

Review Article

The use of erythropoietin in renal failure

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Summary: The treatment of renal anaemia by recombinant human erythropoietin (EPO) is now well established. Several studies have examined the pharmacokinetics and efficacy of the drug given intravenously, intraperitoneally and subcutaneously and there is increasing evidence that the subcutaneous route has several advantages including the requirement for a lower dose. It is also important to stress the need for careful determination of baseline iron status of all patients before commencing EPO therapy. In the long term the extremely high iron stores of transfusion dependent patients will disappear. In the short term, however, the majority of the patients whose serum ferritin is less than 100 µg/l will require iron supplementation to allow an appropriate haemoglobin response. Alternatively, a fall in transferrin saturation to less than 20% is certainly an indication for iron supplementation and if oral iron therapy is not adequate then intravenous preparations may have to be considered. Although the anaemia of renal failure can be fully corrected by EPO, partial correction may be sufficient to reverse the problems of reduced exercise capacity, myocardial ischaemia and cardiomegaly which are frequently associated with end-stage renal disease. Partial correction will also result in a lesser rise in whole blood viscosity and, in turn, possibly reduce hypertension, thrombosis and increased peripheral resistance and thus lessen the side effects of EPO therapy.

Introduction

The synthesis of recombinant human erythropoietin (EPO) represents a significant advance in the therapy of renal anaemia. The earliest studies detailed the treatment of haemodialysis patients and EPO was administered intravenously.^{1–4} More recent reports have examined the use of the drug in pre-dialysis patients^{5,6,7} and in those on continuous ambulatory peritoneal dialysis (CAPD)^{8–11} and have investigated the pharmacokinetics^{12,13} and efficacy^{7–11,14–17} of subcutaneous administration. The introduction of EPO has also highlighted the problem of functional iron deficiency which can have a deleterious effect on the haemopoietic response to such a potent marrow stimulus.^{2,18–21} In addition, the therapeutic response has resulted in a significant improvement in cardiovascular function and in exercise tolerance. This review will consider these above changes as well as such problems as patient selection, target haemoglobin levels and potential side effects.

Patient selection

The proportion of dialysis patients that would benefit from EPO treatment is not clearly defined but estimates of between 50 and 75% have been made.^{19,12} Since the therapy is both expensive and long-term, careful consideration has to be given to the selection of patients.

Individuals who have been on haemodialysis or CAPD for a minimum of 3 months and have a haemoglobin concentration consistently below 8 g/dl should be given priority. Patients who have recently commenced dialysis may experience a spontaneous amelioration of their anaemia^{23–25} thus negating the need for EPO. In contrast dialysis patients with symptoms of ischaemic heart disease, even with haemoglobin concentrations above 8 g/dl, should also be considered for treatment.

Dosage of EPO and routes of administration

By far the greatest experience is with intravenous therapy in haemodialysis patients, and one of the earliest studies showed that there was a dose-dependent rate of response to EPO.² It has, how-

ever, been suggested that the risk of side effects, such as severe hypertension and thrombotic complications may be lessened with a haemoglobin rise not exceeding 1 g/dl/month. As a result the recommended starting dose of EPO is now lower than in earlier studies. More centres now use 100–200 U/kg/week for haemodialysis patients, divided into 2 or 3 doses. A similar dose range has been used with good effect in patients not yet on dialysis.^{5–7}

Intravenous administration is clearly impractical for regular use in CAPD patients. Alternatives to be considered include the intraperitoneal and subcutaneous routes. In a single-dose pharmacokinetic study in CAPD patients the bioavailability of subcutaneous EPO was seven times greater than that of intraperitoneal administration, but was still only 22%.¹² These results have been subsequently confirmed.¹³ Frenken *et al.*,⁸ however, used the intraperitoneal route for treating 5 CAPD patients, and obtained an effective clinical response with a dose of 300 U/kg/week. We have subsequently shown a similar haemoglobin response but with only 120 U/kg/week given subcutaneously in 9 CAPD patients.¹⁰

More recently it has been shown¹⁴ that when the patient has reached optimal haemoglobin concentration a 50% reduction in dose can be achieved by switching from intravenous to subcutaneous administration. Stevens *et al.*⁹ treated 12 CAPD patients with subcutaneous EPO and obtained a brisk response to a starting dose of between 300 and 450 U/kg/week. The individual dose was then reduced to between 37.5 and 150 U/kg/week (median 75 U/kg) to maintain a haemoglobin of 11.0 to 11.5 g/dl. Other studies in children on continuous cycling peritoneal dialysis (CCPD) as well as CAPD and in pre-dialysis patients have confirmed the efficacy of the subcutaneous route.^{7,11,16,17}

