Keynote Lecture

How to get the best out of r-HuEPO

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Abstract. Recombinant human erythropoietin (r-HuEPO) therapy is expensive, and it is therefore important to optimize its use to satisfy the health economist as well as the prescriber. Five main issues can be considered in helping to achieve this goal: (i) Route and site of administration. Much evidence suggests that subcutaneous (s.c.) administration of r-HuEPO is more cost-effective than intravenous (i.v.) administration, i.e. lower s.c. doses may be used to achieve the same effect. There are, however, some studies which suggest that there is little to choose between the two routes. One pharmacokinetic study in normal volunteers found that s.c. injection of r-HuEPO into the thigh resulted in greater peak values and greater bioavailability than s.c. injection into the arm or abdomen. (ii) Frequency of injection. There are now reports of dialysis patients being variously treated with once-weekly, twice-weekly, thrice-weekly, and once-daily s.c. administration of r-HuEPO. Despite some comparative studies, the optimum dosing frequency for s.c. r-HuEPO remains unclear. (iii) Iron status. Failure of an adequate supply of iron to the erythron is probably the most common and most easily treated cause of sub-optimal response to r-HuEPO. Effective and regular monitoring of iron status by measurement of serum ferritin, transferrin saturation, and per cent hypochromic red cells is critical to the management of the patient receiving r-HuEPO, and there is increasing evidence that liberal use of i.v. iron may enhance the response to this treatment. (iv) Other factors affecting response to r-HuEPO. Several other factors or conditions can modulate the response to r-HuEPO and these must be recognized and corrected in order to optimize the use of this drug. (v) Target haemoglobin. There is considerable debate regarding the target haemoglobin which should be aimed for in order to maximize improvements in quality of life and cardiac function. To date, a target of 10-12 g/dl has often been used; aiming for a higher haemoglobin undoubtedly requires larger doses of r-HuEPO, and it is not known whether the increased cost is matched or justified by parallel improvements in quality of life or cardiac function in the long-term.

Introduction

Since its introduction into the pharmaceutical formulary nearly 7 years ago, recombinant human erythropoietin (r-HuEPO) has more than proved its efficacy as a therapeutic agent for the treatment of renal anaemia. Not only is it able to correct the anaemia in approximately 95% of patients treated, but such patients have been shown to benefit considerably in terms of quality of life, cardiorespiratory function, and other physiological effects. As with other pharmaceutical products manufactured by biotechnological means, however, r-HuEPO is expensive, costing somewhere in the region of £2000-3000 per patient per year of treatment. It is therefore important for the prescriber, the patient, and the health economist to consider ways of optimizing its use and improving its cost-effectiveness. To this end, there are several factors which may influence the efficacy of r-HuEPO, and those which will be considered in this article include the route of administration, frequency of injection, iron status and supplementation, other factors known to affect the haemopoietic response to r-HuEPO, and target haemoglobin concentration.

Route of administration

Published reports document four possible routes of r-HuEPO administration, namely intravenous (i.v.), subcutaneous (s.c.), intraperitoneal (i.p.) and intradermal administration. The brief and preliminary account of intradermal injection of r-HuEPO suggests that it is at least as good as, if not better than, i.v. and s.c. administration [1]. The i.p. route, which is clearly appropriate only for patients receiving peritoneal dialysis, is effective in producing a haemopoietic response [2], but the bioavailability of i.p. r-HuEPO is very low (of the order of 3-8% [3]) and larger doses are therefore required compared with i.v. or s.c. administration. Although it has been suggested that administering r-HuEPO into a dry peritoneal cavity will enhance its absorption [4], the i.p. route has not gained widespread popularity as a practical means of administering r-HuEPO, and the only possible indication for...
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This route may be intractable needle phobia in a CAPD patient who is unable to tolerate s.c. injections.

