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Supplementary Paper

Darbepoetin alfa: A new erythropoietic drug for the treatment of renal anaemia*

Amgen Anaemia Advisory Group

SUMMARY: Darbepoetin alfa (Aranesp®, Amgen Ltd) is a long-acting, hyperglycosylated recombinant human erythropoietin (r-HuEPO; epoetin) analogue, developed for the treatment of anaemia in patients with chronic kidney disease (CKD, i.e. end-stage renal failure or progressive renal impairment). Based on previously published European guidelines, this review article presents key recommendations for the use of darbepoetin alfa in Australasian clinical practice.

Darbepoetin alfa is expected to be a valuable alternative therapeutic agent for the management of renal anaemia. Clinical data demonstrate that: Once-weekly administration of darbepoetin alfa – whether by subcutaneous (s.c.) or intravenous (i.v.) injection – is as effective as epoetin therapy, administered two or three times per week; patients receiving once-weekly doses of epoetin can be switched to darbepoetin alfa, once every 2 weeks; target haemoglobin (Hb) concentrations can be successfully maintained in patients switched from epoetin therapy to less frequently administered doses of darbepoetin alfa (administration once every 2 weeks is sufficient for some patients); and darbepoetin alfa has a similar safety profile to epoetin. In addition to addressing a number of practical considerations relating to the use of darbepoetin alfa in clinical practice, this article also highlights principal findings from several key clinical studies.

KEY WORDS: **anaemia, chronic kidney disease, darbepoetin alfa, dosing frequency, efficacy, epoetin, novel erythropoiesis stimulating protein, pharmacokinetics, safety.**

INTRODUCTION

Recombinant human erythropoietin (r-HuEPO; Epoetin) therapy has transformed the management of renal anaemia since its introduction more than a decade ago, and is now the standard of care when treating anaemia associated with chronic kidney disease (CKD).[1–7] This Australasian usage guideline is based on papers by Macdougall,[8] 'An Overview of the Development and Clinical Efficacy of Novel Erythropoiesis Stimulating Protein (NESP)' and the NESP Usage Guidelines Group,[9] 'Practical Guidelines for the Use of NESP in Treating Renal Anaemia'. Members of the Amgen Anaemia Advisory Group have contributed to this usage guideline to reflect the local practice in Australia and New Zealand.

Darbepoetin alfa is a novel erythropoiesis stimulating protein that stimulates erythropoiesis via the same mechanism as epoetin, but which can be administered at a reduced dosing frequency.[8,10,11] Its development arose from basic research, aimed at determining which structural features controlled the *in vivo* biological activity of epoetin.[10–14] Investigators discovered that the serum clearance rate of epoetin is the primary determinant of its *in vivo* biological activity; and the serum clearance rate of epoetin can be reduced by increasing its sialic acid content.[12–14]

Based on these findings, darbepoetin alfa was designed to incorporate more sialic acid residues than conventional epoetin. Specifically, it has five amino acid substitutions, which enable the attachment of two additional sialic acid-containing carbohydrate chains (Fig. 1).[13,14] Erythroid progenitor cell binding is not affected by these additional carbohydrate chains and darbepoetin alfa stimulates erythropoiesis by the same receptor mechanism as epoetin.[13–15]

Studies have since confirmed that darbepoetin alfa has a decreased clearance rate and therefore a two- to three-fold longer serum half-life, compared with epoe-

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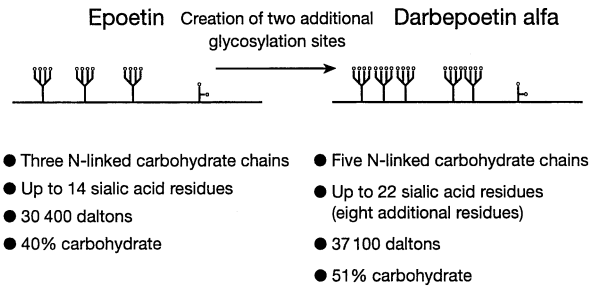

