

The Management of Anaemia in Chronic Kidney Disease – Current and Future Issues

a report by

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Anaemia is an almost universal complication of chronic kidney disease, accounting for much of its symptomatology. The cause of renal anaemia is multifactorial, but one of the major pathogenetic factors is inadequate production of erythropoietin from the diseased kidneys, causing an inappropriately low level of red cell production. Erythropoietin is the major hormone involved in preventing apoptosis of erythroid progenitor cells in the bone marrow, and it is produced in the peritubular fibroblasts of the kidney. It was long-recognised that circulating erythropoietin levels in the blood were inappropriately low for the degree of anaemia, and yet the ability to produce synthetic erythropoietin in concentrations that could be used in clinical practice was lacking until the advent of recombinant DNA technology some 30–40 years ago. The gene for human erythropoietin was isolated and cloned in 1983, and using genetic engineering techniques, sufficient quantities of the human hormone were able to be produced in Chinese hamster ovary cells. Clinical trials began in 1985, and the product became licensed in the US in 1989, and in Europe in 1990.

Following the widespread availability of recombinant erythropoietin (epoetin) therapy, a second-generation erythropoietic agent called darbepoetin alfa appeared at the turn of the century. This agent had a longer half-life *in vivo*, and thus required less frequent dosing. Third-generation erythropoietic agents are also under development, as discussed below.

Impact of Anaemia Correction in Chronic Kidney Disease

The first benefit to be realised with epoetin therapy was a dramatic reduction in transfusion requirements among dialysis patients. Previously, many such patients required red cell transfusions every few weeks to maintain even a subnormal haemoglobin concentration. Administration of epoetin resulted in a much more sustained increase in haemoglobin (see *Figure 1*), and patients became aware of a much improved exercise capacity and quality-of-life. Many symptoms that were previously attributable to

uraemia were reversed or corrected by regular epoetin therapy. In addition to increased physical capacity, patients became aware of increased concentration ability, memory, and general well-being, along with less tiredness and fatigue, sleep disturbance, and depression. In addition to these benefits, improvements in a number of physiological functions became evident, particularly in relation to the heart, neurophysiological function, and the immune system.

All of these dramatic benefits have contributed to the firm establishment of erythropoietic therapy as the mainstay of treatment for the anaemia associated with chronic kidney disease (CKD). Epoetin- α (Eprex, Erypo; Ortho Biotech) and epoetin- β (NeoRecormon; Roche) are usually best administered two or three times a week, whereas darbepoetin- α with its longer half-life may be given once-weekly. In the maintenance phase of treatment, epoetin beta may be given once-weekly in stable patients, while darbepoetin- α may be given once every two weeks. Switching from the epoetins (in international units (IU)) to darbepoetin- α (in micrograms) usually does not present major problems; a very approximate conversion is 200IU of epoetin to 1 μ g of darbepoetin- α , although there may be considerable variability across the whole spectrum of dose requirements.

Intravenous Iron

Along with the expansion of epoetin use came an increased recognition of the need for adequate iron supplementation. Initially, attempts were made to supplement with oral iron preparations, but it soon became evident that the amount of iron absorbed was woefully inadequate to support the increased demands on the bone marrow for iron. Thus, intravenous iron became increasingly used, and this coincided with the introduction of safer IV iron preparations. Thus, the potentially life-threatening anaphylactic complications associated with iron dextran have slowly become less of a concern. Although reactions to all intravenous iron



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Figure 1: Correction of Anaemia from One of the Early Studies of Epoetin Therapy in Haemodialysis Patients