The vast majority of experience with r-HuEPO administration, however, has focused on the i.v. and s.c. routes. All of the earlier studies on r-HuEPO used the i.v. route [5,6], and indeed pharmacokinetic analyses suggested that the bioavailability of s.c. r-HuEPO was disappointingly low at around 20% [3]. It soon became apparent, however, that lower doses of r-HuEPO might be possible if it were given subcutaneously rather than intravenously [7]. Several studies have compared the efficacy of i.v. versus s.c. administration, either by converting patients from i.v.- to s.c.-administered r-HuEPO [7–10] or by randomizing different groups of patients to receive either i.v. or s.c. r-HuEPO [11–14].

I.v. versus s.c. r-HuEPO

As initially reported in a brief letter in 1988 [7], and then in more detail in 1991 [8], Bommer et al. switched 16 haemodialysis patients who were in the maintenance phase of treatment from i.v.- to s.c.-administered r-HuEPO. The mean haematocrit remained at around 30% but there was a considerable reduction in the median dose of r-HuEPO from 155 to 80 i.v./kg/week. This was the first suggestion that s.c. r-HuEPO might be more effective dose-for-dose than i.v. r-HuEPO. In a similar study, Tomson et al. [9] switched 11 haemodialysis patients, who were stable on i.v. r-HuEPO, to the same dose of r-HuEPO subcutaneously. The mean haemoglobin concentration increased from 9.3 to 9.8 g/dl at 1 month, and to 10.4 g/dl at 2 months in the s.c. phase of treatment. Hörål et al. [10] analysed data from the European multicentre study in which a proportion of patients were switched from thrice-weekly i.v. to thrice-weekly s.c. administration of r-HuEPO. A 32% reduction in the mean dose requirements of r-HuEPO was observed in this study. A more recent report from the same authors, however, suggested that there is no reduction in r-HuEPO dose requirements when switching from i.v. to s.c. administration if adequate iron supplementation, particularly in the form of i.v. iron, is given [15].

I.v. versus s.c. r-HuEPO

Several studies have compared the haemopoietic response in different groups of patients receiving i.v. and s.c. r-HuEPO [11–14]. One of the earliest of these was the study of 17 predialysis patients by Eschbach et al. [11] in which four patients received a dose of 150 IU/kg thrice weekly i.v. and four patients a dose of 100 IU/kg thrice weekly s.c. The haematocrit response and erythron transferrin uptake were almost identical for the two groups. In a later study, Eidemak et al. [12] treated three groups of patients with 50 IU/kg of r-HuEPO thrice weekly; 11 haemodialysis patients received i.v. r-HuEPO, nine haemodialysis patients were treated with s.c. r-HuEPO, and nine CAPD patients were given s.c. r-HuEPO. The target haemoglobin concentration was achieved earlier in the two s.c.-treated groups compared with the i.v.-treated group (42 versus 84 days), the cumulative dose was lower in the two groups receiving s.c. r-HuEPO (873 and 924 IU/kg) compared with the group given i.v. r-HuEPO (2066 IU/kg), and the maintenance dose was almost 50% lower in the two s.c. groups (63 and 72 IU/kg) compared with the i.v. group (125 IU/kg) [12]. In the Canadian multicentre study reported by Muirhead et al. [13], 128 haemodialysis patients were similarly randomized to receive 50 IU/kg thrice weekly either i.v. or s.c. aiming for a target haemoglobin concentration of 10.5–12.5 g/dl. As in the study by Eidemak et al., the s.c.-treated patients achieved their target haemoglobin earlier (9.9 ± 4.5 versus 11.9 ± 4.9 weeks; P < 0.05), with a significantly lower dose of r-HuEPO after stabilization (206 ± 135 versus 274 ± 142 IU/kg/week; P < 0.02). However, after 24 weeks of treatment, the difference in r-HuEPO dose requirements was no longer significant (147 ± 114 versus 184 ± 129 IU/kg/week). In contrast to the above studies, Taylor et al. [14] recently reported the results of a prospective randomized i.v. versus s.c. crossover study in which 16 haemodialysis patients received a dose of 40 IU/kg r-HuEPO thrice weekly. The patients were assessed during both the i.v. and s.c. phases of treatment, with r-HuEPO being stopped for a washout period between the two phases. Almost identical haemoglobin responses were observed (mean rise in haemoglobin was 0.24 g/dl/week (range 0.14–0.44) for i.v. r-HuEPO, and 0.29 g/dl/week (range 0.16–0.46) for s.c. r-HuEPO), and likewise there was no difference in the mean r-HuEPO dose used during the two phases of treatment (125 IU/kg/week (range 37–377) for i.v. r-HuEPO, and 120 IU/kg/week (range 30–367) for s.c. r-HuEPO) [14].

