Exploring dosing frequency and administration routes in the treatment of anaemia in CKD patients

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Abstract
Erythropoiesis-stimulating agents have dramatically changed the management of renal anaemia since their introduction almost 20 years ago. However, optimal dosing route and frequency are still a matter of debate. Intravenous application of recombinant human erythropoietin should be limited to haemodialysis patients and must be given three times weekly, as any reduction to this dosing frequency leads to a major increase in dose requirements. Administering recombinant human erythropoietin-β once weekly via the subcutaneous route is effective. If conversion from the subcutaneous to the intravenous route is required, dose requirements for recombinant human erythropoietin therapy remain a subject of discussion.

Keywords: chronic kidney disease; doses and routes; erythropoietin; renal anaemia

Introduction
Substitution therapy with recombinant human erythropoietin (rHuEPO) has improved the management of renal anaemia in chronic kidney disease (CKD) patients for almost two decades [1]. Clinical and patient benefits of treatment include a reduction in blood transfusions, marked improvements in quality of life and general well-being, and improved exercise tolerance and cardiac function, in addition to reductions in hospitalization and mortality rates for CKD anaemia [2].

Initial clinical studies of rHuEPO therapy, which were performed in haemodialysis (HD) patients, examined a three times weekly intravenous (i.v.) administration [3]. Subsequently, the subcutaneous (s.c.) route for rHuEPO therapy has also been shown to be efficacious in HD, peritoneal dialysis (PD) and pre-dialysis CKD patients [3,4]. Although several therapeutic regimens have been used and studied in the years since rHuEPO was first developed as a treatment for anaemia, the optimal frequency, dose and route of erythropoiesis-stimulating agent (ESA) administration in patients with CKD remain a topic of debate.

Pharmacokinetics of ESAs
While rHuEPO-α and -β have quite similar half-lives, darbepoetin-α has a 2- or 3-fold longer circulating half-life [5] (Table 1 [5,6]).

The pharmacokinetic profile of a drug, however, does not always predict its biological response, since the pharmacological effect of an ESA may depend on other mechanisms, such as continuous receptor activation or rHuEPO–receptor interactions, rather than simple plasma half-life [5]. Thus, in spite of its short half-life, adequate clinical responses can be obtained with single weekly doses of conventional rHuEPO treatment.

Intravenous rHuEPO—restricted to haemodialysis patients
I.V. administration is suitable for use only in HD patients. With a half-life of 5–11 h, rHuEPO by the i.v. route needs to be given three times a week. A number of studies have shown that reducing the dose frequency to once or twice per week actually requires a 50% increase in concentration of rHuEPO dose [7–9]. Indeed, when the drug is given i.v. once a week, very high doses would be needed to prolong...
the threshold effect and to avoid a decline in the blood levels of erythropoietin below those necessary for the prevention of apoptosis in the bone marrow [10]. Reflecting this, the current European Best Practice Guidelines (EBPG) for the Management of Anaemia in Patients with Chronic Renal Failure recommend three times weekly doses when the initial administration of rHuEPO is to be via an i.v. route for HD patients [2].

Darbepoetin-α was introduced as an alternative to rHuEPO. This product was developed as a longer acting erythropoietic agent to allow a less frequent dosing by either the i.v. or s.c. route [5]. The extra sialic acid residues that were introduced into darbepoetin-α resulted in an i.v. half-life of 25.3 h compared with only 8.5 h for rHuEPO-α [11]. Practical guidelines for the use of darbepoetin-α in treating renal anaemia for HD patients recommend a starting dose of 0.45 µg/kg using either an i.v. or s.c. route of administration [12].

**Subcutaneous rHuEPO—determining optimal frequency of administration**

For the vast majority of patients requiring rHuEPO, namely patients on PD [13], many HD patients, subjects not yet requiring dialysis and renal transplant patients, the s.c. route is both practical and effective [14].

Although nephrologists have traditionally used twice or three times weekly s.c. dosing for most of their patients, there has been considerable recent interest in the prospect of reducing the treatment frequency to once per week.

A number of early studies attempted to investigate different dosing and frequency regimens [8,9,13,15–17], but offer limited conclusions because of lack of uniformity of study design. These studies differed greatly from each other, both in terms of the frequency of administration (once a week vs twice per week; once vs three times per week; once vs more than three times per week; and daily vs twice per week) and in terms of the type of replacement therapy and patient types (PD or HD). Further confounding factors from these early studies were the small numbers of patients included in the cohorts [8,9,13,15–17].