Fig. 1 Biochemical and biological properties of darbepoetin alfa and epoetin.[10,13,16] Reproduced with permission from WB Saunders from Macdougall IC. *Semin. Nephrol.* 2000; **20**: 375–81.

tin.[13,16] This creates the potential for once-weekly (or even less frequent) dosing, benefiting both patients and health-care providers alike. Such therapy has been initiated among more than 8700 patients with CKD in clinical studies designed to evaluate the efficacy and safety of the drug at different stages of renal anaemia management.[17–23]

DARBEPOETIN ALFA IN CLINICAL PRACTICE

Based on current evidence, darbepoetin alfa is expected to be a valuable alternative therapeutic agent for the management of renal anaemia.[8,10] Clinical practice guidelines have been published to assist clinicians in the administration of erythropoietic therapy to patients with CKD and in the use of darbepoetin alfa.[9,7]

Recommendations that relate to the general use of erythropoietic therapy (e.g. appropriate target haemoglobin (Hb) concentrations, evaluation of anaemia, monitoring of iron stores, etc.), are broadly applicable to both darbepoetin alfa and epoetin treatment.[9] However, darbepoetin alfa differs from epoetin in several important aspects.

One of the major differences is that darbepoetin alfa can be administered less frequently than conventional epoetin therapy in the treatment of renal anaemia, due to its comparatively longer serum half-life. Administered by either subcutaneous (s.c.) or intravenous (i.v.) injection, it has been shown that:

- Once-weekly darbepoetin alfa treatment is as effective as epoetin therapy, administered two or three times per week, in the correction of CKD-related anaemia.[18,21]
- Once-weekly darbepoetin alfa treatment is as effective as epoetin treatment, administered two or three times per week, in the longer-term maintenance of target Hb concentrations.[17]
- The required dose of darbepoetin alfa is similar for both the subcutaneous and intravenous routes of administration.

Table 1 Darbepoetin alfa – Recommended starting dose by patient weight*

Patient type	Recommended starting dose
Peritoneal dialysis and predialysis	0.45 μg/kg once per week (s.c.)
Haemodialysis	0.45 μg/kg once per week (s.c. or i.v.)

* Adapted from The NESP Usage Guidelines Group.[9]

Initiating treatment

Studies have established that it is appropriate to initiate darbepoetin alfa therapy at a dose of 0.45 μg/kg, administered once per week by i.v. or s.c. injection, when treating anaemia in predialysis or dialysis patients who have not previously received epoetin therapy (Table 1).[9,18,21]

Darbepoetin alfa comes in prefilled syringes with marked dosage graduations. In Australia, the available dosage strengths are 10, 20, 30, 40, 50, 60 and 100 μg. Clinicians and/or patients are advised to calculate the required dose, then round up to the nearest available syringe dosage.

Darbepoetin alfa can be administered at any point during the dialysis session; there is no evidence that darbepoetin alfa adsorbs to dialysis membranes or tubing, or that it is cleared by the dialysis procedure.[9] The s.c. route of administration is preferred when treating peritoneal dialysis or predialysis patients. The site of s.c. injection should be changed with each administration.[9]

Dose titration and monitoring

Once initiated, clinicians are advised to adjust the dose of darbepoetin alfa in order to achieve and maintain a target Hb concentration of approximately 120 g/L.[9] Lower target Hb concentrations are recommended for patients with sickle cell anaemia (i.e. 70–90 g/L);[9] a more conservative approach might also be warranted when treating patients with symptomatic cardiovascular disease. Darbepoetin alfa therapy has been associated with no greater variability in Hb response than epoetin during clinical trials, suggesting that it is appropriate to adopt a similar Hb monitoring schedule to that used for epoetin therapy.[9,17,19–21]

A patient's Hb concentration should be measured once every 4 weeks when initiating therapy or after a change of dose, and more frequently if warranted. Less frequent monitoring may be appropriate when both the Hb concentration and the darbepoetin alfa dose have been stabilized, and if there are no intercurrent illnesses dictating more frequent monitoring (e.g. malignancy, infection, haematological disorders).[9]

