

THE TREATMENT OF ANAEMIA IN HAEMODIALYSIS PATIENTS WITH RECOMBINANT D.N.A. DERIVED HUMAN ERYTHROPOIETIN (r-HuEPO)

C.G.Winearls, D.O.Oliver, M.J.Pippard, C.Reid and P.Mary Cotes [1986]

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London; Renal Unit, Churchill Hospital, Oxford; Department of Haematology, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex

Anaemia is an almost invariable feature of chronic renal failure and is particularly severe in anephric patients treated by maintenance haemodialysis. There are several mechanisms postulated to explain this anaemia but the critical defect is inadequate secretion of erythropoietin. Treatment with erythropoietin has hitherto been impossible because there has been no source from which it could be purified in sufficient quantities for clinical testing. Ten anaemic haemodialysis patients (mean Hb 6.1 g/dl; range 4.9-8.9g/dl) were treated with escalating doses of r-HuEPO given as an intravenous bolus thrice weekly after each dialysis. All 10 showed significant rises in haemoglobin levels above pre-treatment levels (mean Hb 10.7 g/dl; range 8.3-13 g/dl). Four patients required blood transfusions early in the study but no further transfusions have been needed since. An increase in absolute reticulocyte numbers was seen at lower doses of r-HuEPO than those at which a therapeutic effect could be discerned. No major side-effects of the r-HuEPO were seen but one patient with labile blood pressure developed hypertensive encephalopathy, and another clotted an arteriovenous fistula, when their haemoglobin levels had doubled. r-HuEPO is a rational and effective treatment for the anaemia of ESRF but the long-term consequences of increasing the haematocrit to near normal levels in this group of patients will require careful prospective study.

Commentary by John Feehally

I am one of those nephrologists who recall practicing in the 'pre-EPO' era. The chief characteristic of the management of renal anaemia until 1986 was collusion - between patient and nephrologists. Both working to convince the other that it was not too bad trying to live with end stage renal disease with haemoglobin infrequently more than 6g/dl apart from those few days when a red cell transfusion gave fleeting glimpses of something near normality.

Nephrologists tried to convince the patients they did not feel too bad because they knew they had nothing else to offer without transplantation; the patients I suspect acted their part, knowing that their nephrologist was impotent.

By the mid 1980s there had been years of patient work exploring the pathophysiology of renal anaemia, with much more to come to understand the many surprises in store unravelling the fundamental biology of oxygen sensing. Despite all those uncertainties, the ‘moment’ arrived: there was human recombinant erythropoietin in a vial, and it was injected into the first patient. Of course - with hindsight – we knew it would work, but nevertheless work it did, the reticulocytes appeared and in a short time the patient had a normal haematocrit and felt remarkably better. Probably the single best thing we have been able to offer in my time as a nephrologist to transform quality of life for dialysis patients.

Of course there were many things to come which we failed to predict – why should there be an immune response producing pure red cell aplasia? Why should a hormone so obviously a restricted erythron stimulant turn out to have pleiotropic effects which included provoking hypertensive encephalopathy? Why should the target haematocrit be below the conventional reference range when EPO was given to people with longstanding kidney disease already marked with significant cardiovascular comorbidity. Why should it be necessary to support the use of EPO with intravenous not oral iron? The last sentence of the abstract was cautious and prescient: “the long-term consequences of increasing the haematocrit to near normal levels in this group of patients will require careful prospective study.”

But work it did and this simple abstract describing a pilot study of modest dimensions left us all in no doubt that EPO was here to stay.