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Darbepoetin Alfa

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Contents

Abstract

▲ Darbepoetin alfa is a novel erythropoiesis-stimulating protein developed for the treatment of anaemia associated with chronic kidney disease.

▲ In single-dose studies in patients undergoing dialysis, the mean terminal half-life for intravenous darbepoetin alfa was approximately 3-fold longer than for intravenous recombinant human erythropoitin (r-HuEPO, epoetin alfa; 25.3 *vs* 8.5 hours). The mean terminal half-life after subcutaneous administration of darbepoetin alfa was 48.8 hours.

▲ In randomised nonblind trials in patients undergoing dialysis, darbepoetin alfa (0.45 μg/kg) given once weekly for the correction of anaemia increased haemoglobin (Hb) levels to a similar extent as darbepoetin alfa three times weekly or r-HuEPO two or three times weekly.

▲ A double-blind, randomised clinical trial reported that switching patients from a three-times weekly regimen of r-HuEPO to once weekly darbepoetin alfa with additional placebo twice weekly (all intravenously) maintained Hb levels between 9.0 and 13.0 g/dl to a similar extent as continued treatment with r-HuEPO three times weekly.

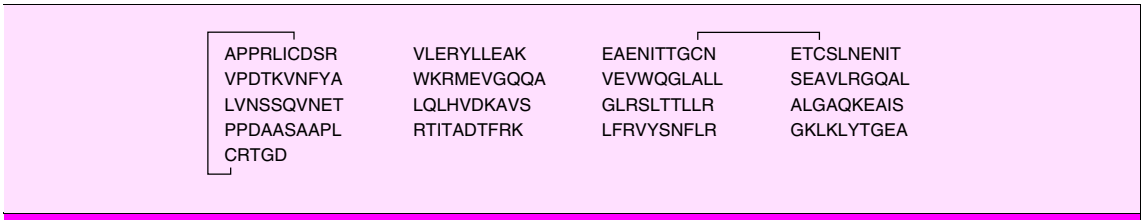
▲ In a randomised nonblind study, r-HuEPO-naive patients with chronic renal insufficiency received either subcutaneous darbepoetin alfa once weekly or r-HuEPO twice weekly. 93% of patients receiving darbepoetin alfa and 92% of patients receiving r-HuEPO achieved a Hb increase of ≥ 1.0 g/dl from baseline and the mean increase in Hb level over the initial 4 weeks was similar for both treatments.

▲ The number and frequency of adverse events, withdrawals and deaths reported in clinical trials did not differ between patients receiving darbepoetin alfa and patients receiving r-HuEPO. There have been no reports of immune responses to darbepoetin alfa in 1534 patients receiving treatment for up to 2 years.

Features and properties of darbepoetin alfa (novel erythropoiesis-stimulating protein, NESP)

Indications		
Anaemia associated with chronic kidney disease (including patients on dialysis and those with chronic renal insufficiency)		
Mechanism of action		
Erythropoiesis-stimulating protein	Stimulates red blood cell production through activation of erythroid progenitor cells in bone marrow	
Dosage and administration in patients with chronic kidney disease		
Recommended starting dose in new patients	0.45 μg/kg once weekly[a]	
For switching from r-HuEPO to darbepoetin alfa	According to the following conversion scheme[a]	
	Previous r-HuEPO dose (unit/wk)	Starting darbepoetin alfa dose (μg/wk)
	<2500	6.25
	2500-4999	12.5
	5000-10 999	25
	11 000-17 999	40
	18 000-33 999	60
	34 000-89 999	100
	≥ 90 000	200
Route of administration	Intravenous or subcutaneous	
Frequency of administration	Once weekly or once every 2 weeks	
Pharmacokinetic profile		
	Intravenous	Subcutaneous
Time to peak plasma concentration (h)	NA	54.1
Mean terminal half-life (h)	25.3	48.8
Adverse events		
Mild and transient injection site pain. Other adverse events similar to that expected with r-HuEPO		
No evidence of antibodies to darbepoetin alfa		

a According to darbepoetin alfa US package insert[1]



For more than a decade, recombinant human erythropoietin (r-HuEPO, epoetin alfa and epoetin beta) has been the first-line treatment for renal anaemia.[2,3]

