
Recombinant Human Erythropoietin in Anaemic Patients with End-Stage Renal Disease

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Abstract:

The effect of erythropoietin (EPO) on the anaemia of end-stage renal disease was investigated in 76 transfusion-dependent haemodialysis patients. EPO was administered intravenously in a dose of 50 μ /kg, 3 times a week for 12 weeks. The haematocrit had risen from 18.7 \pm 1.9 to 26.6 \pm 3.8 on day 84. Fifty-eight patients (76.3%) responded with an increase in haematocrit of \geq 6. Complications included hypertension (21.1%), iron deficiency (18.4%), thrombosis of vascular access (7.9%). This relatively low rate response could be accounted for by differences in the treatment policy. It remains to be seen whether the standard protocol of EPO use in renal failure would improve the response.

Introduction:

Erythropoietin (EPO) is a 34 Kd glycoprotein produced principally by the proximal renal tubular cells whose primary function is the regulation of erythrocyte production. It is essentially lineage specific with regard to its effect on red blood cells and the regulation of EPO production is under the control of a simple feedback mechanism. EPO production is increased in hypoxaemia.^{1,2} The cloning and expression of the EPO gene in Chinese hamster ovary cells, in 1985, led to the production of commercial quantities of recombinant human EPO.³ It was evident very early in the evaluation of the clinical value of EPO that it may have a significant impact on diseases associated with anaemia.

The availability of sensitive radio immunoassays permitted identification of disorders of EPO deficiency.⁴ Among the patients who were initially designated for the study of EPO were those with chronic renal failure (CRF). The use of EPO in this patient population is one of the most important advances in the field of clinical haematology.

As one would expect, patients with nonfunctioning kidneys fail to produce EPO in sufficient amounts to support red blood cell production. The theory that the anaemia related to CRF was at least partially due to EPO deficiency was confirmed by investigators in the United States and England.^{5,6} Doses of 25-500 u/kg 3 times per week were administered intravenously and demonstrated a dose-dependent increase in haematocrits, while significantly reducing and even eliminating the

need for red blood cell transfusions.⁶ In the large multicentre phase III trial reported by Eschboach et al.⁷ patients treated with EPO experienced increases in haematocrits from baseline values of 22 to 35. Those who were treated an initial dose of 300u/kg 3 times per week achieved their target haematocrit within 6-8 weeks. Patients treated with a dose of 150u/kg 3 times per week achieved their target haematocrit in approximately 10 weeks. The 333 patients enrolled in this study required 1030 erythrocyte transfusions over the 6 months before study initiation. Within 2 months of EPO therapy all patients were erythrocyte-transfusion independent and remained as such with continued EPO maintenance.

The aim of the present investigation was to evaluate the efficacy and clinical safety of EPO in anaemic haemodialysis patients.

Methods:

Seventy-six haemodialysis patients (42 males and 34 females) were treated with EPO, in the Nephrology Division of Second March Teaching Hospital, for a period of 12 weeks. The mean age of the patients was 30.7 years (range 15-45 years), and body weight was 54.4kg (range 31-72 kg). They were subjected to stable haemodialysis 3 sessions per week, each session of 4 hours. Forty-six patients were normotensive while 30 patients had medically treated hypertension which was adequately controlled at the onset of therapy.

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The participants met the following criteria:

- (a) a haematocrit equal to or lower than 22,
- (b) stable haemodialysis for at least 6 months,
- (c) received at least 6 blood transfusions,
- (d) no evidence of iron, folic acid or vitamin B₁₂ deficiency,
- (e) no history of seizure, thrombovascular or liver disease.^{8,9}

EPO was provided as recombinant human erythropoietin, Epoetin alfa, manufactured by Ortho Cilag. An intracutaneous test dose of 20u was applied in all patients before the start of regular treatment. No allergic responses were observed. The drug was administered intravenously, in a dose of 50u/Kg, at the end of dialysis, 3 times a week.¹⁰ All patients were maintained on ferrous fumarate, (200 mg/day) and folic acid (5mg/day). The blood pressure was measured before each injection and the patients were interviewed and examined weekly.

