Pharmacology of darbepoetin alfa

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Abstract
The distinct molecular structure of darbepoetin alfa, in both its amino acid sequence and its carbohydrate content, results in a biologic profile with lower binding affinity, longer circulating half-life, and higher in vivo potency compared with the epoetins. The mechanisms responsible for these differences in biological effects have not been fully explained. Pharmacokinetic investigations of darbepoetin alfa using prolonged blood sampling times established that the mean terminal half-life after subcutaneous (SC) administration is 70 to 105 hours. Pharmacodynamic studies were conducted to assess the suitability of darbepoetin alfa for use in weekly or less frequent (once every other week or once a month) dosing regimens to maintain haemoglobin levels in patients with anaemia of renal disease. Regardless of dialysis status, route of administration, or prior treatment with an erythropoiesis-stimulating agent, darbepoetin alfa administered at extended intervals was able to raise or maintain hemoglobin levels to target. More rigorous studies will be needed to confirm these findings.

Keywords: anaemia; chronic kidney disease; darbepoetin alfa; erythropoiesis; pharmacodynamics; pharmacokinetics

Introduction
The erythropoiesis-stimulating agents (ESAs) currently approved in Europe for the treatment of renal anaemia are the recombinant human erythropoietins (epoetin alfa and epoetin beta) and the longer acting ESA (darbepoetin alfa). Darbepoetin alfa has a distinct structure compared with the epoetins, in both its amino acid sequence and its carbohydrate content, which prolongs its half-life following both intravenous (IV) and subcutaneous (SC) administration. Erythropoietin isoforms with a greater number of sialic acid residues have decreased receptor-binding affinity, but increased half-lives and biological activity [1,2]. Moreover, there was an observed association between the sialic acid-containing carbohydrate content of different ESAs and their receptor-binding affinities, circulating half-lives and biological activities. Darbepoetin alfa contains five changes in the amino acid sequence of the human erythropoietin gene, resulting in expression of a protein with two more N-linked carbohydrate chains and up to eight more sialic acid residues than the epoetin alfa molecule. The increased carbohydrate content of darbepoetin alfa compared with the epoetins results in reduced binding affinity for the erythropoietin receptor (EPO-R), but longer half-lives result in enhanced biological activity [1–3].

The present review aims to describe the factors that govern the biological effects of ESAs, focusing on the pharmacokinetic and pharmacodynamic properties of darbepoetin alfa as compared with the epoetins and the linkage of these properties with dosing regimens and clinical efficacy in patients with chronic kidney disease (CKD).

Pharmacokinetics and pharmacodynamics of darbepoetin alfa

There are important similarities and differences between the pharmacokinetic and pharmacodynamic profiles of darbepoetin alfa and the epoetins [4–8]. Endogenous erythropoietin and the ESAs bind to the EPO-R to similarly turn on a complex system of intracellular signalling pathways. Activation of these signalling pathways results in proliferation and terminal differentiation of erythroid progenitors in the bone marrow and protection from apoptosis of mature erythroid cells in the circulation [9]. Endogenous erythropoietin and ESAs bind to, dissociate from and rebind to EPO-Rs, or the ligands may be targeted for intracellular degradation via receptor-mediated endocytosis [10]. Despite the same mode of action, the binding affinities of the various ESAs differ.

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The binding affinity for the highly glycosylated darbepoetin alfa is 4.3-fold lower than that of epoetin alfa [1].

The half-life of darbepoetin alfa also differs from that of the other ESA molecules. The half-life of darbepoetin alfa is longer, meaning that darbepoetin alfa remains in the circulation for a longer period of time and, therefore, available to bind to, activate and release from the EPO-R for a longer period of time [10]. Moreover, in vivo studies in mice showed that the relative potency of darbepoetin alfa for increasing the haematocrit was 13- to 14-fold greater than that of epoetin alfa when the drugs were administered once weekly (QW) IV [1]. The combination of prolonged action and high biological activity of darbepoetin alfa supports its use in less frequent (i.e. QW) or extended [once every other week (Q2W)] dosing regimens to maintain haemoglobin levels in patients with anaemia of renal disease [6].