Endogenous erythropoietin is synthesised predominantly in the cortex and outer medulla of the kidney where gene expression is stimulated by a fall in oxygen tension at the renal parenchyma. Following expression and post-translational glycosylation, erythropoietin is released into the renal circulation and transported to the bone marrow where it stimulates red blood cell production through activation of erythroid progenitor cells.[4]

Cloning and expression of the gene for HuEPO was accomplished in 1983. Within 2 years the recombinant product was being tested in humans, and by 1988 it was licensed for treatment of anaemia of chronic renal failure.[5] Recently, the molecular components of HuEPO which regulate receptor affinity and plasma half-life have been identified and modified, leading to the development of a novel erythropoiesis-stimulating protein, darbepoetin alfa.

This review provides a summary of the currently available information regarding darbepoetin alfa. We have focussed on the use of darbepoetin alfa in anaemia associated with chronic kidney disease; its use in oncology indications is not within the remit of this article. *In vitro* studies have shown that darbepoetin alfa and r-HuEPO share a common mechanism of action and pharmacodynamic studies demonstrate that darbepoetin alfa acts as an erythropoietic protein. Pharmacokinetic studies indicate that darbepoetin alfa has an extended plasma half-life compared with r-HuEPO, which requires administration two to three times weekly.[6] Recent clinical trials suggest that darbepoetin alfa given once weekly or once every two weeks is an effective treatment for anaemia associated with chronic kidney disease.

1. Pharmacodynamic Profile

- HuEPO is a 30 400 dalton glycosylated protein consisting of a 165-amino acid residue chain containing two disulphide bonds. Post-translational processing of this peptide results in the addition of oligosaccharides to either asparagine (N-linked) or serine/threonine (O-linked) amino acid residues. Natural (and recombinant) HuEPO has three N-linked oligosaccharide chains at asparagine 24, 38 and 83 and one O-linked chain at serine 126. The structures of these oligosaccharides are variable, with each of the N-linked chains having 2, 3 or 4 branches terminating with the sugar molecule, sialic acid. Similarly, the O-linked oligosaccharide chain may contain 0 to 2 sialic acid residues, so each erythropoietin molecule may contain a total of 6 to 14 sialic acid residues.[6]

- Removing sialic acid moieties from the molecule increases the affinity for the erythropoietin receptor and decreases serum half-life. A direct relationship therefore exists between sialic acid content, *in vivo* biological activity and serum half-life, but an inverse relationship with receptor affinity.[7] Although increased receptor affinity produces a more biologically active molecule, serum clearance has a more profound influence on *in vivo* activity, and the increases in plasma half-life more than compensate for reduced affinity.[7] Thus *in vivo* biological activity increases with increasing sialic acid

content. This has been demonstrated using isoforms of HuEPO containing 4 to 14 sialic acid residues in a radioassay in OCIM-1 cells (no quantitative data provided) and in pharmacokinetic studies in normal mice.[7]

• New carbohydrate attachment sites were introduced into the amino acid chain without disrupting the tertiary protein structure or adversely affecting receptor affinity using site-directed mutagenesis.[8] These experiments led to the development of darbepoetin alfa, a novel erythropoiesis-stimulating protein. The amino acid sequence of darbepoetin alfa differs from that of HuEPO at five positions (Ala30Asn, His32Thr, Pro87Val, Trp88Asn and Pro90Thr), allowing for two additional oligosaccharide attachments at asparagine 30 and 88.[6] The introduction of these new oligosaccharide chains increases the potential maximum number of sialic acid residues within the molecule from 14 to 22.

In Vivo Studies

The effects of darbepoetin alfa on haemoglobin (Hb) levels and haematocrit were investigated in two experimental rodent models of anaemia.[9,10]

• Long-term cisplatin (2 mg/kg daily) causes a marked elevation of blood urea nitrogen and decrease in red blood cell count, haematocrit, Hb levels and reticulocyte count in rats. After 4 weeks' treatment with cisplatin, haematocrit levels are reduced to <40% of normal and this is maintained for more than 80 days. Weekly intravenous administration of darbepoetin alfa (1 μg/kg/day) for 6 weeks to cisplatin-treated rats resulted in complete recovery of the haematocrit by the second week of treatment. This recovery in haematocrit was then maintained by darbepoetin alfa (0.3 μg/kg) administered once every 2 weeks.[9] In this study, single weekly doses of darbepoetin alfa were as effective as r-HuEPO given three times weekly.