The response to erythropoietin was monitored fortnightly. Hemoglobin concentration, haematocrit, red blood cell count and erythrocyte indices, white blood cell and platelet counts were obtained with an automatic cell counter. Reticulocyte counts were performed by microscopic examination after staining with brilliant crestyl blue. Serum iron and total iron binding capacity were determined by a calorimetric method. Renal and liver function tests, serum electrolytes protein, uric acid, calcium and phosphate were determined monthly according to standard clinical laboratory techniques.¹¹

A substantial response to EPO therapy, for purposes of this analysis was defined as an increase in haematocrit of at least 6 over the course of treatment without transfusion.⁹ The

statistical analysis was performed with the use of the paired student t-test. A probability 'P' value below 0.05 was considered to indicate statistical significance. Values are expressed as means ± SD.

Results:

Base-line and follow up haematological and biochemical values are shown in Table 1. At the outset of EPO therapy, the mean haematocrit of the 76 patients was 18.7 ± 1.9. The haematocrit had risen to 26.6±3.8 (*p* < 0.01) on day 84. Fifty-six of the participants (76.3%) responded with an increase in haematocrit of ≥6 by day 84. However, only 18 Patients (23.7%) were able to achieve a target haematocrit value of 30. The pretreatment reticulocyte count was 22.6 ± 18.1%. EPO elicited a remarkable rise in reticulocyte count with a mean value of 36.4± 23.1% on day 84 (*p* < 0.01). A concomitant increase in the platelet count occurred from 178.3 ±51.2 x 10⁹/L to 220.1 ±62.8 x 10⁹/L (*p* < 0.01).

The initial mean serum iron was 163.9 ± 23.9 ug/dl. This fell to 70.3 ± 25.2 ug/dl by the end of the study (*p* <0.01). Ten non-responders and four responders had serum iron levels ≤ 50 ug/dl. The serum creatinine did not undergo significant change during treatment, 12.6 ±1.7 mg/dl versus 12.7± 1.9 mg/dl, (*p*<0.7). In contrast, the mean serum potassium had increased from 5.3±0.6 mmol/L, on day 0, to 5.8±0.7 mmol/L on day 84, (*p*< 0.01). Sixteen patients (21.1%) developed hypertension. Subnormal serum iron levels (≤50 ug/dl) were observed in 14 patients (18.4%). Six incidents (7.9%) of thrombosis of arteriovenous fistula were documented; whereas four patients (5.3%) had seizures.

Table 1: Impact of EPO on various parameters. Values expressed as mean ± standard deviation.

Mean ±SD	Day 0	Day 84	<i>p</i>
PCV	18.7±1.9	26.6±3.8	<0.01
Ret %	22.6±18.1	36.4±23.1	<0.01
Plat x 10 ⁹ /L	178.3±51.2	220.1±62.8	<0.01
CRE mg/dl	12.6±1.7	12.7±1.9	0.7
Iron ug/dl	163.9±23.9	70.3±25.2	<0.01
K mmol/L	5.3±0.6	5.8±0.7	<0.01

PCV = Packed cell volume

Ret = Reticulocyte

Plat = Platelet

CRE = Creatinine

p = Probability value.

Discussion:

Clinical studies have shown the effectiveness of EPO in correcting the anaemia of end-stage renal disease in patients maintained on haemodialysis.^{12,13}

EPO has also been found to be effective in anaemia in predialysis renal patients. Consistently good results have been obtained with EPO not only for correction of anaemia but also for quality of life and exercise capacity.¹⁴ Over 90% of patients with renal anaemia respond to treatment with EPO.¹⁵

In the present study, EPO therapy has induced only a modest mean increase in haematocrit.^{7,9}