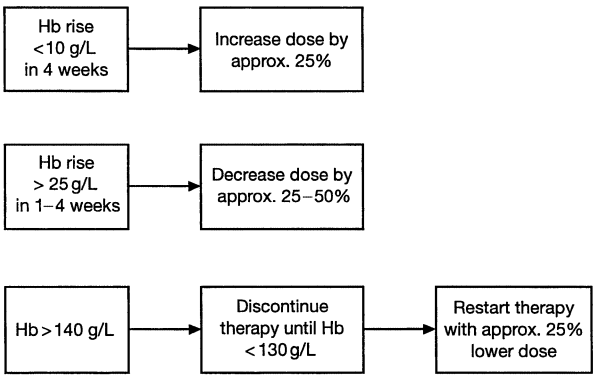

Fig. 2 Titrating darbepoetin alfa.[9] Adapted with permission from the Oxford University Press from the NESP Usage Guidelines Group. *Nephrol Dial Transplant*. 2001; **16** (Suppl 3): 22–8.

The dose of darbepoetin alfa is typically adjusted according to the rate of rise in Hb concentration. Clinicians are advised to increase the dose by approximately 25% if the observed increase in Hb concentration after treatment initiation (or a dose increase) is less than 10 g/L over a 4-week period. Dose increases should not normally be made more frequently than once every 4 weeks.[9]

If the rise in Hb concentration is greater than 25 g/L over 4 weeks, then clinicians are advised to decrease the dose of darbepoetin alfa by 25–50% (i.e. depending on the rate of Hb increase) in order to reduce the risk of adverse events. If the Hb concentration exceeds 140 g/L, therapy should be discontinued until Hb concentrations fall below 130 g/L and then restarted at an approximately 25% lower dose (Fig. 2).[9]

The rate of decline in the Hb concentration following the withdrawal of darbepoetin alfa is similar to that observed following the withdrawal of epoetin.[8,11,21] This is because the decline in Hb concentration is determined by the rate of destruction of red blood cells in circulation, not by the serum concentration of either darbepoetin alfa or epoetin.

It is also possible to titrate the dose of darbepoetin alfa by changing its frequency of administration; patients in clinical studies have been successfully maintained on darbepoetin alfa when administered every second week.[17] Reducing the dose frequency, instead of the dose itself, has the advantage of permitting continuation of the same syringe size.

Hypertension is a common side-effect of treatment, which can nearly always be controlled by the institution or escalation of antihypertensive therapy. Blood pressure should be regularly monitored in all patients receiving erythropoietic agents (i.e. at each clinic visit). If the initiation of appropriate antihypertensive measures fails to produce adequate blood pressure control, the clinician could consider, among other things, decreasing or withholding a patient's erythropoietic therapy.[9]

Converting from epoetin to darbepoetin alfa

Patients may be switched from epoetin therapy to darbepoetin alfa treatment, and maintain stable target Hb concentrations with less frequent dosing.[17,19,20] The first dose of darbepoetin alfa can be administered at the time of the next planned dose of epoetin.[9]

The appropriate subcutaneous dose of darbepoetin alfa can be calculated from the previously administered epoetin dose, using a dose conversion formula as suggested below.[2,13] It should be noted that clinical studies have shown interpatient response to be variable. The recommendations described should be followed initially and then adjusted as clinically indicated.

When converting from epoetin to darbepoetin alfa therapy, clinicians should:

1. Calculate the total weekly dose of epoetin in IU;
2. For s.c. administration, divide the total weekly dose s.c. epoetin by 200 to obtain the total weekly dosedarbepoetin alfa in μg;
3. For i.v. administration, divide the total weekly dose i.v. epoetin by 240 to obtain the total weekly darbepoetin alfa in μg.