**Pharmacokinetics of darbepoetin alfa**

**Pharmacokinetics following IV administration**

Intravenous administration is the recommended and most comfortable and convenient route of ESA administration in haemodialysis (HD) patients [11]. Intravenous administration of ESAs is assumed to result in complete bioavailability. The volume of distribution following IV administration is the same for epoetin alfa and darbepoetin alfa and is approximately equal to the plasma volume, suggesting limited extravascular distribution of ESAs [6,12].

Intravenous dosing of ESAs is not the usual route of administration in peritoneal dialysis (PD) patients [11], but in a study examining the IV pharmacokinetics of darbepoetin alfa in this patient population, the half-life was found to be three times that of epoetin alfa. Following a single IV dose, the mean terminal half-life of darbepoetin alfa in these PD patients was found to be 25.3 h vs 8.5 h for epoetin alfa [12].

Similar results have been observed with IV administration of darbepoetin alfa to haemodialysis patients. Allon and colleagues performed a randomized, controlled, open-label pharmacokinetic study in HD patients that compared IV epoetin (alfa or beta not specified) administered three times weekly (TIW) with IV darbepoetin alfa administered TIW or QW. At haemoglobin steady state, the mean terminal half-life of QW darbepoetin alfa also was approximately three times longer than that of TIW epoetin (23.6 h compared with 8.5 h, respectively). Because of the long half-life of darbepoetin alfa, the brief sampling time between the TIW darbepoetin alfa doses did not provide sufficient time points to accurately characterize the half-life in this group [13].

**Pharmacokinetics following SC administration**

The bioavailability of darbepoetin alfa following SC administration is 37% (relative to IV administration) [12]. Similarly, the SC bioavailabilities of epoetin alfa and beta were determined to be 30–36% and 15–50%, respectively [8]. As stated in the European Best Practice Guidelines (EBPG), SC administration of ESAs is the preferred route for treating anaemia in patients with chronic renal insufficiency (CRI; predialysis) or PD patients [11]. In early studies in humans that used a sampling period of 1 week (168 h), the mean terminal half-life of darbepoetin alfa in PD patients after a single SC dose was found to be 48.8 h, 2- to 3-fold longer than that reported for SC epoetins [12]. More recent studies have estimated an even longer half-life for darbepoetin alfa. Studies investigating the pharmacokinetics of extended SC dosing regimens with darbepoetin alfa employed more protracted sampling periods (up to 28 days). These studies showed that the half-life of SC darbepoetin alfa was approximately 70 h and additional studies confirmed these findings (Table 1) [14–16].

Two studies by Padhi and colleagues conducted in patients with CRI used sampling times of 27–28 days to estimate the SC half-life. The first study, a pilot, was conducted in a subset of five patients from an open-label, multicentre investigation of once monthly (QM) SC administration of darbepoetin alfa. These patients had been receiving darbepoetin alfa Q2W and had stable haemoglobin levels between 10.0 and 12.0 g/dl. They were switched to QM darbepoetin alfa at a dose equal to the total dose received in the previous month. Samples for pharmacokinetic analysis were collected up to 28 days after administration of the first QM darbepoetin alfa.

### Table 1. Recent, single-dose studies of SC darbepoetin alfa half-life

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Max. sampling time (h)</th>
<th>Mean terminal half-life (h)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRI</td>
<td>5 (PK subset)</td>
<td>672</td>
<td>73</td>
<td>[14]</td>
</tr>
<tr>
<td>CRI</td>
<td>20</td>
<td>672</td>
<td>70</td>
<td>[15]</td>
</tr>
<tr>
<td>PD</td>
<td>32</td>
<td>672 h (180 µg group only); 336 h for remainder</td>
<td>64.7–91.4</td>
<td>[16]</td>
</tr>
<tr>
<td>CRI</td>
<td>32</td>
<td>672 h (180 µg group only); 336 h for remainder</td>
<td>73.6–104.9</td>
<td>[16]</td>
</tr>
</tbody>
</table>