Thus, the subcutaneous route appears to be preferable, not only in CAPD patients,^{9–11} but also in haemodialysis subjects^{14–16} when lower doses of EPO may be used. Evidence to date suggests a starting dose of 75–150 U/kg/week in 2 or 3 divided doses. If the patient can be taught to give their own subcutaneous injections then a daily dosing regimen may be worth considering since this may allow an even greater reduction in total weekly dose.¹⁶

Optimum response rate and end-point haemoglobin

Although it is possible to correct fully the anaemia of chronic renal failure with EPO, risk–benefit comparisons suggest that partial correction seems the best compromise. A linear increase in the haemoglobin or haematocrit leads to an exponen-

tial rise in whole blood viscosity^{26–28} which, in turn, is thought to contribute to many of the side effects of EPO therapy such as hypertension, increased peripheral resistance and thrombotic complications. Based on this a rise of 1 g/dl/month appears the best compromise.

The optimum target haemoglobin seems to be in the range of 10–12 g/dl. It is at this level that the risk–benefit ratio appears minimized. Nevertheless, this is a very arbitrary guideline, and some flexibility is clearly necessary in treating individual patients.

Iron availability for the haemopoietic response

It is important to determine the baseline iron status of any patient being considered for EPO therapy. If a patient is iron deficient (serum ferritin < 15 µg/l) then some improvement in the anaemia is seen with iron therapy alone.^{29,30} Patients may also be iron deficient at higher levels of serum ferritin, for example in conditions causing hepatocyte dysfunction where there is significant release of intra-hepatocyte ferritin secondary to tissue damage, or in conditions where there is massive resorption of iron from extravasated blood. In these circumstances the serum ferritin may be raised out of proportion to the iron stores. If there is doubt about the true iron status of anaemic patients a therapeutic trial of oral or intravenous iron should be given for a minimum of 4 weeks. If there is a reticulocyte and haemoglobin response during this period then EPO therapy should be postponed until a new stable haemoglobin concentration is achieved.

In addition it is essential to determine whether there is sufficient readily available iron to meet the anticipated demand. Even patients who are iron replete before starting EPO can rapidly become deficient under the influence of EPO.^{2,17–21,31} This may occur in the presence of a normal serum ferritin as well as with stainable iron in the marrow, and the problem appears to be a limitation in the rate of iron supply, that is, the stores are unable to release iron fast enough to meet the demand.

Previous work has shown that a rise of 1 g/dl in the circulating haemoglobin concentration uses 150 mg of storage iron (equivalent to nearly 20 µg/l of serum ferritin).^{32,33} Thus, for an anticipated haemoglobin rise of 5 g/dl following EPO therapy, the absolute minimum requirements would be 750 mg of storage iron (100 µg/l serum ferritin). Patients with starting serum ferritin levels less than 100 µg/l, therefore, are highly likely to develop functional iron deficiency.

Patients with initial serum ferritin levels greater than 100 µg/l may also develop functional iron deficiency^{2,17,20} which is best detected from changes

in the percentage transferrin saturation with iron. If the transferrin saturation falls below 20% then it is likely that the available iron supply to the erythron is inadequate^{2,18-21} and iron therapy is indicated.

EPO resistance

Large multicentre trials of EPO in North America and Europe indicate that 95–98% of patients treated with EPO will respond.³¹ Nevertheless, there is a small proportion of patients who have either no response or a grossly inadequate one. Even though some of these patients will respond to a much higher dose of EPO an underlying cause of the apparent resistance should first be sought. The most common problem is an inadequate supply of available iron. Other forms of haematinic deficiency, such as B12 or folate, are much less common and should be excluded at an early stage. Aluminium toxicity has to be severe before haemopoiesis is inhibited.³⁴ High parathyroid hormone levels also inhibit erythropoiesis *in vitro*,³⁵ but the clinical relevance of these findings remains controversial.^{34,36,37} Infection, however, either acute or chronic, is a potent suppressor of erythropoietic activity and appears to be clinically a very important cause of apparent resistance.¹ Similarly, occult malignancy has also been associated with a failure to respond. In addition to a lack of response an increased loss of red cells either through haemolysis or blood loss may cause apparent resistance. A clue may be an enhanced reticulocyte response to EPO which is not reflected in any change in the haemoglobin. Thus patients showing a poor response to EPO, or loss of a previous response, require investigation for an underlying cause. It may be possible to override some of these causes of EPO resistance with a higher dose of EPO, but the importance of excluding them should not be disregarded.