When determining doses for administration once every 2 weeks, multiply the calculated total weekly dose of darbepoetin alfa by two.[9]

Patients receiving epoetin two or three times per week may receive darbepoetin alfa once weekly; patients receiving epoetin once weekly may receive darbepoetin alfa once every 2 weeks.[17,20]

These are initial starting doses and variations in individual patient requirements may necessitate titration of the darbepoetin alfa dose, following conversion from epoetin therapy, to maintain the required target Hb concentrations.

Overcoming resistance to darbepoetin alfa

The same criteria are used to define a lack of response to either darbepoetin or epoetin therapy; resistance to darbepoetin alfa may be defined as either: failure to attain target Hb while receiving greater than 1.5 μg/kg per week; or continued need for such a dosage to maintain the target Hb concentration.[9]

The possible causes of a failure to respond to darbepoetin alfa are likely to be the same as those for epoetin therapy. The most common cause is absolute or functional iron deficiency. In the absence of an absolute or functional iron deficiency, the most important possible reasons for resistance are inflammation, infection, malignancy and chronic blood loss. Other possible causes of

Table 2 Potential causes of inadequate response to darbepoetin alfa.[24,25]

Most common
Iron deficiency*
Inflammation/infection/malignancy
Blood loss
Less common
Hyperparathyroidism/marrow fibrosis
Aluminium toxicity
Vitamin deficiency (folate or vitamin B_{12})
Haemolysis
Marrow dysfunction
Red cell enzyme defects/haemoglobinopathies
Other (e.g. drug interactions; inadequate dialysis)
Theoretical
Antibodies

*A serum ferritin concentration of <100 μg/L indicates absolute iron deficiency. If serum ferritin is between 100 and 300 μg/L, functional iron deficiency may still be diagnosed if transferrin saturation is = 30%. Iron deficiency is unlikely if the concentration of serum ferritin is >300 μg/L, although it cannot be ruled out. Similarly, a serum ferritin concentration of >500–1000 μg may be indicative of iron overload, although it must be remembered that ferritin levels can be artificially increased by liver damage, inflammation, infection or cancer.[25]

resistance include hyperparathyroidism/marrow fibrosis, aluminium toxicity, vitamin deficiencies, haemolysis, marrow dysfunction and red cell enzyme defects/haemoglobinopathies (Table 2).[5,9,24,25]

Angiotensin-converting enzymes (ACE) inhibitors have been used in the post-transplant setting to treat erythrocytosis, thereby raising some concerns as to whether they might contribute to a diminished response to epoetin therapy. Data in this area are somewhat limited and conflicting. Several sources suggest that ACE inhibitors may reduce response to epoetin therapy,[26,27] whereas, other data argue against such an effect.[28–30]

If the cause of a failure to respond to darbepoetin alfa therapy cannot be identified or reversed, clinicians have to decide whether attempts should be made to overcome this by increasing the dose or whether the patient should be managed without the use of either epoetin or darbepoetin alfa. Unexplained resistance could theoretically be due to antibody formation; however, no evidence of antibody formation has been observed in 8720 patients treated with darbepoetin alfa in the nephrology clinical trial programme, of whom at least 3119 patients with CKD have been tested for antibodies.

Epoetin therapy has been associated with the development of neutralizing anti-erythropoietin protein antibodies and pure red-cell aplasia in patients with CKD-related anaemia.[31] Amgen scientists have determined that the neutralizing antibodies to epoetin can cross-react with other erythropoietic proteins; medical practitioners are therefore advised not to switch known antibody-positive patients to other erythropoietic proteins, including darbepoetin alfa.[31]

Discontinuing treatment

Darbepoetin alfa therapy should not normally be discontinued in patients who undergo surgery, require blood transfusions to treat acute blood loss or suffer acute intercurrent illness.[9]

There are currently insufficient data to develop recommendations for the withdrawal of darbepoetin alfa following successful renal transplantation, although clinicians are advised to restart therapy if irreversible graft failure occurs. For patients with slowly failing grafts, it is recommended that darbepoetin alfa therapy be administered in a manner similar to that for other patients with CKD. Due to immunosuppressive therapy and the inflammatory state associated with rejection, patients with slowly failing grafts may require a higher dose of darbepoetin alfa, compared with non-transplant patients who have CKD and a similar degree of anaemia.[9]