CRI, chronic renal insufficiency (predialysis); h, hours; PD, peritoneal dialysis.
dose. Absorption after SC injection was slow in all patients, with peak concentrations of 0.75–6.29 ng/ml reached at 34–58 h post-dose, respectively, followed by a generally monophasic decline. The mean terminal half-life of darbepoetin alfa was 73 h (range 39.9–115 h, consistent with variability observed for other ESAs) [14]. The second study was a single-dose, open-label study of SC darbepoetin alfa in 20 adult patients with CRI. The extended sampling period was 27 days. Peak concentrations of darbepoetin alfa were reached in a median of 36.0 h (range 12.0–72.0 h), with a mean terminal half-life of 69.6 h (95% CI, 54.9–84.4 h) [15].

Tsubakihara and colleagues assessed the PK of darbepoetin alfa in patients receiving PD and patients with CRI following single SC doses [16]. Darbepoetin alfa was administered to 32 PD patients at 20, 40, 90, or 180 g (eight patients per treatment group) and to 32 patients with CRI (same dose groups and patient allocation). Serum darbepoetin alfa concentrations were followed for 336 h for patients receiving the 20-, 40-, or 90-μg doses, or 672 h for patients receiving the 180-μg dose. The mean terminal half-life in the different dose groups ranged from 64.7 to 91.4 h in the PD patients and from 73.6 to 104.9 h in CRI patients, but was not dose-dependent.

Effect of renal function on absorption and elimination of ESAs

The 2- to 3-fold longer half-life values for darbepoetin alfa following SC relative to IV administration (approximately 70 h vs 24 h) indicate that absorption is slow from the SC injection site and that it limits the rate of elimination following SC dosing. Thus, the half-life following SC administration for darbepoetin alfa reflects absorption rather than elimination. In addition, Tsubakihara et al. observed that the level of renal function did not affect the terminal half-life of darbepoetin alfa dosed SC in patients receiving PD and patients with CRI [16].

The lack of an effect of renal function on darbepoetin alfa exposure has also been assessed following SC administration. Using data from nine individual studies, Jang and colleagues examined the pharmacokinetics of SC darbepoetin alfa in adults with normal renal function, with CRI, or requiring dialysis and in paediatric CKD patients requiring dialysis (HD or PD not specified) [17]. Renal function did not markedly affect exposure based on the area under the serum darbepoetin alfa-time curve, nor did it affect the terminal half-life of darbepoetin alfa following SC administration as the mean half-life was 70.3 ± 29.1 h in adults with CRI and 69.0 ± 27.1 h in adults with normal renal function [17]. In addition, the mean terminal half-life of darbepoetin alfa after a single IV administration was 25.0 and 22.2 h in adult and paediatric dialysis patients, respectively, demonstrating that darbepoetin alfa elimination did not differ by patient age.

Taken together, the Tsubakihara and Jang studies with darbepoetin alfa indicate that renal excretion may not be a principal mechanism for elimination of darbepoetin alfa and that altered renal function does not influence the rate of darbepoetin alfa absorption (i.e. half-life following SC dosing) [16,17]. These findings are consistent with data from other ESAs. Only a small amount (<5% of the dose) of intact radiolabelled epoetin beta administered to healthy men was found to be excreted in urine following IV administration [18]. Similarly, the PK of epoetin alfa did not differ between HD and PD patients following intervals of IV and SC administration [19]. Epoetin alfa is not altered by differing degrees of renal function [5] or haemodialysis [5,20] and it is not found in the dialysate following IV administration [20].