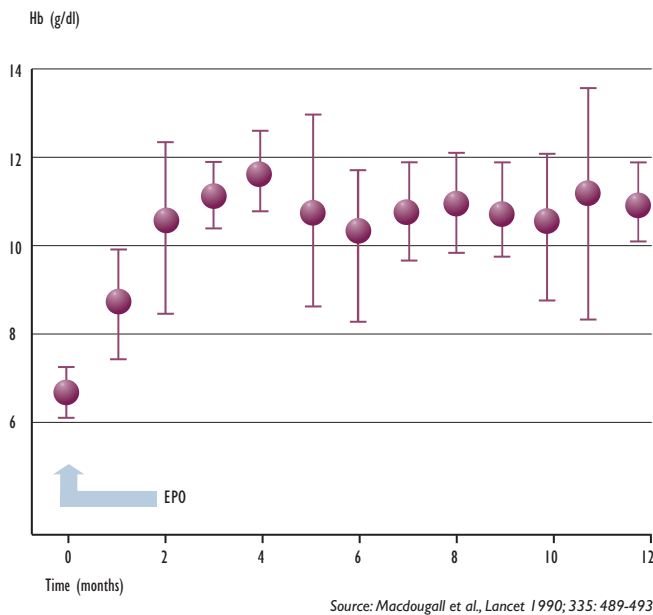
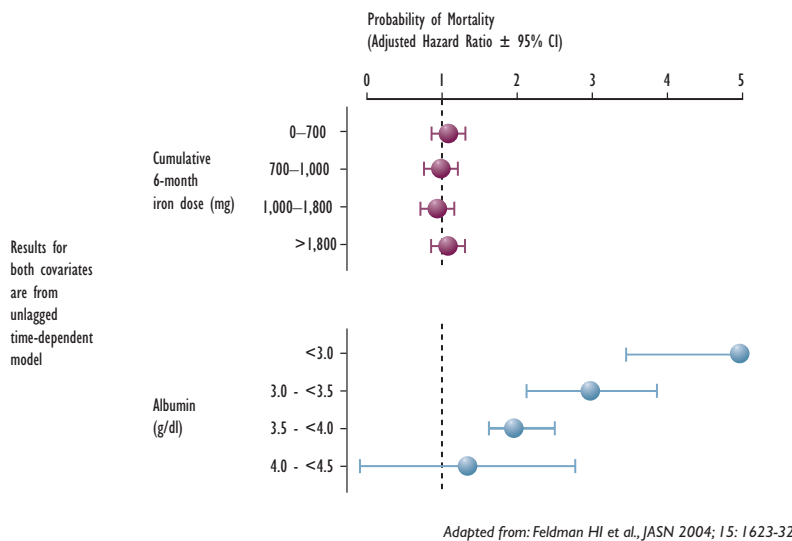


Figure 2: Relationship Between Intravenous Iron Usage and Mortality (Compared with Albumin and Mortality)



preparations can still occur, these usually resolve rapidly, spontaneously, or with minimal support, and are generally believed to be due to too high a dose administered too rapidly. In addition to low molecular weight iron dextran, the most commonly used intravenous iron preparations in Europe include iron sucrose (Venofer) and iron gluconate (Ferrlecit). Mild cases of renal anaemia may respond to the administration of intravenous iron alone, while its concomitant use with erythropoietic agents usually results in a reduction in dose requirements of the latter preparations. There have been concerns that the increased use of intravenous iron may exacerbate infections or oxidative stress in CKD patients, but the few

clinical studies that are available do not support these concerns (see Figure 2). At the present time, the benefits of intravenous iron clearly outweigh any possible deleterious effects.

Epoetin-induced Pure Red Cell Aplasia

For over 10 years, epoetin was regarded as a very safe therapy, causing exacerbation of hypertension in a minority of patients, and possibly an increased propensity to vascular access thrombosis in some haemodialysis patients. In 2002, however, it became apparent that some patients were developing pure red cell aplasia with circulating anti-erythropoietin antibodies, and this was particularly implicated with one of the formulations of epoetin- α manufactured and distributed outside the US. Over 200 cases of antibody-mediated pure red cell aplasia have been reported worldwide (see Figure 3), mainly with Eprex (Erypo in Germany), which is the erythropoietin preparation distributed by Janssen Cilag/Ortho Biotech. The cause of this complication of epoetin- α outside the US seems to be related to a change in formulation, and more specifically to the withdrawal of human serum albumin from the preparation (as mandated by the EU, who had concerns about the possible increased transmission of Jacob-Creutzfeldt prions). The human serum albumin was replaced by polysorbate 80, and the concomitant use of rubber stoppers in the syringes seemed to increase the propensity to develop this complication.

The current hypothesis is that the rapid escalation in cases of epoetin-associated pure red cell aplasia was due to the presence of leachates from the rubber plungers, acting as immune adjuvants to promote the development of anti-erythropoietin antibodies. The rubber stoppers have now been replaced by Teflon stoppers, and it is now hoped that this packaging change will result in a sustained reduction in new cases of this complication to a much more acceptable, and very low, background incidence.