In summary, therefore, evidence for lower r-HuEPO dose requirements with s.c. compared with i.v. administration is conflicting. Results from several studies support this conclusion [8–12], and the study by Muirhead et al. [13] suggests possible advantages of s.c. r-HuEPO compared with i.v. r-HuEPO, while studies by Barclay et al. [16], Taylor et al. [14], and Sunder-Plassmann and Hörål [15] have found no advantage of s.c. over i.v. administration r-HuEPO.

Site of s.c. administration

In contrast to other therapeutic agents such as insulin, there is a paucity of data comparing different sites of s.c. injection of r-HuEPO. No treatment studies have been reported, and there is only one pharmacokinetic randomized crossover study in normal healthy volunteers in which it was found that injection into the thigh resulted in more rapid absorption of r-HuEPO, greater peak serum concentrations, and greater bioavailability compared with injection into the arm or abdomen [17]. Whether this holds true for dialysis patients has not been determined.
Frequency of administration

It is generally accepted that i.v. r-HuEPO should be given twice- or thrice-weekly to coincide with the frequency of haemodialysis. For s.c. r-HuEPO, however, there are studies reporting once-weekly [18–20], twice-weekly [2,18,21], thrice-weekly [19,22,23], and seven times weekly (once-daily) [23,24] administration. Several of these have compared more than one frequency of administration in the same group of patients. Granolleras et al. [23] switched 12 haemodialysis patients who were in the maintenance phase of treatment from once-daily to thrice-weekly administration of r-HuEPO, using the same cumulative weekly dose (median 56 IU/kg). The mean haematocrit declined from 32.3% to 29.6% (P < 0.005) during the subsequent 4 months [23]. Saleh et al. [19] also studied 12 CAPD patients in the maintenance phase of treatment, switching them from thrice-weekly to once-weekly administration, again maintaining the same total weekly dose. The haematocrit remained at the same level after conversion to once-weekly administration. In another study with CAPD patients, Lui et al. [18] started 10 patients on once-weekly and 10 patients on twice-weekly injections of r-HuEPO, with the same weekly dose of 100 IU/kg. The haemoglobin responses were identical between the two groups (6.6 to 10.1 g/dl for once-weekly and 6.4 to 10.2 g/dl for twice-weekly administration) as were the doses of r-HuEPO used (84 ± 16 versus 88 ± 15 IU/kg/week) [18].

In conclusion, although studies clearly indicate that subcutaneously administered r-HuEPO is effective given in dosage frequencies varying from once-weekly to once-daily, current opinion recommends that either twice- or thrice-weekly administration is used. In special circumstances, once-weekly administration may be more convenient. At the present time there are no convincing grounds for using once-daily r-HuEPO, which is clearly more inconvenient for the patient.

Iron status

It has become apparent that large quantities of iron are consumed in the manufacture of new red cells under r-HuEPO stimulation. In some patients the iron stores are inadequate to support the requirements of new red cells has been used as an indicator of functional iron deficiency developing in the marrow or incorporated into red cells. Likewise, measurement of the percentage of hypochromic red cells [30] may indirectly determine how much iron is incorporated into the erythron, but will give no indication on how much iron is present in the stores.