The main site and mechanism for removal of endogenous erythropoietin and the ESAs from the circulation have yet to be fully elucidated [21]. Recently, it was hypothesized that a possible mechanism of degradation of ESAs is intracellular degradation. In vitro, cells that express the EPO-R internalize ESAs to some degree via receptor-mediated endocytosis and the molecules are then either degraded in lysosomes or recycled into the surrounding media [10]. The receptor binding, dissociation and trafficking properties of the ESAs determine their rates of intracellular degradation. Because of its low binding affinity, darbepoetin alfa binds surface EPO-R more slowly than epoetin alfa, but dissociates more quickly. Thus, darbepoetin alfa may be internalized and degraded more slowly than the epoetins [10].

Pharmacokinetics—conclusions

A long terminal half-life characterizes the pharmacokinetic profile of darbepoetin alfa following both IV and SC administration. The most recent pharmacokinetic studies using sampling times of 27 or 28 days established that the mean terminal half-life of darbepoetin alfa is 70–105 h when administered SC. Overall, the analyses performed to date have demonstrated that the pharmacokinetics of darbepoetin alfa do not change with dosing level, administration frequency, level of renal function, or patient age.

Pharmacodynamics of darbepoetin alfa

Although pharmacokinetics are important determinants of an ESA’s clinical advantages as well as its clinical limitations, the pharmacodynamics of an ESA also need to be carefully considered. The pharmacodynamics of ESAs determine the ability to achieve and maintain target haemoglobin levels. It is the clinical activity of an ESA, in addition to its pharmacokinetics, that affects
its utility in managing the treatment of anaemia and improving patient outcomes. Effective anaemia therapy (increases in haemoglobin/haematocrit) can be achieved both via increases in red blood cell (RBC) production and possibly via extension of RBC half-life.

The majority of pharmacodynamic studies in humans have focused on the effect of ESAs on haematocrit or haemoglobin levels. A number of studies have investigated the efficacy and safety of darbepoetin alfa for increasing and maintaining haemoglobin at target levels in patients with anaemia of CKD, with more recent studies assessing the effectiveness of extended dosing regimens. An exploratory study by Jadoul et al., evaluated the efficacy and safety of extended dosing with darbepoetin alfa in dialysis patients [22]. The study group included HD and PD patients (N=54) receiving stable Q2W darbepoetin alfa IV or SC. Patients were switched to once every 3 weeks (Q3W) dosing for 20 weeks, and if Hb levels were stable (−1.0 and +1.5 g/dl of baseline and between 10 and 13 g/dl), patients were then switched to QM dosing for another 20 weeks. The route of administration was unchanged. A total of 38 patients were able to switch to QM darbepoetin alfa, and 83% of these patients, with evaluable data, successfully maintained Hb levels. Similar studies have examined the pharmacodynamics of darbepoetin alfa by dialysis status and route of administration and will be discussed in the following sections.

A few studies in humans also have examined the effects of ESAs on RBC survival. In an observational study, the average RBC half-lives in patients receiving dialysis ranged from 14.5 to 17.1 days and were significantly shorter than the average RBC half-life of 23.5 days in healthy subjects [23]. Mechanical damage to RBCs during dialysis and mild haemolysis, as well as exposure to toxic factors in uraemic patients, all contribute to the shorter life span of RBCs in dialysis patients. There is some evidence to suggest that ESAs, in addition to stimulating erythropoiesis, may also prolong the survival of RBCs [24–26], although this hypothesis remains controversial. A controlled study in HD patients found that the mean RBC half-life increased from a baseline of 23.3 days before ESA therapy to 27.2 days after one year of ESA therapy, then declined to 22.1 days one year after the termination of ESA therapy [25].

There is a growing body of evidence that suggests neocytolysis is an important issue in patients with renal disease. Neocytolysis is a physiological mechanism by which the body destroys young erythrocytes when excessive red cells are present—e.g. in people descending from high altitude or during space travel [27–29]. When erythropoietin levels fall below a threshold level, neocytolysis is initiated, lasting approximately nine days and resulting in a 10–15% reduction in RBC mass. Neocytolysis may contribute to the anaemia of renal disease [28] and may be mitigated by ESA therapy [29].