PHARMACOKINETICS

Macdougall *et al.* conducted a randomised, double-blind, crossover study to compare the single-dose pharmacokinetics of epoetin (100 IU/kg) with those of a comparable dose of darbepoetin alfa, based on peptide mass (0.5 μg/kg); both drugs were administered i.v. to peritoneal dialysis patients with CKD.[16] Data from this investigation were consistent with earlier preclinical observations, demonstrating that darbepoetin alfa has a slower clearance rate and significantly longer elimination half-life than epoetin (25.3 *vs* 8.5 h after intravenous administration; $P = 0.001$; Fig. 3).

In an open-label phase of the same study, a subset of patients was subsequently randomised to receive a single, s.c. dose of darbepoetin alfa (0.5 μg/kg). The mean serum terminal half-life of s.c. administered darbepoetin alfa was 48.8 h, approximately twice as long as the terminal half-life of intravenously administered darbepoetin alfa.[16,32,33]

Evidence indicates that darbepoetin alfa, whether administered i.v. or s.c., exhibits similar single-dose pharmacokinetics in both paediatric and adult patients with CKD (Table 3).[34]

The pharmacokinetics of darbepoetin alfa have also been evaluated following chronic, multiple-dose administration.[35] Once again, it was shown that i.v. darbepoetin alfa has an approximately three-fold longer serum half-life than that of i.v. epoetin. The pharmacokinetics of chronic darbepoetin alfa therapy did not appear to change as a function of time or dose, nor was there any evidence of drug accumulation.[35]

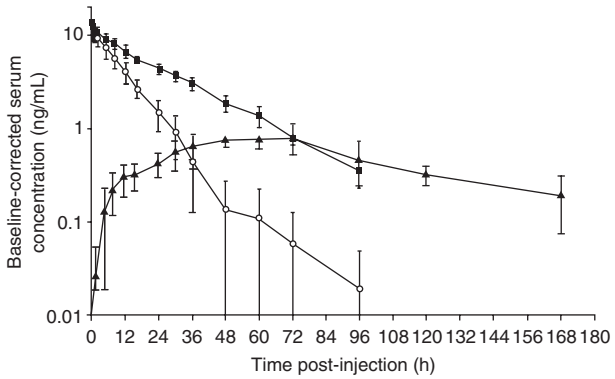

Fig. 3 Darbepoetin alfa versus epoetin – comparative pharmacokinetics in patients with CKD (mean ± SD).[16] (■) i.v. darbepoetin alfa ($n=11$); (▲) s.c. darbepoetin alfa ($n=6$); (○) i.v. epoetin ($n=10$). Adapted with permission from Lippincott Williams and Wilkins from Macdougall IC, Gray SJ, Elston O *et al. J. Am. Soc. Nephrol.* 1999; **10**: 2392–95.

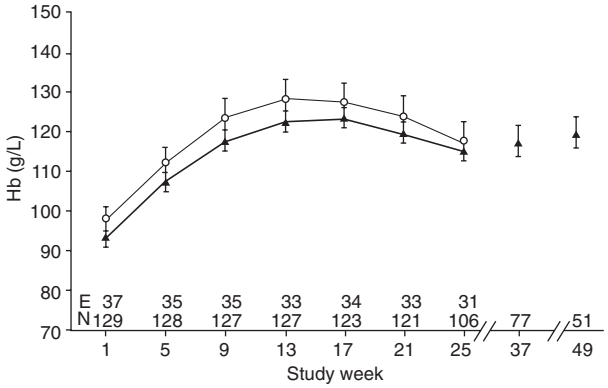

Fig. 4 Mean haemoglobin (Hb) concentrations (95% CI) following subcutaneous injection: darbepoetin alfa versus epoetin. E, number of patients receiving epoetin; N, number of patients receiving darbepoetin alfa.[21] (○) Epoetin, (▲) Darbepoetin alfa. Reproduced with permission from Blackwell Science from Locatelli *et al.* 2001. *Kidney Int.* 2001; **60**: 741–7.