Cardiovascular benefits of EPO

Chronic severe anaemia results in an increase in cardiac output, a decrease in peripheral resistance due to compensatory vasodilatation secondary to tissue hypoxia, and reduced whole blood viscosity.³⁸⁻⁴² The anaemia of end-stage renal failure may play a major role in the development of left ventricular hypertrophy in patients receiving long-term dialysis^{43,44} and is an independent determinant of survival in such individuals.⁴⁵ Renal patients with chronic anaemia have a grossly impaired exercise capacity, lowered maximal oxygen consumption, and reduced threshold for anaerobic metabolism during physical activity.⁴⁶⁻⁴⁹ They also

have an increased predisposition to coronary artery disease, in part related to abnormal lipoprotein profiles, but almost certainly exacerbated by severe anaemia causing myocardial ischaemia.⁵⁰⁻⁵³

Studies prior to the advent of EPO therapy showed that acute reversal of uraemic anaemia by red cell transfusion was followed by a reduction in cardiac output and an increase in total peripheral resistance, but that the overall result was an increase in diastolic blood pressure.⁶⁹ Several studies have assessed the haemodynamic effects in patients treated with EPO. Buckner *et al.*⁵⁴ found a reversal in the compensatory vasodilatation of anaemia without complete normalization of the elevated cardiac output. Akiba *et al.*⁵⁵ observed a significant fall in cardiac index along with increases in blood viscosity and systemic vascular resistance after 12 weeks of EPO. Similar results have been obtained by others,^{56,57} although one group inexplicably found an increase in cardiac output and a decrease in peripheral resistance after EPO.⁵⁸

A number of studies have confirmed the expected increase in working capacity, maximal oxygen consumption, and anaerobic threshold after EPO therapy,⁵⁹⁻⁶⁴ consistent with the subjective improvement in the patients' physical well-being and exercise capacity. Before EPO therapy 7 out of 10 of our patients had electrocardiographic (ECG) evidence of myocardial ischaemia during exercise. This was reversed in all but one after 4 months of EPO, and by 12 months none of the patients had any evidence of an ischaemic ECG during exercise.⁶⁴ Acute reversal of myocardial ischaemia after 3 months of EPO was also observed by Wizemann in 8 haemodialysis patients.⁶⁵

Since it has been suggested that chronic anaemia is a major determinant of left ventricular hypertrophy in long-term haemodialysis patients,^{43,44} reversal of renal anaemia by EPO might result in a decrease in left ventricular hypertrophy. We noted a significant progressive reduction in left ventricular mass, measured using echocardiography, in 10 haemodialysis patients monitored over the first 12 months of EPO therapy.⁶⁴ A similar regression of left ventricular hypertrophy was recently reported following renal transplantation.⁶⁶

Hypertension related to EPO therapy

Hypertension has been the most frequently reported side effect associated with EPO therapy.^{1-4,18,19,22,26,67-70} Casati *et al.*⁴ found that all 8 previously hypertensive patients required treatment for elevated blood pressure whereas none of 6 normotensive patients demonstrated any change in blood pressure during EPO therapy. In contrast, results of a multicentre clinical trial of EPO in 309

evaluable patients showed that although 72% of the patients had existing hypertension at baseline, they proved to be at no greater risk of increased blood pressure than those who were normotensive to begin with. Only 35% of the patients in the study developed sustained increases in diastolic blood pressure of 10 mmHg or more.⁷⁰

This increase in blood pressure is thought to be mediated via a number of pathophysiological changes occurring secondary to the increase in haematocrit. These include an increased peripheral vascular resistance, an increased blood viscosity, and a failure of reduction of the elevated cardiac output of anaemia.

