due to a lack of well-controlled studies, inconsistent results and multiple confounding factors, general recommendations for l-carnitine supplementation in haemodialysis patients cannot be given [66].

Zinc is highly bound to albumin, and plasma levels do not really reflect zinc status. In animal experiments, zinc deficiency reduced insulin-like growth factor-1 (IGF-1) levels and decreased gene expression of the hepatic IGF-1 and GH receptors. Zinc supplementation will reduce requirements for erythropoiesis-stimulating agents via enhanced bioavailability of IGF-1, particularly in patients who are malnourished or zinc depleted (for a review, see Deicher and Hörl [67]).

**Androgens** should be prescribed for anaemic males in parts of the world where erythropoietin is not available due to economic constraints. However, liver toxicity should be weighed against the benefits [1,60,68]. Where androgens are used in male patients <50 years old, prostate-specific antigen concentrations should be checked before and during administration.

**GH** treatment in elderly patients on haemodialysis may stimulate erythropoiesis [67,69]. Links to IGF-1 are unclear; suggestions have been published that GH may stimulate erythropoiesis. Stem cell factor, IL-1, IL-3, IL-4, IL-9, IL-11 and granulocyte–macrophage colony-stimulating factor all interact with GH.

**Aluminium** overload is a well-known factor of microcytic anaemia due to inhibition of haem synthesis [24]. Aluminium intoxication can still occur in patients treated with aluminium-containing phosphate binders or when centres replace the filters in the reverse osmosis circuit. Deferoxamine treatment
Table 2. Drugs that may affect haemoglobin levels in haemodialysis patients

<table>
<thead>
<tr>
<th>Decreases Hb</th>
<th>Increases Hb</th>
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<tbody>
<tr>
<td>Azathioprine</td>
<td>Anti-TNF-α</td>
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<tr>
<td>MMF</td>
<td>Anticytokine therapy</td>
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<tr>
<td>Antimetabolites</td>
<td>Thalidomide</td>
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<tr>
<td>ACE inhibitors (?)</td>
<td>Statins (?)</td>
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<tr>
<td>Angiotensin II receptor blockers (?)</td>
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ACE inhibitors = angiotensin-converting enzyme inhibitors; Hb = haemoglobin; MMF = mycophenolate mofetil; TNF-α = tumour necrosis factor-α.

should be administered when aluminium overload is detected by a deferoxamine challenge test.

Recommendation

- In patients treated with aluminium-based phosphate binders, serum aluminium levels should be measured twice a year. Similar monitoring should be done in parts of the world where adequate water treatment facilities (reverse osmosis) are still not available.

Concomitant therapy (Table 2)

Several drugs concomitantly prescribed in haemodialysis patients may increase or decrease epoetin dose. Studies with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers are not yet conclusive.

Co-morbid diseases: malignancies

Patients on maintenance haemodialysis are potentially at increased risk of developing cancer or malignant haemopathy. Several factors, including a weakened immune system and previous treatment with immunosuppressive or cytotoxic drugs [70], favour development of such pathology. Haemoglobinopathy, sickle cell anaemia or thalassaemia should be excluded. Activation of systemic diseases, such as systemic lupus erythematosus should also be considered.

Recommendation

- In patients with a documented history of malignancy, a rise in CRP concentration may indicate recurrence of the disease. In patients with hypo- or unresponsiveness to epoetin therapy, de novo or recurrent systemic diseases, malignancy should be considered.

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References

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