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Iron management in patients on rHuEPO

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Recombinant human erythropoietin (rHuEPO) is widely used to treat the anaemia associated with chronic renal failure. Many physicians are unsure of the role of iron in the treatment of this condition and therefore fail to achieve the optimum response to rHuEPO. A roundtable meeting of European experts was held to discuss issues relating to iron management, with the aim of producing guidelines on assessment and treatment of chronic renal failure for nephrologists and haematologists.

Iron status before rHuEPO treatment

Patients considered for rHuEPO treatment are likely to have been identified from their low haemoglobin (Hb) concentrations, but it is also important to consider their iron status to assess their need for supplementary iron.

The normal distribution of body iron and pathways of iron metabolism are shown in Figure 1. Patients with chronic renal failure may have Hb concentrations as low as 6 g/dl (normal range, 12–18 g/dl). Each rise of 1 g/dl in the circulating Hb requires approximately 150 mg of storage iron, which is equivalent to a serum ferritin concentration of about 20 µg/l. To increase a

patient's Hb concentration from 6 to 12 g/dl will require iron stores equivalent to a serum ferritin concentration of at least 120 µg/l.

Before rHuEPO treatment has begun ferritin levels will provide a measure of storage iron. Patients with serum ferritin concentrations below 15 µg/l have virtually no available iron and are unlikely to respond well to rHuEPO without iron supplementation. Even where serum ferritin concentrations are up to 200 µg/l, iron supplementation may still improve the patient's response to rHuEPO. If serum ferritin levels are over 200 µg/l, extra iron is probably unnecessary (Figure 2).

Iron status during rHuEPO treatment

Correction phase

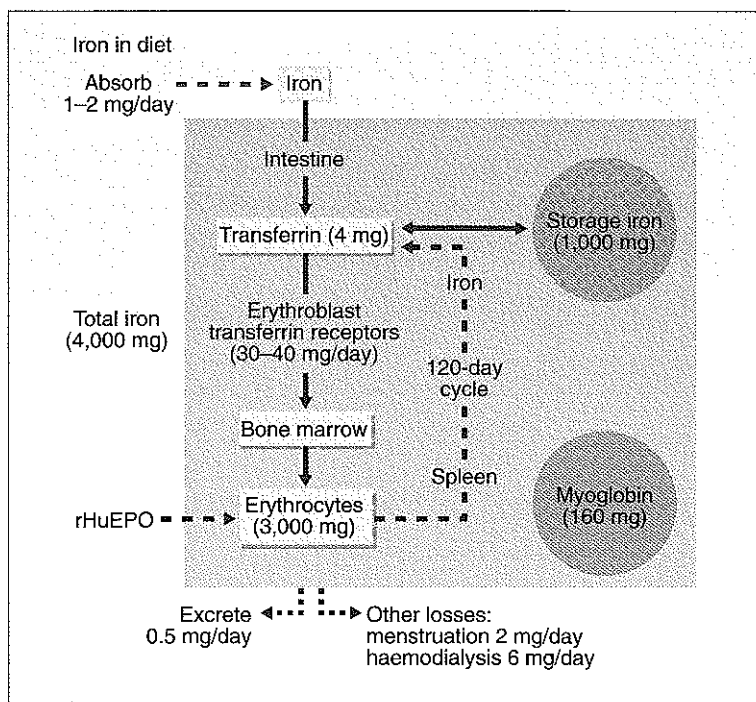
Once rHuEPO treatment has begun, serum ferritin levels may become a less reliable measure of iron stores, since ferritin concentrations are affected by the rHuEPO treatment itself and also by treatment with intravenous (IV) iron. For this reason, measurement of ferritin concentrations should be performed at least 2–3 weeks after the end of IV iron therapy.

The most direct method of assessing the iron available to erythroid tissue is the measurement of the red cell Hb concentration by flow cytometry. Functional iron deficiency (see below) may be diagnosed when more than 10% of the circulating red cells are hypochromic – that is, have an individual cell Hb concentration below 28 g/dl.

The ability to assess the proportion of hypochromic red cells as part of the full blood count is an important tool in managing rHuEPO-treated patients. However, not all centres currently have access to the automated blood cell analysers that can perform this measurement, and many physicians are therefore required to use other methods for measuring iron status during rHuEPO treatment.

Several indirect techniques have been proposed, but none is as reliable as direct measurement of red cell hypochromia. Transferrin levels fluctuate widely both within and between individuals, and single measurements are not useful during rHuEPO treatment, although repeated measurements may provide more information. Patients with a transferrin saturation consistently below 20% are likely to be experiencing

Figure 1. Overview of iron metabolism and storage (average values for a 70 kg adult)



functional iron deficiency. However, where levels are above 20%, this diagnosis still should not be ruled out. Transferrin receptor levels reflect erythropoietic activity rather than iron status during this phase of therapy and do not provide a useful measurement of functional iron deficiency.