However, two more recent large-scale randomized studies have reported that once weekly s.c. administration of rHuEPO-β is as effective as two or three times weekly s.c. administration for the maintenance of anaemia correction in stable HD patients [18,19]. In the first of these randomized studies, Weiss et al. [18] investigated whether s.c. rHuEPO-β, used as a maintenance dose once weekly, was as effective as the same total s.c. dose when administered 2–3 times weekly in patients undergoing long-term HD treatment. This controlled multicentre trial randomized 158 patients either to treatment with s.c. rHuEPO-β once weekly (n = 118) or to maintenance therapy on their original dosage two or three times weekly (control group, n = 40), for 24 weeks. The results showed that stable haemoglobin (Hb) levels were maintained without any rHuEPO dose increase being needed in 73% of patients in both groups. Weiss et al. therefore concluded that a once weekly s.c. administration of rHuEPO-β is as well tolerated and effective in maintaining Hb levels in well-dialysed and iron-replete HD patients as the twice to three times weekly regimen of rHuEPO-β. Importantly, the use of the once weekly regimen also allowed patients to avoid up to 104 unnecessary administrations per year [18].

In the second of the studies, Locatelli et al. [19], in an open-label multicentre study, randomized 173 maintenance HD patients to receive either once weekly or three times weekly s.c. rHuEPO-β. Locatelli et al. showed that the regimens were therapeutically equivalent in maintaining stable haematocrit (Hct), and these authors also suggest that once weekly dosing could provide greater opportunities for individualizing treatment regimens according to patient-specific needs [19]. Recent studies have also shown that darbepoetin-α administered once monthly either i.v. or s.c. maintains Hb effectively and safely in most dialysis patients (83% of those evaluable successfully achieved target Hb) previously stabilized on once every 2 weeks dosing [20]. In this study, patients gradually moved from treatment every 2 weeks through to every 3 weeks and then to monthly therapy.

**Dosage reductions: s.c. vs i.v.**

Reduced dosing frequency when using the s.c. route of administration for rHuEPO can be explained in part by the pharmacokinetic profile of the molecule. When given i.v., rHuEPO has a half-life of just 5–11 h, whereas following s.c. administration the half-life is prolonged to 19–25 h [6].

Kauffmann et al. [21] reported a randomized, unblinded trial including 208 patients receiving long-term HD and rHuEPO therapy who were assigned to treatment with either s.c. or i.v. rHuEPO. The dose of rHuEPO was initially reduced until the Hct was <30% and was then gradually increased to a level that maintained the Hct within a range of 30–33% for 26 weeks.

Kauffmann et al. compared average rHuEPO doses received during the 26 week maintenance phase. For the 107 patients treated by the s.c. route, the average

<table>
<thead>
<tr>
<th>Half-life (h, mean ± SEM)</th>
<th>I.V. route</th>
<th>S.C. route</th>
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<tbody>
<tr>
<td>Darbepoetin-α [5]</td>
<td>25.3 ± 2.2</td>
<td>48.4 ± 5.2</td>
</tr>
<tr>
<td>rHuEPO-α [6]</td>
<td>6.8 ± 0.6</td>
<td>19.4 ± 2.5</td>
</tr>
<tr>
<td>rHuEPO-β [6]</td>
<td>8.8 ± 0.5</td>
<td>24.2 ± 2.6</td>
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**Table 1. Pharmacokinetics of existing erythropoiesis-stimulating agents [5,6]**
weekly dose of rHuEPO during the maintenance phase was 32% less than that needed for the 101 patients treated by the i.v. route. Kauffmann et al. concluded that, for selected HD patients, s.c. administration of rHuEPO can maintain Hct within a desired target range and that this can be achieved with a dose of rHuEPO lower than that required for i.v. administration [21].

Besarab et al. [22] conducted a meta-analysis of comparative studies of rHuEPO administered i.v. vs s.c. to assess the relative costs of these two different routes of drug administration [22]. Twenty-seven prospective clinical studies involving a pool of 916 patients were included. The average reduction in rHuEPO dose in patients treated s.c. vs i.v. was 48 IU/kg/week, representing an important average annual cost saving with s.c. administration. This study indicates that the cost of rHuEPO use is reduced substantially when administered s.c. compared with i.v.