Of the tests shown in Figure 1, three have become accepted as useful measurements to perform in patients receiving r-HuEPO: serum ferritin [28,29], transferrin saturation (serum iron/total iron binding capacity [TIBC]) [31], and percentage of hypochromic red cells [30,32]. As mentioned above, the serum ferritin gives a reasonable indication of how much storage iron is present; a value of <100 μg/l before starting r-HuEPO suggests that the iron stores may be insufficient to support erythropoiesis if a rise of 5 g/dl in the haemoglobin concentration is anticipated [25]. Furthermore, the serum ferritin may be spuriously raised in inflammatory conditions, infection, and liver disease [33,34]. The transferrin saturation reflects the amount of iron circulating in the plasma relative to TIBC [31]. Previous studies suggest that once the transferrin saturation falls below 16%, the iron supply for erythropoiesis will be inadequate [35]. The main problem with this measurement, however, is that it shows a marked diurnal variation due to wide fluctuations in plasma iron concentration. Thus, even in normal subjects the transferrin saturation can vary from 15% to 70% depending on the time of sampling [36]. More recently, measurement of the percentage of hypochromic red cells has been used as an indicator of functional iron...
deficiency [30,32,37]. This method, which relies on recent technological advances in some of the automated blood count analysers, is not only very simple to perform, but also appears to be a sensitive and early indicator of iron insufficiency. Thus, if the proportion of hypochromic red cells (defined as an individual cell haemoglobin concentration <28 g/dl) in the circulation increases to more than 5–10% during r-HuEPO therapy, more intensive iron supplementation may be required [27]. Several other tests for iron deficiency in patients receiving r-HuEPO have been reported, including red cell ferritin [38,39], free erythrocyte protoporphyrin [40,41] and red cell zinc protoporphyrin [42,43], but all of these lack widespread validation, and further information is required before they can be widely used.

In summary, a reliable indicator of iron deficiency in patients receiving r-HuEPO is lacking. The serum ferritin and transferrin saturation remain the most widely used methods but both have drawbacks; measurement of the percentage of hypochromic red cells seems a promising alternative.

Iron supplementation in patients receiving r-HuEPO

Many patients treated with r-HuEPO are also concurrently given oral iron supplementation, but it is increasingly recognized that this is often unable to keep pace with the requirements of the marrow, and i.v. iron supplementation is needed (Table 1) [26,27]. The reasons for this are unclear but it would seem that iron requirements in patients receiving r-HuEPO are often much greater than expected. Other possible explanations include poor absorption of oral iron from the gut, poor bioavailability of oral iron, and poor compliance due to gastrointestinal side effects.

There is some controversy over whether oral iron is well absorbed in renal patients receiving r-HuEPO. Earlier studies suggested that iron absorption from the gut was enhanced in dialysis patients who were iron-deficient [44,45]. Skikne and Cook [46] also found that iron absorption was increased by r-HuEPO therapy in normal healthy volunteers, although two studies have suggested impaired absorption in dialysis patients on r-HuEPO [47,48].

A randomized prospective controlled study of iron supplementation in renal patients receiving r-HuEPO was recently reported [49]; in this study, i.v. iron supplementation (iron dextran 5 ml every 2 weeks) was compared with oral (ferrous sulphate 200 mg t.d.s.) and no iron supplementation. All patients were iron-replete (serum ferritin >100 µg/l) at the start of the study. The group receiving regular i.v. iron had a significantly enhanced haemoglobin response, better maintained serum ferritin, and lower r-HuEPO dosage requirements than the other two groups; there was no difference in the results between those receiving regular oral iron and those taking no iron supplementation [49]. Another study by Sunder-Plassmann and Hör [15] also demonstrated significant (around 70%) reductions in r-HuEPO dose (and hence cost) in haemodialysis patients treated aggressively with i.v. iron supplementation (mean r-HuEPO dose 217±179 IU/kg/week prior to i.v. iron; 62±70 IU/kg/week after 6 months of i.v. iron treatment). Two further reports by Schaefer and Schaefer [50] and Nyvad et al. [51] also provide evidence that intensive i.v. iron supplementation can enhance the haemoglobin response to r-HuEPO and result in savings in r-HuEPO usage. Thus, it is becoming increasingly apparent that iron supply to the erythron is a rate-limiting step in the process of erythropoiesis under r-HuEPO stimulation, and i.v. iron should be used in such circumstances. Suggested indications for the use of i.v. iron in patients receiving r-HuEPO are given in Table 2.