'Biosimilar' Erythropoietins

The patent for epoetin has expired in Europe, and this has opened the door to the widespread introduction of 'biosimilar' or 'generic' erythropoietin. Several years ago, many companies were developing such products, but the advent of antibody-mediated pure red cell aplasia, which highlighted the importance of the formulation of epoetin, caused the American and European regulatory authorities to produce much more stringent regulations for the production of these products. Several companies, therefore, ceased to

Venofer®

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Redefines
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Iron Management according to
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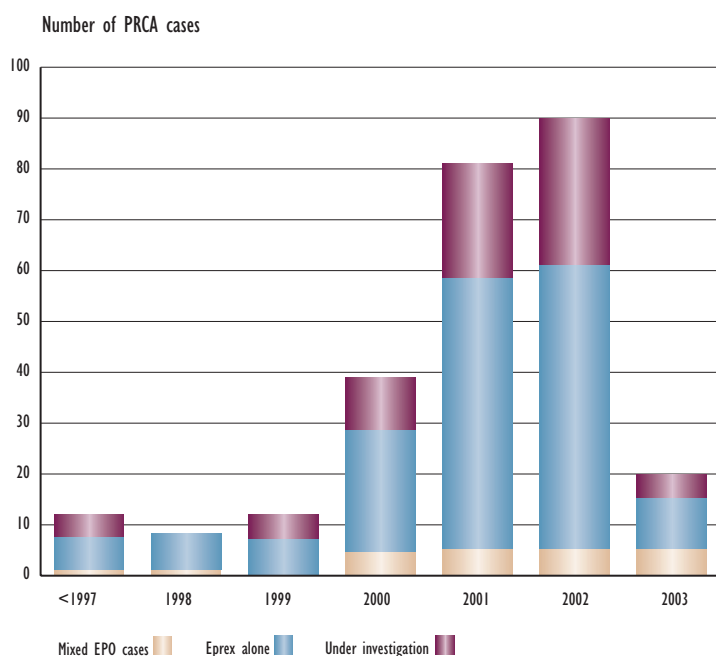
Iron sucrose
is generally considered to
be the **safest form** of
i.v. administered iron⁽¹⁾ ...

...i.v. administration of iron dextran
(...) is **not** generally
recommended⁽¹⁾

References: (1) Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure, *Nephrol Dial Transplant* (2004) **19** (Suppl. 2): ii1-ii47.

Abbreviated prescribing information: Before prescribing Venofer® please refer to the full local approved data sheet. **Pharmaceutical Form:** Solution for injection or concentrate for solution for infusion. Each 5 ml ampoule contains 20 mg/ml iron as iron sucrose corresponding to 100 mg iron per ampoule. Venofer® is a dark brown, non transparent, aqueous solution with a pH of 10,5 – 11,0 and an osmolarity of 1250 mOsmol/l. **Indications:** Venofer® is indicated for parenteral treatment of iron deficiency in the following indications: - where there is a clinical need for a rapid iron supply, - in patients who cannot tolerate oral iron therapy or who are non-compliant, - in active inflammatory bowel disease where oral iron preparations are ineffective. **Dosage & Administration:** The dosage has to be individually adapted according to the total iron deficit. Venofer® must only be administered intravenously by drip infusion, slow intravenous injection or directly into the venous limb of the dialyser. **Infusion:** Venofer® should preferably be administered by drip infusion in a dilution of 1 ml Venofer® (20 mg iron) in max. 20 ml NaCl (sodium chloride) solution. The normal posology is 5 ml Venofer® (100 mg iron) administered in at least 15 min. up to 10 ml Venofer® (200 mg iron) administered in at least 30 min. once or three times a week depending on the hemoglobin level. If the clinical situation demands, the maximum tolerated single dose is 7 mg iron/kg body weight given once per week, but not exceeding 500 mg iron (administered in at least 3,5 hours). **Intravenous injection:** Venofer® can also be administered undiluted by slow intravenous injection at a rate of 1 ml Venofer® (20 mg iron) in at least one minute. A maximum of 10 ml Venofer® (200 mg iron) can be administered per injection in at least 10 min. Before administering the first dose to a new patient, a test dose of Venofer® should be given. **Contraindications, Warnings, Precautions, Overdose:** Venofer® is contraindicated in cases of anemia not caused by iron deficiency, iron overload or disturbances in iron utilization, known hypersensitivity to Venofer® or any of its inactive ingredients and in the first trimester of pregnancy. Caution in patients with asthma, low iron binding capacity and/or folic acid deficiency, liver dysfunction, acute or chronic infection. **Venofer® has exclusively to be administered intravenously.** Parenterally administered iron preparations can cause allergic or anaphylactoid reactions. Hypotensive episodes may occur if the injection is administered too rapidly. Paravenous leakage must be avoided. Venofer® must only be mixed with 0,9% NaCl solution, and no other agent should be added. Overdosage can cause acute iron overload, manifesting itself as haemosiderosis and should be treated with supportive measures and, if required, an iron chelating agent. **Undesirable Effects:** Common (greater than or equal to 1% and less than 10%), Uncommon (greater than or equal to 0,1% and less than 1%), Rare (greater than or equal to 0,01% and less than 0,1%), Common: transient taste perversions in particular metallic taste. Uncommon: headache, dizziness, hypotension and collapse, tachycardia and palpitations, bronchospasm, dyspnoea, nausea, vomiting, abdominal pain, diarrhoea, pruritus, rash, exanthema, erythema, muscle cramps, myalgia, fever, shivering, flushing, chest pain and tightness, injection site disorders such as superficial phlebitis, burning, swelling. Rare: anaphylactoid reactions (rarely involving arthralgia), peripheral oedema, fatigue, asthenia, malaise. Isolated cases: reduced level of consciousness, light-headed feeling, confusion, angio-oedema, swelling of joints. **Legal category:** POM **Date of preparation:** 09/03. **For further information please contact:** Vifor (International) Inc., Rechenstrasse 37, 9001 St.Gallen, Switzerland – Phone ++41 71 272 84 84, Telefax ++41 71 272 84 85.

