Meeting the challenges of a new millennium: optimizing the use of recombinant human erythropoietin

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Abstract. Optimizing the use of recombinant human erythropoietin (r-HuEPO) involves choosing an appropriate dose regimen and target haemoglobin level, addressing factors that inhibit response, and considering appropriate adjuvant therapy. Subcutaneous administration of r-HuEPO two or three times weekly is optimal for most patients. Early detection and treatment of iron deficiency is mandatory. Measurement of the percentage of hypochromic red blood cells is a reliable marker of functional iron deficiency, and the treatment of choice is intravenous iron. Other factors that can affect the response to r-HuEPO include blood loss (sometimes occult), infection, inflammation, hyperparathyroidism with marrow fibrosis, aluminium toxicity, vitamin B₁₂/folate deficiency, haemolysis, bone marrow disorders, haemoglobinopathies, under-dialysis and possibly angiotensin-converting enzyme inhibitors. These factors should be identified and corrected where possible. Ascorbic acid, vitamin D, folic acid, carnitine, other cytokines and growth factors have all been shown to augment the response to r-HuEPO in some patients. Further research is required before any of these adjuvant therapies can be incorporated into routine clinical practice. With regard to target haemoglobin value, the current practice is to aim for a level of 10–12 g/dl, but it may be argued that a higher target would achieve greater benefits in terms of physical performance, quality of life, and possibly cardiac morbidity and mortality. International multicentre trials are currently in progress to address this issue, as are studies on other substances that may be able to stimulate erythropoiesis.

Key words: anaemia, erythropoiesis, iron, hypochromic red blood cells, r-HuEPO

Introduction

We have now enjoyed the benefits of using recombinant human erythropoietin (r-HuEPO) in dialysis patients for more than a decade and its benefits are now being extended to pre-dialysis patients. Much has been learned about ways of optimizing the effects of r-HuEPO, while controlling the costs of treatment. Much still remains to be learned. This paper reviews our current knowledge and highlights ongoing research that may allow us to use r-HuEPO even more effectively in future. Key issues include the optimum route and frequency of administration for r-HuEPO, the importance of intravenous (i.v.) iron supplementation, the correction of factors inhibiting a response to r-HuEPO, the potential role of adjuvant therapies, and the selection of an appropriate target haemoglobin value. These issues will be discussed in turn.

Intravenous or subcutaneous r-HuEPO?

A number of studies suggest that less r-HuEPO is required to maintain a given target haemoglobin level if the hormone is given subcutaneously (s.c.) rather than i.v. [1–5]. For example, the study reported by Bommer et al. in 1991 [2] showed that when patients were switched from i.v. to s.c. administration, haemoglobin was maintained at the same level, with a 30% reduction in total weekly r-HuEPO dose. Other studies have shown only a small advantage of s.c. versus i.v. r-HuEPO [6], and a few have shown no advantage at all [7–9].

Taken together, the evidence suggests that s.c. r-HuEPO does have a marginal benefit over i.v. administration in haemodialysis patients, but there is a wide variation between countries as to which route is used. In the US, the majority of patients receive i.v. r-HuEPO, while in Europe, the s.c. route is normally used. In pre-dialysis patients or those on continuous ambulatory peritoneal dialysis (CAPD), s.c. administration is more convenient and therefore preferable.

Dosage frequency for s.c. r-HuEPO

There are studies showing the efficacy of s.c. r-HuEPO over a wide range of dosage frequencies—once weekly [10–12], twice weekly [10,13,14], three times weekly...
[11, 15, 16] and even daily [16, 17]. From the practical point of view, the optimal dosage frequency for s.c. r-HuEPO in most patients is two or three times weekly. However, there is no doubt that, in certain patients, once-weekly administration produces a satisfactory effect, though a slightly higher dose may be required. While there was some early evidence that once-daily administration might minimize the total dose requirement, this has not been substantiated, and it has not been taken up in routine clinical practice.

Iron monitoring and supplementation

Early detection and treatment of functional iron deficiency is mandatory in optimizing the use of r-HuEPO. Methods of iron monitoring and supplementation are described in full elsewhere in this supplement. Measurement of the percentage of hypochromic red blood cells is undoubtedly the most reliable method currently available for detecting functional iron deficiency. It should be used along with the serum ferritin or transferrin saturation wherever possible.