• Immunisation of rats with a peptidoglycan-polysaccharide polymer (PPP) induces chronic systemic inflammation and ultimately a chronic, moderately severe anaemia. In this model, treatment with darbepoetin alfa (30 μg/kg every 2 weeks; route not stated) resulted in Hb levels returning to pre-PPP concentrations within 28 days of initiating treatment.[10]

2. Pharmacokinetic Profile

• The pharmacokinetic profile of a single intravenous dose of epoetin alfa (100 IU/kg) was compared with that of an equivalent peptide mass of intravenous darbepoetin alfa in a double-blind, randomised, crossover study in 11 adult patients receiving peritoneal dialysis (figure 1).[11] The mean terminal half-life ($t_{1/2}$) for darbepoetin alfa was significantly longer than for epoetin alfa (25.3 *vs* 8.5 hours), a difference of 16.6 hours [95% confidence interval (CI): 9.4, 24.2; p = 0.0008]. In addition, the area under the serum concentration-time curve was significantly greater for darbepoetin alfa (291.0 *vs* 131.9 mg/L.h; p < 0.0005) and clearance (CL) was significantly lower (0.002 *vs* 0.004 L/h/kg; p < 0.0005) compared with epoetin alfa. The volume of distribution was similar for both treatments (0.052 *vs* 0.049 L/kg).[11] Comparable values for $t_{1/2}$ and CL of intravenous darbepoetin alfa have also

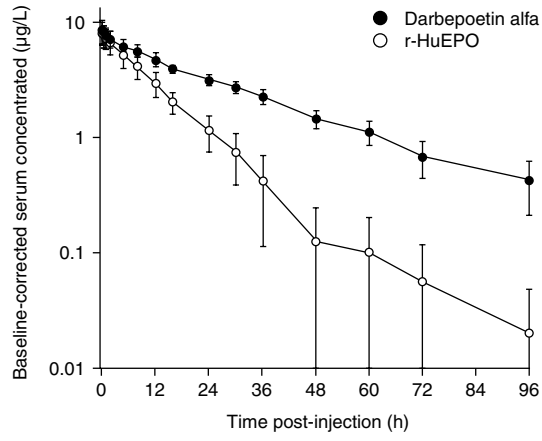


Fig. 1. Comparison of intravenous pharmacokinetic profiles of darbepoetin alfa (n = 11) and recombinant human erythropoietin (r-HuEPO; n = 10). Reproduced from Macdougall et al.,[11] with permission from Lippincott, Williams and Wilkins.

been reported in 13 paediatric patients (aged 3 to 16 years) with chronic renal failure.[12]

• Six patients from the double-blind intravenous study[11] continued into a nonblind investigation of the pharmacokinetic profile of a single dose of subcutaneous darbepoetin alfa (using the same dose that they received intravenously). Mean $t_{1/2}$ in these patients was about twice that achieved after intravenous administration (48.8 hours) and peak serum concentration (C_{max}) was approximately 10% of that achieved following intravenous administration. The mean bioavailability of subcutaneous darbepoetin alfa was 36.9% and mean time to C_{max} (t_{max}) was 54.1 hours.[11] In paediatric patients (n = 10 evaluable), the bioavailability of subcutaneous darbepoetin alfa was slightly higher (54%, range 32 to 70%) and t_{max} shorter (36.2 hours, range 10 to 58 hours) than in adult patients.[12]

• The pharmacokinetic profile of long-term intravenous darbepoetin alfa was studied in 47 patients undergoing haemodialysis who were randomised to one of three groups. Darbepoetin alfa (2.6 to 302.9μg) administered once or three-times-weekly was compared with intravenous r-HuEPO (5400 to 42900 IU/week) in a three-times-weekly regimen.[13] At weeks 1 and 12, and during steady-state Hb, mean $t_{1/2}$ and CL values for once-weekly darbepoetin alfa were comparable to those for the three-times-weekly regimen. The mean $t_{1/2}$ for darbepoetin alfa when administered either once or three-times-weekly, was approximately three-fold longer than for r-HuEPO administered three times weekly (23.4 *vs* 8h at week 12).[13]