Other factors affecting response to r-HuEPO

In addition to iron availability, many other factors have been found to inhibit or prevent a response to r-HuEPO [52], and these may be classified as ‘major’ and ‘minor’ factors. Major factors include iron deficiency [53,54], blood loss, which may be occult [55], and infection or inflammatory conditions, including malignancy [56,57]. Minor factors consist of hyperparathyroidism with marrow fibrosis [58,59], aluminium toxicity [60,61], vitamin B12 or folate deficiency [62], haemolysis [63], marrow dysfunction [64], red cell enzyme defects and haemoglobinopathies [65,66]. The resistance to r-HuEPO therapy in these conditions may be transient and reversible (e.g. acute infective or bleeding episode) or permanent and irreversible (e.g.

Table 1. Iron supplementation—possible routes of administration

<table>
<thead>
<tr>
<th>Oral</th>
<th>Ferrous sulphate</th>
<th>Ferrous fumarate</th>
<th>Ferrous gluconate</th>
<th>Ferrous succinate</th>
<th>Ferrous glycine sulphate</th>
<th>I.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran</td>
<td>Iron sorbitol citrate</td>
<td>Iron hydroxy saccharate</td>
<td>Iron sodium gluconate</td>
<td>I.m.</td>
<td></td>
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(A) During correction phase
- If initial serum ferritin <100 µg/l
- If poor response / loss of previous response esp. if TS <20% or % hypo RBC >10%
- If oral iron not tolerated and ? iron deficient
- ? If initial TS <20% and/or % hypo RBC >10% (or if either develops during r-HuEPO therapy)
- ? Routinely if serum ferritin <600 µg/l
(B) During maintenance phase
- If loss of response and serum ferritin <100 µg/l
- Or TS <20% or % hypo RBC > 10%

TS, transferrin saturation; RBC, red blood cells.
marrow fibrosis, haemoglobinopathies). Identification of the cause is not always easy, and multiple factors may be contributing. Nevertheless, every attempt should be made to investigate thoroughly any patient with r-HuEPO resistance, particularly since the treatment is expensive and some causes are easily corrected.

It is also becoming increasingly apparent that erythropoiesis is a much more complex process than was once believed, and that r-HuEPO stimulation of the proliferation and differentiation of erythroid progenitor cells is but one, albeit fundamental, mechanism in this process. Evidence from in vitro studies suggests that there may be modulating influences from cytokines and growth factors released from other cellular elements in the marrow such as lymphocytes and macrophages [67]. Such influences may be stimulatory (such as interleukin-3 which promotes the differentiation of stem cells into primitive erythroid cells) [67, 68] or inhibitory (such as interleukin-1α, tumour necrosis factor-α, or interferon-γ) [67, 69]. Involvement of the latter factors probably accounts for much of the pathogenesis of the anaemia of chronic disease [67], and may well explain why patients with infection or inflammatory disease are often very resistant to r-HuEPO therapy. Hopefully as our understanding of erythropoiesis advances, and the contribution of other cytokines and growth factors in this process is elucidated, alternative therapeutic strategies will become available which will increase r-HuEPO responsiveness.

Factors other than cytokines have also been shown to potentiate the response to r-HuEPO. It has been known for some time that androgens stimulate r-HuEPO production and enhance erythropoiesis; a study by Ballal et al. [70] showed that androgens can potentiate the effect of r-HuEPO in dialysis patients. Likewise, Carozzi et al. [71] found that regular vitamin D supplementation with 1,25(OH)2D3 enhanced the haemoglobin response to r-HuEPO and reduced the r-HuEPO dose. Pronai et al. [72] demonstrated that folate acid supplementation could improve the response to r-HuEPO in patients with a raised mean cell volume even if there was no evidence of folate deficiency on biochemical measurement. Although these are only preliminary reports, they do emphasize the potential value of searching for alternative ways of enhancing r-HuEPO sensitivity, and thereby increasing the efficiency and reducing the cost of r-HuEPO treatment.