A significant increase in peripheral resistance was found by Neff *et al.*⁷¹ after haematocrit levels were increased from 20 to 40% by red cell transfusion over a 3 week period. It was concluded that hypoxic peripheral vasodilatation, which occurs as a compensatory response in chronic anaemia, is reversed as the anaemia is corrected, resulting in relative vasoconstriction which increases the peripheral resistance. Similar effects on peripheral vascular resistance have been found during correction of renal anaemia by EPO.⁵⁴⁻⁵⁷

Another mechanism which may also contribute to the increase in peripheral resistance and blood pressure is the rise in blood viscosity associated with the increase in haematocrit.²⁶⁻²⁸ As the haematocrit rises in a linear manner, there is an exponential rise in whole blood viscosity. In addition there is a direct relationship between blood viscosity and vascular resistance.^{72,73} Finally, although there is usually a normalization of the elevated cardiac output as the anaemia is corrected, occasionally this does not occur,⁵⁴ and a sustained high cardiac output in the presence of a reversal of the compensatory vasodilatation of anaemia would result in an increase in blood pressure.

In the majority of instances, blood pressure can be easily controlled by the use of hypotensive drugs, and it is very rare to have to discontinue EPO therapy for severe uncontrollable hypertension.⁷⁰ However, EPO should be stopped immediately if hypertensive encephalopathy ensues. More importantly, however, the aim should be to increase the haemoglobin gradually by the use of an appropriate dosage regimen of EPO with a view to reducing the chances of encephalopathy.

Side effects and complications of EPO

A further major complication of EPO therapy is thrombosis of the arteriovenous fistula. This occurred in 9.3% of haemodialysis patients entered into a European multicentre study.⁷⁴ Many other published reports have documented small but

significant numbers of patients experiencing this problem,^{1,3,4} often early in the course of EPO treatment. A recent placebo-controlled multicentre trial suggested that there was a significantly increased risk of this complication developing in patients receiving EPO.⁷⁵ As with hypertension, the rise in haematocrit and associated increase in blood viscosity are thought to be contributory, although the absolute levels of blood viscosity attained at the target haemoglobin are still considerably lower than those from normal subjects. Other factors which may contribute to an increased predisposition to thrombosis include a normalization of bleeding time and alterations in platelet function⁷⁶⁻⁷⁹ and a reduction in protein C and protein S levels in patients treated with EPO.⁸⁰

Less serious side effects noted during EPO therapy include transient myalgia and flu-like symptoms occurring shortly after administration of the first few doses of EPO,^{1,4,31,74} conjunctival injection,³¹ and headache. In addition there have been a few reports of nausea, vomiting, shortness of breath, diarrhoea, and abdominal or loin pain.^{1,2,81} Genuine intolerance to EPO sufficient to warrant stopping the hormone is rare. To date there have been no reports of antibody formation.⁸²

In some haemodialysis patients higher pre-dialysis potassium and phosphate levels accompany the rising haematocrit.^{2,4} This may be due to increased dietary intake resulting from the general improvement in well-being. However, it is possible that dialyser potassium clearance is lower with higher haemoglobin concentrations.⁸³ Thus, dietary guidelines should be reinforced for all subjects starting EPO treatment.

EPO in pre-dialysis patients

Several studies have confirmed the efficacy of EPO in reversing the anaemia of end-stage renal failure in patients not yet requiring renal replacement therapy.^{5,6,7} Lim *et al.*⁵ treated 14 anaemic pre-dialysis patients with intravenous EPO in a double-blind placebo-controlled trial and observed an increase in the mean haemoglobin from 9.1 ± 0.2 (s.e.) to 12.3 ± 0.4 g/dl over a 2 month period. In a further study by Eschbach *et al.*⁷ all 17 pre-dialysis patients with anaemia responded to EPO with a median haematocrit rise from 0.27 to 0.37. Similar results were obtained by Stone *et al.*⁶

The concern that the resultant increase in blood viscosity and possible exacerbation of hypertension might cause a more rapid decline in renal function⁷² has not been borne out by the evidence to date. Lim *et al.*⁵ found no change in renal function as judged by blood urea nitrogen, serum creatinine, and creatinine clearance, although the follow-up was only for 2 months. Eschbach *et al.*⁷ likewise

observed no change in the rate of deterioration in renal function measured by the reciprocal of the serum creatinine over 6 months in 17 pre-dialysis patients treated with EPO. Longer term studies will be required, however, before the safety of EPO in pre-dialysis patients can be more confidently established.

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