Optimizing anaemia management with subcutaneous administration of epoetin

Anatole Besarab

Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI, USA

Abstract

European and US guidelines for renal anaemia management recommend subcutaneous (s.c.) epoetin as the preferred route of administration in predialysis, peritoneal dialysis and haemodialysis patients. However, the restriction of Eprex®/Erypro® to intravenous (i.v.) administration in Europe has increased the interest of health care professionals regarding the optimal route of administration for all epoetin formulations. There are five major considerations for the 'optimal' route of epoetin administration: efficacy; dosing frequency; convenience; safety and tolerability; and cost. Although epoetin bioavailability is lower after s.c. administration, its efficacy is higher, owing to its prolonged elimination half-life compared with i.v. epoetin. Several studies and clinical surveys comparing s.c. and i.v. administration have demonstrated that equivalent target haemoglobin levels can be maintained at much lower doses of epoetin when administered s.c. Furthermore, s.c. epoetin dosing frequency can be reduced in some patients to once every 2 weeks, without compromising efficacy. Devices such as the Reco-Pen® have been specifically designed to facilitate self-administration of s.c. epoetin-β. An upsurge in the incidence of pure red cell aplasia (PRCA) was linked to the epoetin-α product Eprex/Erypo in Europe, and an increase in PRCA cases of the same magnitude was not seen in patients taking other epoetin products s.c. Therefore, PRCA should not be used as an argument against s.c. administration. The reduced dose with s.c. administration of epoetin-β provides significant cost benefits, without compromising either safety or efficacy, and may also increase patient satisfaction and compliance with treatment.

Keywords: anaemia management; cost-effectiveness; dose; epoetin, safety and tolerability; subcutaneous administration

Introduction

The introduction of recombinant human erythropoietin (rhEPO; epoetin) revolutionized the management of anaemia in patients with chronic kidney disease (CKD). Early studies were predominantly in patients on haemodialysis (HD) and used the intravenous (i.v.) route because these patients had ready vascular access for drug administration [1,2]. Subsequent studies, however, demonstrated that subcutaneously (s.c.) administered epoetin could achieve the same therapeutic targets, but with much lower doses [3,4].

Large studies have confirmed that the s.c. route provides more efficient stimulation of erythropoiesis than the i.v. route and, in most European countries, s.c. administration is the preferred route [5,6]. Furthermore, reviews of studies by both the European Best Practices committee [5] and the NKF-K/DOQI committee in the USA [7] resulted in the recommendation that s.c. administration should be the preferred route for epoetin administration. The debate on the route of administration of epoetin has been reopened recently, however, by reports of an upsurge in incidence of pure red cell aplasia (PRCA) primarily associated with s.c. administration of one epoetin-α product (Eprex®/Erypo®, Johnson & Johnson) available in Europe [8].

Here, the optimal route for epoetin administration is considered under five major headings: efficacy, i.e. the quantity of epoetin needed to achieve the target haemoglobin (Hb) or haematocrit (Hct) level; dosing frequency; convenience for both the patient and the medical staff who administer the drug; safety and tolerability of a particular route and its effect on the generation of PRCA; and cost per patient, or the number of patients it is possible to treat within a given health care system.
Subcutaneous epoetin administration

Efficacy

Bioavailability of epoetin

The average bioavailability of s.c. epoetin is 48.8% (±5.2%) [9] compared with 100% for i.v. administration [4], as with all i.v. administered drugs. Despite this difference in bioavailability, numerous trials have shown that s.c. administration is more effective than the i.v. route, allowing the same target Hb or Hct level to be maintained with a reduced epoetin dose [3,10,11]. For example, a parallel-group, randomized, multicentre, US study found that ~32% less epoetin was required to maintain the same stable Hct when administered s.c. rather than i.v. in patients on HD (Table 1) [12].