Maintenance phase

Once steady-state erythropoiesis is achieved, measurements of serum ferritin may once again reflect a patient's levels of storage iron. Similarly, measurements of transferrin receptor concentrations could prove useful. Receptor synthesis is likely to be increased under conditions of inadequate iron supply to the marrow; its exact role, however, has yet to be defined.

Functional iron deficiency - definition and effects

Erythropoietin treatment places extreme demands on the erythropoietic system, and the rise in Hb concentration may be limited by the rate at which iron can be supplied to the developing erythrocyte progenitor pool in the bone marrow. Functional iron deficiency develops when iron supplies are insufficient to meet demand. Iron-deficient erythropoiesis can occur despite the presence of apparently adequate iron stores as judged by serum ferritin levels. Even patients with serum ferritin concentrations above 100 µg/l will frequently exhibit functional iron deficiency. The development of functional iron deficiency may depend on the speed of erythroid expansion, although it may be evident even with low doses of rHuEPO.

Patients with functional iron deficiency are likely to show a poor response to rHuEPO (Figure 3), and the availability of iron probably influences the dose-response curve of rHuEPO. Thus, maintenance of an adequate iron supply may reduce rHuEPO requirements, and the same rise in Hb concentration may be achieved with a lower dose of rHuEPO.

Choice of iron treatment

Preventing iron deficiency during rHuEPO therapy will increase the cost-effectiveness of treatment. There is increasing evidence that patients who receive more frequent IV iron treatment require lower doses of rHuEPO. Decisions about the best dosage, formulation and delivery route of iron will depend on practical considerations. These decisions will also be influenced by the availability of different forms of iron supplementation in different countries.

IV iron

Various IV iron formulations are available for treating patients receiving rHuEPO - iron