Table 3 Pharmacokinetics of darbepoetin alfa in adult and paediatric patients with CKD[16,34]

	Terminal phase elimination half-life of darbepoetin alfa (h)	
	Adult[16]	Paediatric[34]
i.v. Administration	25.3 ($n=10$)	22.1 ($n=11$)
s.c. Administration	48.8 ($n=6$)	42.8 ($n=6$)

Graf *et al.* made similar observations over the course of an 8-week study, involving the subcutaneous administration of darbepoetin alfa to dialysis patients with CKD.[20]

EFFICACY IN CORRECTION OF ANAEMIA

Locatelli *et al.* assessed the efficacy and safety of darbepoetin alfa as a treatment for anaemia in predialysis patients with CKD.[21] More than 160 adults with CKD and a baseline Hb concentration of less than 110 g/L, and who had not received epoetin during the previous 12 weeks, took part in this multicentre, open-label study; 26 study participants were from Australian centres. Each patient was randomised to receive either darbepoetin alfa (0.45 μg/kg, once a week; $n = 129$) or epoetin (50 IU/kg, twice a week; $n = 37$), administered by s.c. injection, for up to 24 weeks.

The mean increase in Hb concentration over the first 4 weeks of this study was 13.8 g/L among patients treated with darbepoetin alfa and 14.0 g/L among epoetin recipients; the percentage of patients in each group who achieved a Hb response (i.e. an increase from baseline of at least 10 g/L and an absolute Hb concentration of at least 110 g/L) was 93% and 92%, respectively. At the time of Hb response, the median dose of darbepoetin alfa was 0.46 μg/kg per week and the median dose of epoetin was 100 IU/kg per week. In both treatment groups, target Hb concentrations were reached after a median of 7 weeks and then maintained for the duration of the 24-week treatment period (Fig. 4).[21]

Suranyi *et al.* have since evaluated the efficacy of subcutaneous darbepoetin alfa once every 2 weeks administered in predialysis patients with CKD (mean baseline Hb < 100 g/L) and who had not received epoetin during the previous 12 weeks.[22] Interim data from this Australian study (i.e. for the first 23 patients enrolled in the study and who completed at least 10 weeks of therapy) reveal that the mean increase in Hb concentration over the first 4 weeks of therapy was 13.7 g/L, with 96% of patients reaching the target Hb range (110–130 g/L) within 10 weeks of commencing fortnightly therapy. This is just one of several studies currently being conducted to explore the utility of less frequent darbepoetin alfa dosing in this clinical setting.

EFFICACY AS MAINTENANCE THERAPY

Vanrenterghem *et al.* randomised 522 adult patients with CKD undergoing either haemodialysis or peritoneal dialysis to receive either darbepoetin alfa ($n=347$) or epoetin ($n=175$) for up to 52 weeks.[17] All patients in this multicentre, open-label investigation had been receiving epoetin prior to study entry, administered either s.c. or i.v., and each had a stable Hb concentration of 95–125 g/L at baseline. Eighty-three study participants were from Australian centres.

Pre-study epoetin treatment had been administered three times per week ($n=244$), twice per week ($n=177$) or once per week ($n=101$). Patients randomised to