The response to EPO, defined as an increase in haematocrit of ≤ 6 , was achieved by 56 patients. This relatively low rate of response could be accounted for by differences in selection of patients, EPO dosage and regimen and iron status. Bleeding, inter-current infection and aluminum toxicity also impair the erythropoietic response to EPO.^{9,15}

Endogenous serum EPO levels are generally related to response in anaemic patients though a wide variability exists. As might be expected patients with a low EPO level respond better to exogenous EPO than those with a high level. In general, patients are likely to respond if their EPO level is < 100 mU/ml, less likely to respond if its between 100-500 mU/ml and very unlikely to respond if their EPO is > 500 mU/ml.^{9,16} Therefore, selection of patients for EPO therapy, in the future studies needs to be on the basis of endogenous EPO level.

Target haematocrit in adult haemodialysis patients should be 30 to 36. In the correction phase, a low starting dose (50u/kg) three times weekly is recommended in order to allow the circulation to adapt to changes in haematocrit and viscosity. The dose of EPO should be increased if the haematocrit does not increase at least 3/month. Dose adjustment should be made in increments of 25 u/kg 3 times per week at intervals of at least 4 weeks until the target haematocrit is achieved. To minimize the risk of hypertension the rate of increase in haematocrit should not exceed 6/month. Once the target haematocrit is achieved, the dose should be decreased by 25 u/kg/dose in order to avoid exceeding the target range. In addition, if the haematocrit exceeds 36, therapy should be withheld. In the maintenance phase, the usual dose to maintain the target haematocrit is between 30 and 100 u/kg 3 times per week.

In the United Kingdom the average annual cost of EPO maintenance is approximately \$ 4500.⁹

In a cost benefit analysis of EPO treatments, this must be weighed against the cost of red cell concentrates, admission for transfusion and disposables. Thus, the effective cost of reduction in morbidity was reported, in a comprehensive study, to be about \$ 1800 per year.¹⁷ A study in Australia found a net cost-benefit to the whole community when the savings of return to work, social security payments and transfer to home dialysis were taken into account.¹⁸

According to Mosby's 1997 medical drug reference, the cost of EPO treatment in our series must be about \$1150 per patient over the study period.¹⁰ Thus, in view of the expense of the drug and lack of information about individual endogenous EPO levels, we were unable to readjust EPO dose according to response. Therefore, it would be extremely important to select patients, in the future, on the basis of endogenous EPO levels. Moreover, conversion of the route of administration of EPO from intravenous to subcutaneous injection is recommended for forthcoming studies.^{9,10,17} EPO delivered subcutaneously produces lower but more sustained plasma concentrations. Comparative studies have shown that total weekly maintenance doses are reduced by between 35-52% with the subcutaneous rather than intravenous administration.^{18,19} The frequency of administration may also be important in maximizing the response to treatment. Daily subcutaneous administration has been reported to give a better response than the same total weekly dose given 2 or 3 times a week.^{13,20}

Monitoring of iron status during therapy with EPO is obligatory as suboptimal responses are frequently due to development of iron deficiency. Such monitoring is usually performed by measurement of serum ferritin. The latter has been clearly shown to correlate closely with marrow iron estimations in haemodialysis patients.²¹

Thus all patients are maintained on ferrous fumarate, equivalent to 200 mg iron/day. Should ferritin fall below 100ug/L, iron dextran is given intravenously.⁹ However, like other acute phase protein ferritin may be falsely elevated in the presence of inflammatory disease. The use of radio active H*I blood counter with its ability to estimate the proportion of hypochromic red cells which increase when iron deficiency develops, provides an inexpensive and immediate method of monitoring iron status.²²

The mean pretreatment serum iron was 163.9 ug/dl. The significant decline in mean serum iron to 70.3 ug/dl, on day 84, was a reflection of increased iron turnover. In addition, 14 patients (18.4%) had serum iron levels \leq 50 ug/dl. These findings emphasize adequate iron supply to patients on EPO and careful assessment of body iron status throughout treatment. Hypertension (21.1%) was the commonest side effect despite the modest response.⁹ The significant increase in serum

potassium during therapy should not be overlooked. Six patients (7.9%) developed thrombosis of arteriovenous fistula. Thus patient with functioning arteriovenous fistulas might benefit of antiplatelet therapy.