Pharmacodynamics following IV administration—time to achieve haemoglobin steady state

As discussed previously, IV administration of ESAs is often the most convenient route for patients receiving HD [11]. The study by Allon and colleagues, discussed in the pharmacokinetics section, showed that the median time required for the haemoglobin level to reach a steady state after initiation of IV QW darbepoetin alfa was shorter than that required with more frequent IV epoetin (alfa or beta not specified): the time required to reach haemoglobin steady state with darbepoetin alfa QW dosing was 19 weeks vs 24 weeks with epoetin TIW dosing. There were no unexpected adverse events with the faster response times and the safety profiles were similar for darbepoetin alfa and epoetin [13].

Pharmacodynamics following IV administration—maintaining haemoglobin levels

Results from two studies support the conclusion that IV darbepoetin alfa is clinically efficacious in maintaining haemoglobin levels without a need to increase the dose in HD patients when administered at longer intervals compared with epoetin alfa. In a 28-week, randomized study, Nissenson et al., assigned HD patients receiving stable therapy with IV epoetin alfa TIW to continue treatment or to switch to IV darbepoetin alfa QW. There was no statistically or clinically significant change in mean haemoglobin levels from baseline to the evaluation period (the final 8 weeks of the study). During the evaluation period, 49% of patients in the epoetin alfa group vs 44% of patients in the darbepoetin alfa group required a dose change in order to maintain haemoglobin levels within the 9–13 g/dl target range. The mean dose during the evaluation period did not differ statistically from baseline values in either treatment group. Safety profiles were comparable between the two treatments, with similar rates of adverse events [30]. Locatelli and colleagues showed that haemoglobin levels were maintained in HD patients over 30 weeks of treatment with QW or Q2W darbepoetin alfa. Importantly, this study also demonstrated that there was no significant dose increase with the extension of the darbepoetin alfa interval out to Q2W and that the treatment was well-tolerated at both dosing schedules [31].

A prospective, multicentre, 24-week study determined the bioequivalent dose of darbepoetin alfa given IV QW in stable HD patients who had previously received epoetin alfa SC or IV and who had haemoglobin levels between 10.8 and 13 g/dl. Using the recommended dose conversion ratio on the European label (200 μg darbepoetin alfa to 11U epoetin alfa), patients previously stable on epoetin alfa BIW or TIW were converted to darbepoetin alfa QW and patients previously stable on epoetin alfa QW were converted to darbepoetin alfa Q2W. The dose of darbepoetin alfa was...
subsequently adjusted to maintain haemoglobin levels within ±1 g/dl of the baseline value. In the 100 study completers, haemoglobin was well-maintained. The dose of darbepoetin alfa was 45.6 μg and 25.8 μg at baseline for the QW and Q2W groups, respectively, and 31.5 μg and 21.4 μg at the end of the study, respectively [32].

Although PD patients are more likely to receive ESA therapy via the SC route, the efficacy and safety of IV darbepoetin alfa at various dosing frequencies was also investigated in these patients. In one study, PD patients either naïve to ESAs or previously receiving epoetin (alfa or beta not specified) were treated with darbepoetin alfa Q2W. Once stable, patients could extend the dosing interval out to QM. All patients received darbepoetin alfa for up to 28 weeks to achieve and maintain haemoglobin levels between 11 and 13 g/dl. Haemoglobin in ESA-naïve patients increased from 8.15 to 11.0 g/dl over the first 10 weeks of darbepoetin alfa therapy and all patients’ haemoglobin levels were successfully maintained within the target range regardless of whether darbepoetin alfa was dosed Q2W or QM [33]. It should be noted, however, that only stable patients were included in this study and QM administration may not be appropriate for an unselected dialysis population.