Several US studies have indicated an advantage to using the s.c. route in terms of trying to achieve a given response [3,12,13]. The Core Indicators Project [13] mandated by the Center for Medicare and Medicare Services—the primary health care payer for patients on dialysis in the USA—studied 7092 patients on HD to determine how anaemia is managed in the USA. The data showed that there was no significant difference in Hct level between patients administered epoetin s.c. compared with i.v., yet the mean s.c. dose was 14% lower (P<0.001) than with i.v. administration. This difference is less than the 32% reported by Kaufman et al. [12], but the discrepancy could result from possible differences in the weekly s.c. administration frequency between the two studies. Kaufman et al. [12] administered s.c. epoetin three times per week, while the number of weekly doses of epoetin was not reported for patients in the Core Indicators Project [13]. A careful pharmacodynamic study showed a slight change in the required weekly epoetin dose at different administration frequencies [9].

Mechanisms for increased effectiveness

with s.c. administration

Although it seems paradoxical that the lower bioavailability with s.c. epoetin should increase the drug’s effectiveness [14], this observation can be explained by several inter-related mechanisms.

Decreased neocytolysis. During neocytolysis, newly released red blood cells are destroyed prematurely because of inadequate circulating levels of erythropoietin (EPO), and this process may occur between epoetin doses, particularly after i.v. administration [15–17]. There is less neocytolysis in patients receiving s.c. rather than i.v. epoetin, most probably because of the greater half-life obtained using the former route of administration.

Pharmacokinetic mechanisms. The difference in bioavailability between the two routes of administration is due to distinct pharmacokinetic mechanisms [14,18]. For example, when administered i.v., epoetin has an elimination half-life of 5–11 h compared with 19–25 h with s.c. administration [4]. The prolonged half-life following s.c. administration results in sustained stimulation of progenitor cells due to continued receptor binding of epoetin during progenitor cell differentiation and maturation [19,20].

Other cytokine systems. Activation of other cytokine systems, e.g. suppressor cytokines [4] or interferon-γ (IFN-γ) [20], may occur during HD, which could initially impair the ability of the bone marrow to respond to epoetin. In the case of IFN-γ, this is due to downregulation of EPO receptors on human erythroid progenitor cells.

Type of epoetin. The type of epoetin administered may be important. According to Halstenson et al. [21], drug absorption was delayed significantly (P<0.05) after s.c. epoetin-β (NeoRecormon®; Roche Pharmaceuticals) compared with s.c. epoetin-α, and the absolute reticulocyte response after s.c. epoetin-β was 12% higher compared with s.c. epoetin-α (P<0.05). This observation supports earlier findings by Flaharty et al. [22] that the greater erythropoietic efficacy of s.c. epoetin is probably caused by the delay in absorption.

Dosing frequency

Erythropoiesis

Primitive stem cells are unresponsive to EPO, but respond to a variety of growth factors including interleukin-3 (IL-3), insulin-like growth factor I (IGF-I) and stem cell factor [23,24]. Once the stem cells develop EPO receptors, they become less responsive to growth factors and more responsive to EPO. When this happens, adequate EPO levels are required to sustain the cells, otherwise they undergo apoptosis. The period during which the cells are vulnerable to inadequate EPO levels lasts 3–5 days. Once this period is passed, however, the cells become EPO independent until they mature into reticulocytes and progress into the circulation. Once in the circulation, the cells again become EPO dependent and are at risk of premature removal by neocytolysis, which occurs within the reticulo-endothelial system, primarily the
spleen. This period lasts for 9–11 days and neocytolysis can be prevented by administration of epoetin. It is clear that adequate levels of epoetin are required during the periods when the cells are EPO dependent in order to prevent apoptosis and neocytolysis. To maintain maximum epoetin effectiveness, the route of administration must ensure adequate blood levels during the EPO-dependent periods [9].

The effects of various epoetin doses are summarized in Figure 1, which depicts a series of simulated epoetin concentration–time profiles. When epoetin (40 IU/kg) is given i.v. three times weekly (total 120 IU/kg/week), blood levels are high initially but rapidly fall below the concentration required for efficient erythropoiesis (40–200 IU/kg; Figure 1a). In other situations where EPO levels are inadequate, neocytolysis or apoptosis may occur regardless of how often epoetin is administered. The trends following i.v. administration are in contrast to those following s.c. administration.