3. Clinical Trials

To date, several clinical trials have reported the effects of darbepoetin alfa in patients with anaemia associated with chronic kidney disease. These trials have assessed the use of darbepoetin alfa for Hb correction in r-HuEPO-naive patients, for switching from r-HuEPO to darbepoetin alfa, and for the long-term maintenance of Hb levels. The severity of disease in these patients ranged from chronic renal insufficiency (CRI), a condition where renal function is compromised but that does not require dialysis, to end-stage renal disease (ESRD) which requires regular dialysis. Randomisation ratios of either 2 : 1[14,15] or 3 : 1[16,17] were used in studies comparing darbepoetin alfa with r-HuEPO. One study has been published in full[16] whilst all other studies have been published as posters and/or abstracts.

• Two randomised dose-escalation studies have investigated the optimal dose and frequency of darbepoetin alfa for treating anaemia in patients with ESRD.[18] In the first study, darbepoetin alfa (0.075, 0.225, 0.45 or 0.75 μg/kg) was administered subcutaneously either as a once-weekly dose or in three divided doses each week to patients undergoing peritoneal dialysis (n = 58). In the second study, darbepoetin alfa was administered intravenously at the same doses and frequencies to haemodialysis patients (n = 78).

• In both studies, 4 weeks of treatment with darbepoetin alfa increased Hb levels by ≥1 g/dl in >50% of patients at the two highest doses. No differences were observed between the once and three-times-weekly regimens via either route of administration. High Hb levels observed in the highest-dose group were addressed by dose reduction or withholding darbepoetin alfa until Hb levels decreased to within the target range (11 to 13 g/dl). These studies suggest that 0.45 μg/kg administered intravenously or subcutaneously once weekly is an optimal starting dose in patients with ESRD. [18]

• One hundred and sixty-six patients with CRI and no prior treatment with r-HuEPO during the 12-week period prior to the study (r-HuEPO-naive) were randomised to nonblind treatment with subcutaneous darbepoetin alfa (0.45 μg/kg once weekly) or r-HuEPO (50 IU/kg twice weekly) for 24 weeks (figure 2).[16] Ninety-three percent of patients receiving darbepoetin alfa (95% CI: 87, 97), and 92% of patients receiving r-HuEPO (95% CI: 78, 98) achieved a Hb increase of ≥1.0 g/dl from baseline and a Hb level ≥11.0 g/dl. The mean increase in Hb level over the initial 4 weeks of therapy was similar for both treatments (darbepoetin alfa

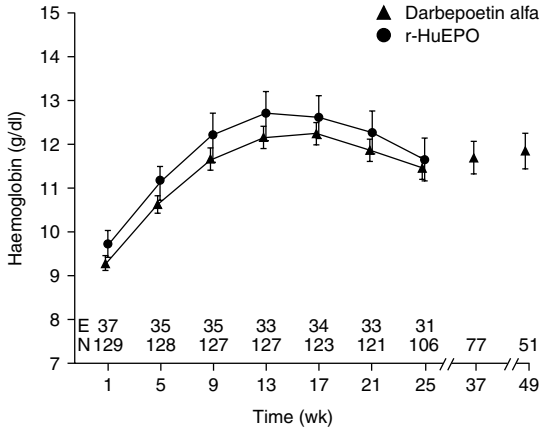


Fig. 2. Comparison of the effects of darbepoetin alfa (0.45 μg/kg once weekly) or recombinant human erythropoietin (r-HuEPO, 50 IU/kg twice weekly) on mean haemoglobin (Hb) levels. Target Hb range in this study was 11.0 to 13.0 g/dl. **E** = number of patients receiving r-HuEPO; **N** = number of patients receiving darbepoetin alfa. Reproduced from Locatelli et al.,[16] with permission from Blackwell Scientific Publishing (http://www.blackwellscience.com).