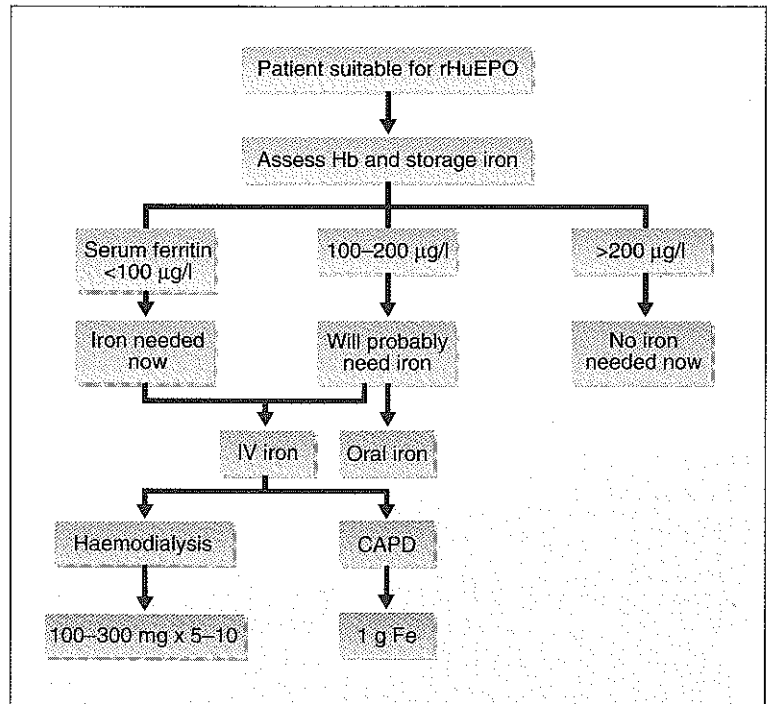


Figure 2. Assessing iron status at the start of rHuEPO treatment

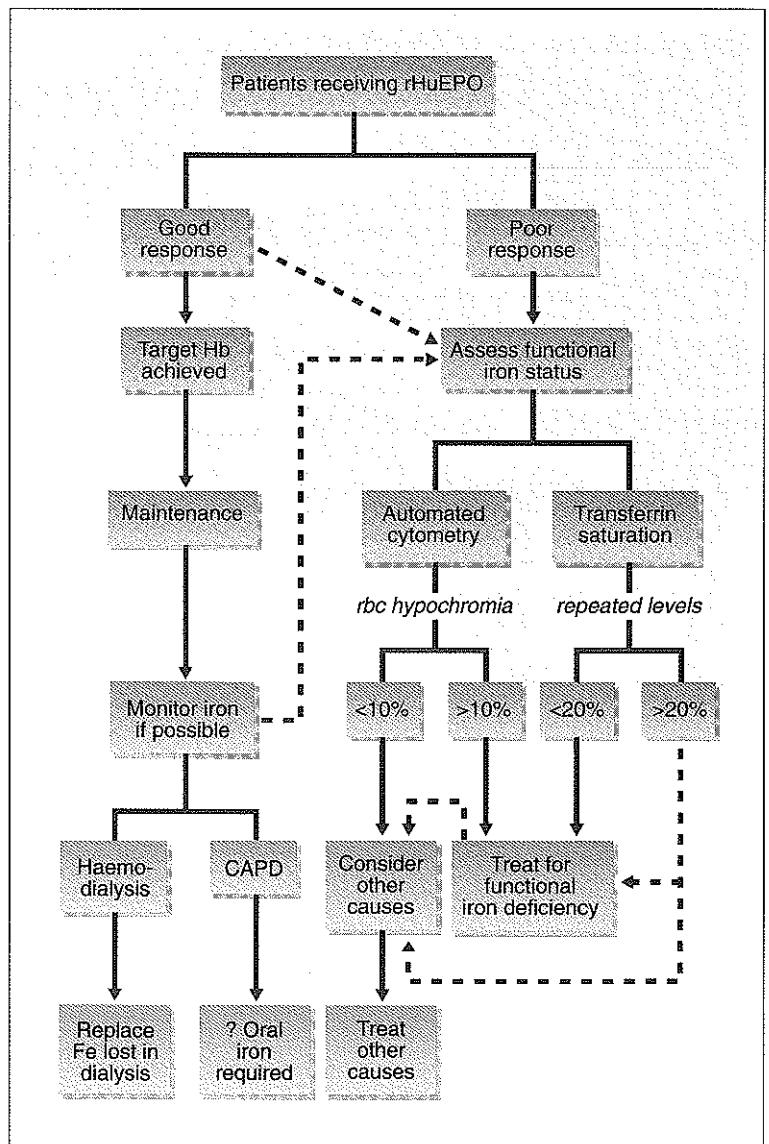


Figure 3. Guidelines for iron management during rHuEPO treatment

dextran is used in North America, iron dextran (polymaltose) and hydroxysaccharate are available in continental Europe and iron sodium gluconate has been used occasionally. The major disadvantage of iron dextran is the occasional development of acute anaphylactic reactions. A test dose should be administered initially, and resuscitation facilities should always be available during its use. Less life-threatening, but nonetheless problematic, side-effects of IV iron dextran include arthralgia and myalgia, but these may be avoided by using low repeated doses. Small-weight molecules such as iron sodium gluconate may cause problems of free iron toxicity.

Patients receiving haemodialysis are best treated with repeated small doses of IV iron

Patients receiving haemodialysis in hospital are best treated with repeated small doses of IV iron. Decisions regarding frequency and dose will depend on the individual clinician. A typical dose would be 100–300 mg in the last 1–2 hours of up to ten weekly or fortnightly dialysis sessions.

For patients attending hospital less frequently and those without IV access, such as predialysis and CAPD patients, a much larger loading dose of IV iron (1 g) may be given at a single session, but this could increase the risk of adverse reactions.

At the start of rHuEPO treatment and during the correction phase, IV iron is more effective than oral iron. This may be because chronic renal failure, chronic inflammation and rHuEPO treatment itself may affect the absorption of oral iron.

However, IV iron should be used with caution in patients with a bacterial infection, since it may encourage bacterial growth.

Oral iron

During the maintenance phase, oral iron may be sufficient to achieve an adequate iron supply. However, preparations providing the most readily absorbable iron are also most likely to cause gastrointestinal side-effects. Thus the dose and

formulation may need to be adjusted to achieve a regimen that is acceptable to the patient and is least likely to reduce compliance. Most patients should start with ferrous sulphate 200 mg *tid*, 30 minutes before meals. If this is not well tolerated they should be advised to take the iron tablets after meals.

If side-effects persist, reducing the frequency or lowering the dose of ferrous sulphate should be tried. If this is still unacceptable, patients may try other ferrous compounds that contain less elemental iron in each tablet.

Other causes of hyporesponsiveness

While iron supplementation may be the key to optimising rHuEPO therapy in the great majority of patients receiving treatment for anaemia of renal origin, a small proportion of patients may have a poor response to rHuEPO for other reasons.

Poor response may be due to infection, inflammatory disease, malignancy, blood loss, hyperparathyroidism, aluminium overload (causing a functional deficiency that is unresponsive to extra iron) or haemolysis. The assessment of iron status may also be affected by some of these factors.

Optimising therapeutic efficacy

Serum ferritin should be measured before rHuEPO treatment and any storage iron deficiency treated, preferably with IV iron. During rHuEPO treatment, functional iron deficiency should be monitored by measuring the percentage of hypochromic red cells. This parameter is an important tool in the management of rHuEPO-treated patients and should be more widely available. When this information is not available, repeated measures of serum ferritin concentrations are an unreliable substitute. Iron supplementation should be introduced during the correction phase.

Good maintenance of iron status in patients receiving long-term rHuEPO treatment will optimise therapeutic efficacy and may permit cost savings ■

Key points

- Recombinant human erythropoietin (rHuEPO) is widely used to treat the anaemia associated with chronic renal failure (CRF). However, many physicians are unsure of the role of iron in CRF and therefore fail to achieve the optimum response to treatment.
- Decisions about the best dosage, formulation and delivery route of iron will depend on practical considerations – IV iron is more effective than oral, but the patient may develop an acute anaphylactic reaction.
- Good maintenance of iron status in patients receiving long-term rHuEPO treatment will optimise therapeutic efficacy and may permit cost savings.

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