When an equal dose of epoetin (120 IU/kg) is given s.c., divided as three doses during the week, the concentration of epoetin is cyclical but usually remains within the critical range (40–200 IU/kg) for erythropoiesis (Figure 1b). Similarly, when the same total weekly s.c. epoetin dose is given in two separate 60 IU/kg doses (Figure 1c), there is only a very short period during which the epoetin level falls below the critical range. These periods are somewhat longer with a single weekly s.c. epoetin dose of 120 IU/kg (Figure 1d), which also generates higher peak concentrations and leads to the formation of more red blood cells, but effective erythropoiesis still occurs. The following clinical studies support the mechanisms described here.

**Clinical studies**

It has been shown recently that the frequency of epoetin-β administration may be reduced without compromising efficacy [25–27]. In an open-label, multicentre study by Weiss et al. [26], two parallel groups of patients were randomized to receive s.c. epoetin-β either once weekly or two or three times weekly. Hb levels in both groups were maintained between 11.0 and 11.5 g/dl over the 24 week treatment period and there were no significant between-group differences (Table 2). These results demonstrated that it was possible to maintain stable Hb levels with once weekly s.c. epoetin-β without the need to increase the overall dose compared with two or three times weekly administration. In addition, the once weekly regimen allowed these patients to avoid up to 104 injections per year, which could reduce clinic time, would encourage self-administration and could improve
Subcutaneous epoetin administration

Table 2. Once weekly and two to three times weekly s.c. epoetin maintain target Hb levels after 24 weeks of treatment [26]

<table>
<thead>
<tr>
<th></th>
<th>Baseline Hb (g/dl)</th>
<th>Epoetin-β dose (IU/kg/week)</th>
<th>24 weeks Hb (g/dl)</th>
<th>Epoetin-β dose (IU/kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once weekly</td>
<td>11.4</td>
<td>102</td>
<td>11.1</td>
<td>106</td>
</tr>
<tr>
<td>(n = 80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3 times weekly</td>
<td>11.2</td>
<td>109</td>
<td>11.2</td>
<td>115</td>
</tr>
<tr>
<td>(n = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Subcutaneous epoetin administered once weekly and once every 2 weeks maintains target Hb levels after 13–25 weeks [27]

<table>
<thead>
<tr>
<th></th>
<th>Mean Hb (g/dl)</th>
<th>Change (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13–25</td>
<td></td>
</tr>
<tr>
<td>Group A: once weekly</td>
<td>11.16</td>
<td>−0.34 (−0.14 to −0.54)</td>
</tr>
<tr>
<td>(n = 54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B: once every 2 weeks (n = 74)</td>
<td>11.1</td>
<td>−0.39 (−0.24 to −0.55)</td>
</tr>
</tbody>
</table>

compliance. In an equivalence study by Locatelli et al. [25], patients stable on HD (n = 173) were randomized to once weekly or three times weekly treatment with epoetin-β. Mean Hct levels in both treatment groups remained stable throughout the study.

Another multicentre, non-randomized, open-label study demonstrated that target Hb concentrations were maintained in two groups of patients stable on peritoneal dialysis. For 25 weeks, both groups received the same weekly dose of epoetin-β as they had received during the 4 week run-in period [27]. Group A, who had previously received epoetin-β two or three times weekly, was switched to a single dose once weekly, while group B, who previously received epoetin-β once weekly, was switched to double the dose administered to group A, but at half the frequency, i.e. once every 2 weeks. Hct and Hb levels remained stable in both groups of patients (Table 3) and both regimens were well tolerated.

Convenience

S.c. epoetin administration is more convenient for both patients and medical staff than the i.v. route, particularly for patients not yet on HD who have no readily accessible i.v. route. As a result, s.c. administration may encourage patients to self-administer, which will lead to a concomitant reduction in nursing time and associated costs, and may improve compliance. When combined with the Reco-Pen® (Roche Pharmaceuticals) device [28], epoetin-β multidose cartridges may provide convenient and easy to use treatment that can be titrated to individual patients’ needs [29]. With this device, epoetin-β is administered in a low injection volume (≤0.5 ml) via a very fine (29 gauge) needle to minimize discomfort, and 81% of patients (n = 418) rated their injections as pain free.

Safety and tolerability

Epoetin-β is well tolerated when administered i.v. or s.c. [28–30]. The degree of local pain with s.c. epoetin-β administration is similar to that with placebo and is less than that associated with s.c. epoetin-α, because of differences in the formulation of the two products [31].