Figure 3: The Rise and Fall of the Pure Red Cell Aplasia 'Epidemic' – Global Cases of Antibody-mediated PRCA



progress their clinical development programmes. Nevertheless, it is expected that within the next couple of years, biosimilar epoetin will be available, not only with epoetin- α or - β , but also with other products such as epoetin- δ (now acquired by Shire Pharmaceuticals). While it is likely that all of the biosimilar epoetins will be clinically effective in correcting anaemia, it may be many years before the safety profile of these alternative formulations becomes apparent, given the experience with Eprex described above.

Future Therapies in the Management of CKD Anaemia

Since the treatment of anaemia is such a lucrative market, many companies are currently in the process of developing other therapies for anaemia. Many of these are still in the laboratory or pre-clinical stage of development, but several are in various stages of clinical development. The latter agents include Continuous Erythropoietin Receptor Activator (CERA), Hematide, and the hypoxia-inducible factor (HIF) stabilisers.

CERA has recently completed its phase III clinical development programme, involving nearly 2,000 patients with CKD (both those on dialysis and those not yet requiring renal replacement therapy). CERA differs from erythropoietin by the integration of a large polymer chain linked via amide bonds between amino groups and methoxy-polyethyleneglycol-succinimidyl butanoic acid.

The resulting molecule has a molecular weight of approximately 60 kilodaltons, which is around twice the size of erythropoietin. Studies in both healthy subjects and CKD patients have shown that CERA has a greatly prolonged half-life compared with existing erythropoiesis-stimulating agents, and reduced dosing schedules up to once-every-four weeks have been investigated in the phase III clinical trials.

Hematide is a smaller molecular weight erythropoietin-mimetic peptide. This product, which is the property of Affymax in Palo Alto, California, is currently in phase II of its clinical development programme. Again, reduced dosing frequencies of once-monthly administration are currently being investigated. This molecule is potentially more stable than any of the other erythropoiesis-stimulating agents, since it is not protein-based, and this may allow Hematide to be stored at room temperature rather than in a refrigerator. Anti-erythropoietin antibodies do not cross-react with Hematide, and thus pure red cell aplasia is not expected to be a complication with this agent.

The first of the HIF stabilisers (FG 2216; FibroGen, San Francisco, California) is also in phase II of its clinical development programme. These agents are orally active, and inhibit the degradation of HIF via a prolyl hydroxylase enzyme which, in turn, increases erythropoietin production. While preliminary data suggest that these agents can enhance erythropoiesis, several other genes, such as vascular endothelial growth factor (VEGF) and genes associated with iron availability, may be upregulated in addition to erythropoietin.

Conclusion

The advent of agents able to improve the anaemia associated with CKD has been a major breakthrough in the treatment of both dialysis and non-dialysis patients. These agents are able to cause a progressive and sustained increase in haemoglobin concentration in such patients, and a large number of clinical benefits are associated with this. The safety profile of these agents is very acceptable, with the exception of the extremely rare complication of antibody-mediated pure red cell aplasia, and several new agents are likely to enter the market within the next few years. In addition to agents that enhance erythropoiesis, the pivotal role of intravenous iron in the management of renal anaemia should also not be underestimated. ■

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