In functional iron deficiency occurring as a result of r-HuEPO treatment, iron must be administered by the i.v. route in order to have an immediate and sustained impact on erythropoiesis. Aggressive i.v. iron therapy is increasingly recognized as a means of enhancing the response to r-HuEPO, with obvious implications for an improved cost/benefit ratio. Evidence from 10 studies conducted since 1992, including a total of more than 450 patients, shows that intensive i.v. iron supplementation allows a reduction in dose of 19–70% [9, 18–26].

The benefits of using the i.v. route are demonstrated by a randomized controlled study by Macdougall et al. in 37 patients. Of these, 12 received i.v. iron dextran (250 mg every 2 weeks), 13 received oral ferrous sulphate, 200 mg t.d.s., and 12 received no iron [22]. The starting haemoglobin was < 8.5 g/dl, and ferritin 100–800 μg/l. Over the 16 weeks of the trial, the group receiving i.v. iron had by far the best response (Figure 1). The responses of the no-iron and oral iron groups were remarkably similar, indicating that oral iron conferred no benefit over no-iron administration. This may be partly due to non-compliance, as oral iron is poorly tolerated. In this study, the mean ferritin level on entry was around 300 μg/l (i.e. patients were initially not iron-deficient). In patients receiving i.v. iron, ferritin remained at around 300 μg/l throughout the study. In contrast, in the no-iron and oral iron groups ferritin levels fell. The dose of r-HuEPO required was significantly lower in the i.v. iron group compared with the no-iron group.

The findings of this study were similar to those of Fishbane et al., who studied 52 patients in whom anaemia had already been partially corrected with r-HuEPO [21]. In this study, patients randomized to oral iron showed no further change in haematocrit, whereas those who received aggressive i.v. iron supplementation showed a significant increase. The oral iron group required a slight increase in r-HuEPO dose to maintain their starting haematocrit, whereas those receiving i.v. iron showed a striking reduction in dose requirement during the first two months of the study. This lower dose requirement was then maintained for a further two months to the end of the period of follow-up.

Other factors affecting the response to r-HuEPO

Although iron deficiency is probably the most important factor affecting the response to r-HuEPO in most patients, blood loss (often occult), infection and inflammation are also important. Factors affecting a minority of patients include hyperparathyroidism with marrow fibrosis, aluminium toxicity, vitamin B12/folate deficiency, haemolysis, bone marrow disorders, haemoglobinopathies, under-dialysis and carnitine deficiency. Whether angiotensin-converting enzyme (ACE) inhibitors affect the response to r-HuEPO is still a matter of controversy.

Role of adjuvant therapy

In addition to i.v. iron supplementation, a number of other measures have been examined as a means of optimizing the effect of r-HuEPO, as described below.

Intravenous ascorbic acid

Although very limited data are available, ascorbic acid is a promising adjuvant therapy in patients with iron overload showing a suboptimal response. At present there is only one published paper on the role of i.v. ascorbic acid in patients on r-HuEPO: an uncontrolled study by Gastaldello et al. [27] in four haemodialysis
patients. All these patients were iron-overloaded, with very high serum ferritin levels—almost 1000 μg/l. They were given high-dose ascorbic acid: 500 mg i.v. after each haemodialysis session, three times weekly. The haemoglobin rose after each period of ascorbic acid administration, then fell again when ascorbic acid was stopped (Figure 2).

**L-Carnitine**

A recent placebo-controlled study by Labonia et al. treated 13 dialysis patients (already receiving r-HuEPO) with high doses of L-carnitine, 1000 mg i.v. after every dialysis session for 6 months. The L-carnitine-treated group showed a 38% reduction in r-HuEPO requirements compared with the placebo group (11 patients) ($P < 0.02$) [28]. This difference was due to a marked response in about half the patients: seven patients appeared to show a reduction in r-HuEPO dose requirements while the remaining six did not (Figure 3).

**Folic acid**

Aggressive treatment with oral folic acid (10 mg/day) has been shown to improve the response to r-HuEPO, but only in patients with a high mean cell volume [29]. This effect occurred even when the baseline folic acid levels were normal.