Pharmacodynamics following SC administration—dialysis patients

A number of studies support the efficacy of SC darbepoetin alfa administered to HD and PD patients who were switched from more frequent epoetin therapy (alfa or beta). In these studies, the patients receiving SC epoetin therapy were switched to darbepoetin alfa: epoetin BIW/TIW to darbepoetin alfa QW and epoetin QW to darbepoetin alfa Q2W. Haemoglobin levels were successfully maintained within the target range (for the majority of studies, 10–13 g/dl) and without the need for darbepoetin alfa dose increases [34–38]. In addition, a small study by Theodoridis et al. showed that haemoglobin levels in 11 PD patients were maintained following conversion from SC QW epoetin alfa to SC QM darbepoetin alfa [39], although once again the patients in this study were stable, and therefore, extrapolation into routine clinical practice may be inappropriate. In all of these studies, darbepoetin alfa was considered safe by the investigators and was generally well-tolerated at these extended dosing intervals.

Administration of darbepoetin alfa SC was also shown to be effective in PD patients not previously treated with an ESA. As part of a larger study, Macdougall and colleagues administered a range of darbepoetin alfa doses TIW or QW to 47 PD patients [40]. The investigators found that overall, both 0.45- and 0.75-μg/kg/week doses increased mean haemoglobin levels ≥1 g/dl/4 weeks and that there was no apparent difference in efficacy between the TIW and QW regimens. The individual patients who achieved a haemoglobin rate of rise ≥1 g/dl/4 weeks continued darbepoetin alfa treatment for up to 52 weeks with haemoglobin levels being maintained between 10 and 13 g/dl. The safety profile of darbepoetin alfa was similar to that expected for this patient population, thus demonstrating that PD patients can safely achieve a haemoglobin response within a month of initiating darbepoetin alfa therapy.

Pharmacodynamics following SC administration—CRI patients

In addition to dialysis patients, studies have also investigated the efficacy and safety of Q2W and QM dosing with darbepoetin alfa in CRI patients [41–46]. Two large, 24-week studies by Suranyi et al. and Toto et al. examined the administration of darbepoetin alfa in CRI patients not previously receiving an ESA. Within approximately 5 weeks of initiating SC de novo Q2W darbepoetin alfa, 95–97% of these patients achieved haemoglobin levels between 11 and 13 g/dl [41,42]. These results were supported by a chart review that compared de novo Q2W or QM epoetin alfa therapy with de novo Q2W or QM darbepoetin alfa. The proportion of patients achieving a mean haemoglobin level ≥11 g/dl within 100 days was recorded. Of the patients dosed with Q2W or QM darbepoetin alfa, 66.7% and 80.0%, respectively, achieved the haemoglobin target. In comparison, of the patients with Q2W or QM epoetin alfa, 53.8% and 50.0%, respectively, achieved the haemoglobin target [46]. These findings are of interest, but would need confirmation in a randomized controlled trial before any definite conclusions can be made about QM dosing.

Three recent studies have examined the efficacy of SC QM darbepoetin alfa in maintaining haemoglobin levels in CRI patients following extension of the dosing interval from previous Q2W darbepoetin alfa. In the study by Disney and colleagues, 83% of patients who received at least one QM dose of darbepoetin alfa (the modified intent-to-treat population; mITT) and 95% of the patients who completed the study achieved a target haemoglobin level of ≥10 g/dl [43]. Likewise, Ling et al. reported that the haemoglobin target of 10–12 g/dl was achieved in 79% of the mITT population and in 85% of those patients completing the study following extension of the darbepoetin alfa dosing interval to QM [44]. Finally, the study by Agarwal et al. further confirmed the efficacy of QM darbepoetin alfa by showing that following a switch from Q2W darbepoetin alfa dosing, haemoglobin levels could be maintained ≥11 g/dl in 76% of the mITT population and in 85% of patients who completed the study [45]. As before, however, all of these studies are non-randomized and uncontrolled, and thus, no definite conclusions can be made about QM dosing until more robust scientific evidence is obtained.