Switching from i.v. to s.c. administration also reduces the hypertension that develops in a large number of patients during the early correction phase of anaemia. Navarro et al. [32] reported that s.c. epoetin reduced vascular resistance and blood pressure significantly (by 8 mmHg; P < 0.05) when patients were switched from i.v. epoetin to s.c. administration.

Route of administration and PRCA

It is now generally agreed that an upsurge in the incidence of PRCA [8] was primarily because of the change in formulation of the epoetin-α product in Europe (Eprex/Erypo), and was not as a result of using the s.c. administration route [31,33, Schellekens (this Supplement)]. Therefore, it is not necessary to switch patients from s.c. to i.v. epoetin to avoid PRCA. The consequences of doing so must be considered. Since funding is finite, such a change would limit either the target Hb that could be attained or the number of patients that could be treated. It has been estimated that it would cost US$9 million per year to prevent one case of PRCA in Italy, and that to switch all Italian patients from s.c. to i.v. epoetin would cost US$15.6 million per year [34]. Importantly, only the administration of s.c. epoetin-α (Eprex/Erypo) has been contraindicated by the European Health Authorities because of its association with PRCA, thought to be due to the change in its formulation. Furthermore, there has been no increase in the incidence of PRCA associated with other epoetins. Therefore, it makes sense to change the brand of epoetin used rather than the route of epoetin administration [33]—especially since s.c. administration is the internationally preferred route and is associated with several other important advantages. Epoetin-β has had a strong safety record since it was introduced over a decade ago. Its safety was also confirmed by the European Regulatory Authorities in 2002, who made no suggestion that its route of administration should be changed or restricted.

Cost implications

A meta-analysis of 27 prospective clinical studies involving 916 patients showed that s.c. epoetin administration enabled a significant (P < 0.001) reduction
in the average weekly dose (48 IU/kg; 30%), while still maintaining target Hb levels compared with i.v. administration [3]. This dose reduction was similar to that reported by Kaufman et al. [12]. Importantly, the dose reduction equated to annual savings of US$1761 per patient [3]. In an economic analysis, Hynes et al. [35] estimated that a 32% reduction in epoetin dose would allow Medicare cost savings of US$47–142 million annually if 25–75% of patients on HD were switched from i.v. to s.c. administration, while a 50% dose reduction in all such patients would save an estimated US$295 million annually (Table 4).

**Conclusions**

Although the bioavailability of s.c. epoetin is less than that with i.v. administration, its efficacy is substantially greater. This is probably due to s.c. epoetin having a longer elimination half-life than i.v. epoetin. As a result, the dosing frequency of s.c. epoetin may be substantially reduced to once weekly or even every 2 weeks without any loss of efficacy in some patients, and s.c. epoetin administration leads to a reduced overall epoetin dose.

Subcutaneous administration of epoetin is more convenient both for patients and for medical staff, particularly when combined with devices such as the Reco-Pen and epoetin-β multidose cartridges. Furthermore, s.c. administration of epoetin-β is safe and well tolerated, and it provides significant cost benefits without compromising safety or efficacy.

Current international guidelines recommend s.c. administration of epoetin-β, including patients on peritoneal dialysis who do not have an existing i.v. access [5,7]. Subcutaneous administration is the most effective route of epoetin administration in patients receiving HD and also enables a tailored approach to the management of renal anemia. As a result, individualized treatment, reduced administration frequency and convenience of administration may encourage patients to self-administer s.c. epoetin, in accordance with current international guidelines.

**Table 4.** The potential cost savings (million US$) of switching patients from i.v. to s.c. epoetin administration in the USA [36]

<table>
<thead>
<tr>
<th>Reduction in epoetin dose (%)</th>
<th>Patients switched to s.c. administration (%)</th>
<th>Savings (million US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>32</td>
<td>47</td>
<td>75</td>
</tr>
<tr>
<td>50</td>
<td>74</td>
<td>100</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>100</td>
</tr>
</tbody>
</table>


20. Taniguchi S, Dai CH, Price JO, Krantz SB. Interferon γ downregulates stem cell factor and erythropoietin receptors but

**Conflict of interest statement.** None declared.