Linde et al. [23], in a Swedish, retrospective, 25 centre survey, studied 223 HD patients who were switched from s.c. to i.v. rHuEPO use. They reported an increase in the mean dose requirement of 15% upon changing to the i.v. route, yet also suggested that, for patients on high s.c. doses, a switch to i.v. administration could lower the overall dose requirement of rHuEPO [23].

Conversely, recent observations have suggested that a higher dose of rHuEPO is not required to achieve target Hb when patients switch treatment from s.c. to i.v. [24,25]. Moist et al. [24] studied 426 switched HD patients with a 2 month follow-up period. The authors concluded that patients receiving s.c. rHuEPO 2–3 times weekly needed similar doses when given i.v. therapy.

Jacobs et al. [25] have also evaluated the effect of route of administration in >7000 patients involved in the European Survey on Anaemia Management (ESAM) who were iron replete during the entire 6 months of the survey. They concluded that similar Hb levels were achieved, with only a 4–6% increase of rHuEPO dose being necessary with i.v. administration.

**Pure red cell aplasia**

Anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) is a clinical condition that particularly affects those patients with chronic renal failure who are receiving exogenous ESAs for the treatment of renal anaemia [26,27]. Studies of other therapeutic proteins, including interferon, have shown that the likelihood of an immune response is increased when the protein is given s.c. vs i.v. One of the factors suggested to be associated with the development of anti-ESA antibodies is s.c. administration of ESA. Very few patients, if any, treated by the i.v. route only have ever developed this complication [26,28]. Physicians and health care professionals must remain vigilant in monitoring for the development of antibody-mediated PRCA in patients receiving erythropoietic agents because little is known about the immunological factors that contribute to the onset of this disorder. It is important therefore to understand that simply switching from the s.c. to i.v. administration route if a product is known to be immunogenic may not eliminate the risk of antibody formation [29]. A group of experts convened by the Canadian Society of Nephrology has concluded that there is no clear evidence that the route of administration alone is the main causative factor behind the increase in PRCA cases [30].

**From clinical studies to daily practice**

However compelling the evidence provided by clinical studies, the reality of everyday clinical practice rarely mimics the rigours of clinical trial protocols but reflects instead a mixture of evidence-based practice, local policies and national practices [31].

For example, in 2000, the United States Renal Data System (USRDS) reported use of higher rHuEPO doses than those recorded by the ESAM (15 500 U/week vs 110.1 IU/kg/week) despite similar Hb targets set out by these two organizations [32]. US studies usually report the i.v. route as preferable while, in the pre-PRCA era, s.c. was the usual administration route in Europe [31,32]. Indeed, the ESAM data reflect that practice varies within Europe from between >90% s.c. in the UK to 50% s.c. use in Germany [31]. Interestingly, 76.3% of i.v. patients vs 36.4% of s.c. patients received three times weekly doses. In this wide survey, no significant dose differences were found between s.c. and i.v. routes [31].

Clinical practice evolves with time. Consecutive studies in Spain demonstrate a progressive increase in the use of the s.c. route in the pre-PRCA era, as shown in Table 2 [31,33,34]. This is supported by a recent publication from Pisoni et al. who demonstrate that i.v. therapy seems to be the most frequently preferred route in the majority of countries assessed since the emergence of PRCA [35].

**New developments in anaemia management**

CERA (Continuous Erythropoietin Receptor Activator) is a new development in the field of anaemia management in CKD patients. Pre-clinical studies have shown that CERA is a more potent stimulator of erythropoiesis than rHuEPO [36,37], and phase I studies have shown CERA to offer potent, prolonged, dose-dependent erythropoietic activity by either an i.v. or s.c. route of administration [38]. In healthy volunteers, half-life has ranged from 70 to 122 h after i.v. injection and from 102 to 216 h after s.c. injection [39]. Initial phase II data indicate that its unique activity at the receptor level provides rapid, sustained and stable Hb levels with extended dosing intervals [39–41]. Ongoing phase III clinical trials will help to establish the role of this innovative erythropoietic agent.
Great strides have been made in improving the management of anaemia of CKD. In particular, many patients can now expect to receive more convenient and less frequent s.c. dosing for management of their condition. Despite concerns over PRCA and its suggested links with s.c. dosing, many patients continue to be managed successfully via this route, with i.v. treatment reserved for patients requiring HD. New ESA therapies are in development; these may offer further improvements in therapeutic efficacy and patient convenience.

Conflict of interest statement. None declared.

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