It remains to be seen whether the standard protocol of EPO use in renal failure will improve the response. The present results give an optimistic outlook.

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References:

1. Kraut S & Jacobson, L. Erythropoietin and the regulation erythropoiesis, University of Chicago Press, Chicago, 1970.
2. Goldberg M., Dunnig, S. & Bunnett, H. Regulation of the erythropoietin gene. *Science*, 1988; 242:1412.
3. Brown J., Cohen A. & Egrie, J. Erythropoietin, gene cloning protein structure and biologic properties. *Symp. Quant Biol*, 1986; 51:693.
4. Choen R., demons G. & Ebbe S. Correlation between bioassays and radio-immunoassay for erythropoietin in human serum and urine concentrates. *Proc. Soc. Exp. Biol. Med.* 1985; 110:29.
5. Whineral C., Oliver D., & Pippard M. et al. Effect of human erythropoietin derived from recombinant DNA-on the anaemia of patients maintained by chronic haemodialysis. *Lancet*, 1986; 2:1175.
6. Eschbach J., Egrie J., Downing M. et al. Correction of the anaemia of end stage renal disease with recombinant human erythropoietin. *N. Engl. J. Med.* 1987; 316:37.
7. Eschbach J., Abdulhadi M., Browne J. et al. Recombinant human erythropoietin in anaemic patients with end stage kidney disease. Results of a phase III multicentre clinical trial. *Ann. Intern. Med.* 1989; 111:992.
8. Nielsen O. & Thaysen J. Response to erythropoietin in anaemic haemodialysis patients. *J. Int. Med.* 1989; 226:89.
9. Pattern K. G. The uses of recombinant human erythropoietin. *Saudi Med. J.* 1994; 15:1.
10. Ellsworth A., Dugdale D., Wilt D. & Oliver L. *Mosby's 1997 Medical Drug Reference*. Mosby. Philadelphia, 1997.
11. Tietz N. W. *Clinical guide to laboratory tests*. W. B. Saunders Company. Philadelphia, 1995.
12. Winearb C. Treatment of anaemia in renal failure. *Prescriber's J.* 1992; 32:238.
13. De March S. Erythropoietin in anaemia of chronic diseases. *Clin. Exp. Rheumatol*, 1993; 11:429.
14. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *B. Med. J.* 1990;300:573.
15. Macdougall I. Poor response to erythropoietin. *B. Med. J.* 1995; 310: 1424.
16. Ludwig H, Fitz E, Leitgeb C. et al. Prediction of response to erythropoietin treatment in chronic anaemia of cancer. *Blood*, 1994; 84:1056.
17. Stevens M, J, Summerfield GP, Hall AA et al. Cost benefits of low dose subcutaneous erythropoietin in patients with anaemia of end stage renal disease. *B. M. J.* 1992; 306:474.
18. Hams DC, Chapman JR, Stewart JH. et al. Low dose erythropoietin in maintenance haemodialysis: improvement in quality of life and reduction in true cost of dialysis. *Austral N Z J Med*, 1991; 21:693.
19. Zachee P. Controversies in selection of epoietin dosages: issues and answers. *Drugs*, 1995; 49:536.
20. Abraham P. A. Controversies in determination of epoietin dosages. *Clin pharmacokinet*, 1992; 22:409.
21. Milman N. Stranberg PN & Visfeldt J. Serum ferritin in patients on regular peritoneal and haemodialysis treatment: relation to marrow haemosiderin iron stores. *Dan Med Bull*, 1984; 31:245.
22. Macdougall IC, Cavill I, Blum B. et al. Detection of functional iron deficiency during erythropoietin treatment: a new approach. *BMJ*, 1992; 304:225.