**Target haemoglobin concentration**

There is currently much debate and controversy over the appropriate target haemoglobin to aim for in a patient receiving r-HuEPO. At the Seville meeting, there was no clear consensus, with some units aiming for 9 g/dl, and others aiming for 14 g/dl. A critical factor in this decision must be whether a higher target haemoglobin results in additional improvements in quality of life, cardiac function, and long-term morbidity and mortality. Data on morbidity and mortality are lacking, although a few studies have examined the effects of different target haemoglobin concentrations on quality of life and exercise capacity [73–75]. The first of these was the Canadian multicentre study involving 118 haemodialysis patients [73], 40 of whom were set a target of 9.5–11.0 g/dl and 38 of whom aimed for a target of 11.5–13.0 g/dl. Although the study was not specifically designed to investigate the differential effects of the two target haemoglobin ranges, and the mean target haemoglobin concentrations in the two groups were not dissimilar (10.2 versus 11.7 g/dl), the extra improvements in quality of life and exercise capacity seen in the higher haemoglobin group were fairly small. The higher target haemoglobin group, however, required on average 44 IU/kg/week more r-HuEPO than the lower target haemoglobin group [73].

In contrast, Eschbach et al. [74] increased the haematocrit from a mean of 32.6% to 42.0% in 13 haemodialysis patients, and demonstrated significant improvements in quality of life, exercise capacity, and cardiac function. Exercise duration increased by 20%, maximum oxygen consumption increased by 24%, the distance achieved during the 6-minute walk increased from 494 to 520 (P=0.03), cardiac output declined from 5.1 to 4.3 l/min, and left ventricular mass decreased in two patients. As in the Canadian study, however, significantly more r-HuEPO was required to achieve the higher haematocrit (mean r-HuEPO dose increased by 69% from 64 to 108 IU/kg thrice weekly) [74].

In a recent study involving 102 haemodialysis patients, Moreno et al. [75] measured various quality-of-life parameters at different haematocrits, and found that there was a direct relationship between the two, which did not tail off at the higher haematocrits. Also providing evidence to support a higher target haemoglobin was the study by Hirakata et al. [76], who found that the optimum haematocrit for maximum oxygen supply to the brain (calculated from measurements of regional cerebral blood flow using positron emission tomography and arterial oxygen content) was about 40%.

Thus, there is preliminary evidence indicating that there may be additional improvements in a number of physiological functions at a higher target haemoglobin, although significantly larger doses of r-HuEPO are required to achieve this. Results from long-term morbidity and mortality studies, currently underway in both Europe and America, are eagerly awaited before firm guidelines can be issued with regard to the appropriate target haemoglobin in patients on r-HuEPO.

**Conclusions**

In this article, various issues have been discussed with respect to optimizing the use of r-HuEPO. Regarding the route of administration, the balance of evidence in the literature suggests a marginal benefit for s.c. over i.v. r-HuEPO. Thus, s.c. r-HuEPO is the route of choice for CAPD, pre-dialysis, and transplant patients; i.v. r-HuEPO is still a reasonable alternative for haemo-
dialysis patients. R-HuEPO should be administered twice- or thrice-weekly; in special instances, once-weekly dosing may be more suitable but this is only an acceptable option for s.c. administration. There are no reasons for using once-daily r-HuEPO, which is clearly less convenient for the patient.

Regular monitoring of iron status is a fundamental part of the management of patients on r-HuEPO, and the most useful tests for this purpose are serum ferritin measurement, transferrin saturation, and percentage of hypochromic red cells. The benefits of early and aggressive i.v. iron supplementation are becoming increasingly recognized, and its liberal use can almost certainly promote reductions in r-HuEPO dose and hence cost.

Other factors affecting the response to r-HuEPO also merit consideration, although determining the cause of r-HuEPO resistance is not always easy. Hopefully as our understanding of the process of erythropoiesis advances, alternative therapeutic strategies (possibly involving other cytokines) will become available which will increase r-HuEPO responsiveness. Further studies are also required to determine the appropriate target haemoglobin for patients on r-HuEPO, but there seems little doubt that full correction of the anaemia will require considerably larger doses of the drug.

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