In a setting representative of current nephrology practice, nephrologists at centres participating in the
Pharmacology of darbepoetin alfa

Aranesp Registry Group in the Netherlands enrolled patients in a registry to investigate the feasibility of administering darbepoetin alfa QM. Nephrologists were first informed of the possibility of dosing darbepoetin alfa QM, and then their patients’ treatments were monitored for a 12-month period. The patients had CRI, were not receiving renal replacement therapy and were currently receiving or about to initiate QM darbepoetin alfa therapy. Of 108 patients completing the 12-month follow-up period, 66% were found to be receiving QM darbepoetin alfa and mean haemoglobin levels were maintained at approximately 12 g/dl throughout the study. Fifty-nine percent of the patients who had ever received a QM dose of darbepoetin alfa preferred this regimen over any other and 31% had no preference. These results are interesting, but clearly the potential for selection bias in this study is considerable as nephrologists are far more likely to select patients for QM dosing if they are stable and likely to manage with less frequent dosing [47,48].

Pharmacodynamics—conclusions

Overall, the studies in patients with CKD reviewed here indicate that darbepoetin alfa administered at weekly or Q2W intervals was able to raise and/or maintain haemoglobin levels to target, regardless of dialysis status, route of administration, or prior ESA therapy.

Discussion

Erythropoiesis-stimulating agents are active at several points in the erythropoiesis sequence, including the proliferation and maturation of progenitor cells and prevention of apoptosis in mature RBCs. The carbohydrate content of ESAs affects the receptor-binding affinity, serum half-life and biological activity. Together, the pharmacokinetic and pharmacodynamic properties of ESAs influence the clinical use (e.g. dosing frequency) of an ESA.

The pharmacokinetic–pharmacodynamic profile of darbepoetin alfa means that it is able to correct and maintain haemoglobin levels at a less frequent dosing regimen than is traditionally used with epoetin alfa or beta. For many patients with renal anaemia, haemoglobin levels can be corrected and maintained within weeks of initiating darbepoetin alfa therapy at a range of dosing regimens. For those patients switching from an ESA to a less frequent dosing schedule with darbepoetin alfa, haemoglobin levels can be successfully maintained with the same dose requirements or possibly even with some dose savings. In addition, and as detailed in a recent review on extended dosing of ESAs [49], data from several large studies have shown no significant difference in the dose required by patients when comparing route of administration (i.e. IV vs SC) [34,37,50].

Flexibility in dosing is an important part of trying to optimize therapy with ESAs. Dosing flexibility includes the ability to tailor the route and frequency of ESA administration to the needs of different patient groups. Intravenous administration is a convenient route of administration for patients receiving HD who have established vascular access and who report to a dialysis centre several times a week. In the meantime, newer ESAs that are not yet licensed for clinical use such as CERA (a 31 kDa epoetin beta covalently linked to a 30 kDa methoxypolyethylene glycol molecule; Roche Pharmaceuticals, Basel, Switzerland), and Hematide™ (a modified erythropoietin-mimetic peptide; Affymax, Palo Alto, California, USA), have also investigated the potential for QM dosing, but again randomized controlled data are lacking [51]. For patients with CRI, self-administered SC ESA therapy is much more convenient. The revised European Best Practice Guidelines (EBPG) for the Management of Anaemia in Patients With Chronic Kidney Disease recommend use of the IV route in patients receiving HD and the SC route in CRI patients and patients receiving PD [11].

Conclusions

The use of an ESA in clinical practice is affected by the combination of its pharmacokinetic and pharmacodynamic properties. The molecular structure of darbepoetin alfa confers differences in binding affinity, serum half-life and biological activity compared with those of other ESAs. Darbepoetin alfa has been shown to be a safe and effective treatment for correcting anaemia in patients with CKD at a wide range of dosing regimens. Clinical trials conducted in a number of CKD patient populations showed that darbepoetin alfa administered IV or SC and on an extended schedule can safely increase haemoglobin levels to target and/or maintain them in this range in the majority of patients. Decreasing the administration frequency of ESAs in CKD patients as part of an improved anaemia management protocol may be more convenient for patients and for their healthcare providers. Preliminary data on QM dosing of darbepoetin alfa are interesting, but all studies reported to date are non-randomized and uncontrolled. There is a pressing need for more robust scientific studies, such as the ongoing TREAT trial, investigating the efficacy of QM dosing of darbepoetin alfa.

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