**Vitamin D**

A recent study by Albitar et al. found an enhanced response to r-HuEPO when vitamin D was given as an adjuvant therapy to patients with mild-to-moderate hyperparathyroidism [30]. However, it is not clear whether this was a specific effect of vitamin D, or simply a consequence of the reversal of secondary hyperparathyroidism. Suppression of parathyroid hormone (PTH) did occur in this study. However, a previous study showed a benefit of vitamin D in r-HuEPO-treated dialysis patients, even though there was no effect on PTH [31]. It therefore remains debatable whether vitamin D has a specific effect on erythropoiesis, or whether it acts via suppression of hyperparathyroidism. The importance of hyperparathyroidism in inhibiting the response to r-HuEPO is itself controversial.

**Cytokines and growth factors**

So far, the only evidence for the potential role of cytokines and growth factors as adjuvant therapies comes from animal studies. In a study in mice by Brox et al., insulin-like growth factor-1 (IGF-1) reduced the threshold concentration of r-HuEPO required to increase haemoglobin levels [32]. A study by Macdougall et al. [33] found that s.c. interleukin-3 (IL-3) augmented the effect of r-HuEPO in uraemic anaemic rabbits. In these 5/6 nephrectomized rabbits, r-HuEPO alone at a dose of 50 IU/kg, three times weekly s.c., produced an increase in haemoglobin levels, which was enhanced by co-administration of IL-3. This is what would be expected, given the known action of IL-3 in mobilizing erythroid progenitors from the stem cell pool.

**Target haemoglobin and long-term morbidity and mortality**

Optimizing the response to r-HuEPO is not only a matter of enhancing the response to currently used doses, but of setting a target haemoglobin level that will achieve the greatest possible benefits for our patients. The current practice is to aim for a target haemoglobin of 10–12 g/dl. There is, however, much controversy over whether this level should be higher. There is already evidence that increasing the target haemoglobin to a near-normal level improves exercise capacity. It has been hypothesized that it may, by reducing both cardiac ischaemia and left ventricular hypertrophy, improve the high cardiovascular morbidity and mortality associated with end-stage renal fail-
ure. Three multicentre studies were set up to investigate this issue: the US Amgen study in high-risk cardiac patients, and ongoing studies in Scandinavia and Canada.

**US Amgen study**

The Amgen study, which is due to be published shortly, had recruited 1265 patients at the time it was aborted prematurely. Of 634 patients in the higher target haemoglobin group, 35% died, compared with 29% in the standard haemoglobin control group of 631 patients (not significant). However, it is important to note that this study was in high-risk cardiac patients. Publication of the details of this study is needed before we can draw any firm conclusions.

**Scandinavian study**

This open-label, randomized, multicentre study has recruited over 300 patients. Half are randomized to a haemoglobin of 14.5–16.0 g/dl (males) or 12.5–14.0 g/dl (females). The remainder are aiming for a conventional target haemoglobin of around 10.0–11.0 g/dl, and the follow-up period is 18 months. In contrast to the US Amgen study, high-risk cardiac patients have been excluded from the Scandinavian study. An extensive battery of assessments is being used, including morbidity, mortality, safety, adverse events, exercise testing, echocardiography, blood rheology, brain blood flow, coagulation studies, dialysis efficiency, iron requirements, endocrine effects, nutritional status, results after renal transplantation, effects on the immune system and cost utility. Publication is expected in early 1999.

**Canadian study**

This open-label, randomized, multicentre trial is recruiting 140 asymptomatic haemodialysis patients with echocardiographic evidence of left ventricular hypertrophy or left ventricular dilatation. Half the patients are being randomized to a relatively low target haemoglobin of 9.0–10.5 g/dl. The other half are aiming for a near-normal target haemoglobin of 13.0–14.0 g/dl. At follow-up periods of 12 and 18 months, cardiac and other endpoints will be examined, including left ventricular mass, left ventricular cavity volume, quality of life, side-effects and cost-effectiveness. Publication is expected in 1999 or early 2000.

**The future**

In future, we are likely to see new and more convenient means of administering r-HuEPO. Research is also focusing on alternative ways of stimulating erythropoiesis. The compounds under investigation have been synthesized by modifying the erythropoietin molecule by genetic engineering, or by creating smaller peptides to mimic the action of erythropoietin on its receptor. Whether these substances, or erythropoietin gene therapy, will ever become a clinical reality, only time will tell. In the meantime, i.v. iron and perhaps other adjuvant therapies offer a real possibility of maximizing the potential of the treatment we have already.

**References**