1.38 g/dl [95% CI: 1.21, 1.55]; r-HuEPO 1.40 g/dl [95% CI: 1.07, 1.72]). In both treatment groups, the median time to achieve target Hb response was 7 weeks (range 3 to 25 weeks).[16]

• The efficacy of subcutaneous darbepoetin alfa given once every other week for the treatment of anaemia in patients with CRI has been evaluated in a noncomparative study.[19] An interim analysis was conducted of the first 23 patients enrolled into the study who successfully completed at least 10 weeks of darbepoetin alfa treatment. The starting dose of darbepoetin alfa was 0.75 μg/kg and this was titrated to maintain Hb levels within the target range of 11 to 13 g/dl. The median time to achieve a Hb response was 6 weeks (range, 0 to 17 weeks), and 91% of patients (95% CI: 73.2, 97.6) reached the target Hb range within 10 weeks of initiating darbepoetin alfa therapy. The median darbepoetin alfa dose at the time of Hb response was 50μg every other week (range, 30 to 130 μg).[19]

• Darbepoetin alfa (0.45 μg/kg once weekly; equivalent to total weekly dose of 90 IU/kg r-HuEPO) was also compared with r-HuEPO (50 IU/kg three times weekly, total weekly dose = 150 IU/kg) in a 20-week nonblind study in r-HuEPO-naive patients (n = 122) receiving dialysis for chronic renal failure.[17] Both intravenous and subcutaneous routes were used for administration and target Hb response was defined as a Hb level ≥11.0 g/dl. Seventy-two percent of patients receiving darbepoetin alfa (95% CI: 62, 81), and 84% of patients receiving r-HuEPO (95% CI: 66, 95) achieved the target Hb response during the study. The median time to achieve Hb target response was 10 weeks in patients receiving darbepoetin alfa (range 1 to 20 weeks), and 8 weeks in patients receiving r-HuEPO (range 3 to 20 weeks).[17]

• Two nonblind studies[14,20] have examined the effect of switching patients from r-HuEPO to darbepoetin alfa. In these studies, a total of 1225 patients were receiving r-HuEPO between once and three times each week and either peritoneal or haemodialysis at baseline. Those patients receiving r-HuEPO once weekly at baseline were switched to darbepoetin alfa once every 2 weeks, while those patients receiving r-HuEPO twice or three times per week were switched to darbepoetin alfa once weekly. In one of these studies, patients were diagnosed with ESRD prior to entry into the study (n = 522) and were randomised to continue r-HuEPO or to receive darbepoetin alfa.[14] In the other study, all patients were switched to darbepoetin alfa.[20]

• In all cases switching patients from r-HuEPO to darbepoetin alfa administered by the same route once weekly or once every 2 weeks resulted in no significant change in Hb levels compared with those in patients who continued with r-HuEPO or baseline Hb levels. In patients switching to darbepoetin alfa, Hb levels changed by –0.08 g/dl (95% CI: –0.29, 0.12) at week 36[20] and –0.03 g/dl at week 32[14] compared to baseline, whilst in patients maintaining their r-HuEPO medication, Hb levels changed by –0.06 g/dl at week 32 compared with baseline.[14]

• A single double-blind, randomised clinical trial has examined the effect of switching patients from

r-HuEPO to darbepoetin alfa.[15] Five hundred and seven patients undergoing haemodialysis were randomised to receive either darbepoetin alfa once weekly and placebo twice weekly, or to continue to receive r-HuEPO three times weekly. Study drug was administered intravenously and doses were adjusted as necessary to maintain Hb levels between 9.0 and 13.0 g/dl for up to 28 weeks (20-week dose titration period followed by 8-week evaluation period; actual dosages not given). The mean change in Hb level between baseline and the evaluation period was 0.16 g/dl for patients randomised to darbepoetin alfa and 0.00 g/dl for patients receiving r-HuEPO. There was no significant difference between treatment groups.[15]

• Recent evidence suggests that, in some patients, darbepoetin alfa administered once every 4 weeks may be sufficient to maintain Hb levels within their target range. In a nonblind study, 34 patients receiving darbepoetin alfa once every 2 weeks were switched to a once every 3 weeks regimen for a 20-week evaluation period.[21] Thirty-two of these patients completed the evaluation period and of these 28 (87.5%) were successfully maintained in the study target Hb range (−1.0 to +1.5 g/dl from their mean baseline level between 10.0 and 13.0 g/dl). These 28 patients underwent a further reduction in their dosage frequency to a once every 4 weeks regimen for a further 20-week period. Twenty-two patients completed the second evaluation period, of whom 19 (86.4%) maintained the study target Hb. Throughout the study, five patients had their dosage frequency increased per protocol although they maintained their Hb levels within the study target range. Thus, the dosage regimen was successfully reduced from once every 2 weeks to once every 4 weeks in 19 out of the original 34 study entrants.[21]

• Practical guidelines for the use of darbepoetin alfa in the treatment of anaemia associated with chronic renal failure are available in the US Physician Package Insert.[1] European guidelines for the use of darbepoetin alfa have also been developed based on the European Best Practice Guidelines for the Management of Renal Anaemia in Patients with Chronic Renal Failure.[22] Subcutaneous darbepoetin alfa is recommended in patients with CRI (Europe only) and receiving peritoneal dialysis whilst either the subcutaneous or intravenous route can be used in patients undergoing haemodialysis.

• The recommended starting dose of darbepoetin alfa is 0.45 μg/kg and target Hb levels should be ≤12 g/dl.[1] If Hb levels are increasing towards 12 g/dl, the dosage should be reduced by approximately 25%.[1] If Hb levels continue to increase following dosage adjustment, darbepoetin alfa should be temporarily withheld until Hb begins to decrease, at which point therapy should be restarted at a dosage approximately 25% below the previous dosage.[1] If Hb levels increase by more than 1.0 g/dl in a 2 week period, the dosage should be decreased by approximately 25%.[1] When darbepoetin alfa therapy is initiated or adjusted, Hb levels should be monitored each week until stable, and monthly thereafter.[1] The relationship between dose of r-HuEPO and darbepoetin alfa is affected by factors such as patient age, baseline r-HuEPO dose, degree of hospitalisation and route and schedule of administration of darbepoetin alfa. Because of the wide degree of variability, a dose conversion schedule has been constructed for patients switching from r-HuEPO to darbepoetin alfa (see Features and properties table).[1]

4. Tolerability

• From the clinical trials (see section 3) that have been reported, it appears that darbepoetin alfa has an adverse event profile very similar to that of r-HuEPO. In each study, the number and frequency of adverse events, withdrawals and deaths did not differ between patients receiving darbepoetin alfa and patients receiving r-HuEPO.[14-17,20] The percentage of patients with Hb levels defined as unstable was similar for treatment with either darbepoetin alfa (35%) or r-HuEPO (38%).[15] Injection site pain was reported as attributable to treatment in studies where darbepoetin alfa was administered via subcutaneous injection. This was generally mild and tran-

sient in nature and occurred predominantly after the first injection.[22] Darbepoetin alfa should be used with caution in patients with liver disease, sickle-cell anaemia or epilepsy.[22]

• The amino acid sequence of darbepoetin alfa differs from the sequence of endogenous erythropoietin at five positions and, as a result, it is theoretically possible that darbepoetin alfa could be immunogenic. This immunogenicity is a potential issue with all members of this class of drug; erythrocyte aplasia in association with antibodies to erythropoietin, has been reported on rare occasions in patients treated with recombinant erythropoietins.[1] To date, there are no reports of immune responses to darbepoetin alfa in 1534 patients receiving treatment for up to 2 years.[23]

5. Darbepoetin Alfa: Current Status

Darbepoetin alfa is a novel erythropoiesis-stimulating protein for the treatment of anaemia associated with chronic kidney disease. It has been approved by the European Commission and is available in a number of European markets (for use in patients aged ≥11 years), and has also recently been approved for use in other markets worldwide including the US. Compared with r-HuEPO, treatment with darbepoetin alfa requires less frequent administration (once weekly or once every 2 weeks) and may therefore relieve the need for provision of r-HuEPO two to three times per week, especially in patients with CRI who do not otherwise need to visit the clinic this frequently.

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