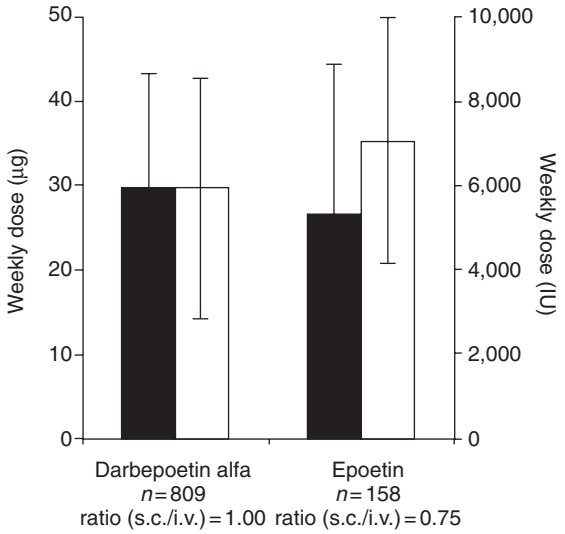

Fig. 5 Median doses (interquartile range) in weeks 21–24: darbepoetin alfa versus epoetin. (■) s.c., subcutaneous; (□) i.v., intravenous.

receive ongoing epoetin treatment were maintained on an unchanged dosing schedule.[17] Patients randomised to receive darbepoetin alfa were switched to an equivalent dose, but at a reduced frequency of administration: either once-weekly ($n=281$) or once every second week ($n=66$). Both drugs were titrated to maintain Hb concentrations between 90 and 130 g/L (and within −10 and +15 g/L of baseline concentrations), for up to 52 weeks.[17]

The mean change in Hb concentrations from baseline to evaluation (i.e. at weeks 25–32) was similar in the two treatment groups (i.e. Hb concentrations remained stable in both groups). Among darbepoetin alfa recipients, target Hb concentrations were successfully maintained in 97% of those treated every week and 95% of those treated every second week.[17]

Notably, over the first 24 weeks of this study, the mean doses of darbepoetin alfa that were required to maintain target Hb concentrations via the s.c. and i.v. routes of administration were 31.8 and 32.3 µg/week, respectively; this apparent dose equivalence was sustained throughout the study period.[16] In contrast, dose requirements for epoetin were, on average, 22% higher by the i.v. route of administration, compared with the s.c. route.[17]

Analyses of data from 809 patients who have received darbepoetin alfa in Australian and European clinical studies have revealed no difference in the average weekly dose administered by either i.v. or s.c. injection (Fig. 5).

Walker, on behalf of the Amgen 20000144 study group, has conducted another study that demonstrates the efficacy of darbepoetin alfa (s.c. or i.v.) when administered to dialysis patients once every 3 weeks ($n=54$) or once every 4 weeks ($n=38$).[36] All patients in this study, approximately 23% from Australia, had previously been receiving darbepoetin alfa on a once every 2 weeks basis, maintaining mean baseline Hb concentrations of 110–130 g/L.[36]

Forty-seven of the patients who were switched to dosing every 3 weeks completed the evaluation period (weeks 16–20), with 91% maintaining a Hb concentration of no less than 100 g/L. The mean Hb concentration among this group was 112 g/L.[36] Similarly, the mean Hb concentration among patients who were switched to dosing every 4 weeks, and who completed the evaluation period ($n=35$), was 113 g/L, with 83% maintaining a Hb concentration of no less than 100 g/L.[36]

Nissenson *et al.* conducted a double-blind, multicentre study among 507 clinically stable haemodialysis patients with CKD, each receiving i.v. epoetin three times per week.[19] Patients were randomised to either continued epoetin treatment or switched to once-weekly i.v. darbepoetin alfa therapy (plus twice-weekly doses of placebo). Both study treatments were titrated to maintain Hb concentrations at 90–130 g/L (and within −10 and +15 g/L of baseline concentrations), for up to 28 weeks.

Over the course of this study, treatment with darbepoetin alfa was found to maintain target Hb concentrations as effectively as epoetin therapy, despite less frequent dosing. During the evaluation period (weeks 20–28), no significant between-group differences were observed with regard to mean changes in Hb concentration (0.5 g/L for darbepoetin alfa *vs* 0.0 g/L for epoetin), the frequency of dose changes, or the proportion of patients having variable or unstable Hb concentrations (i.e. Hb concentrations that necessitated a dose adjustment; 24% among darbepoetin alfa recipients *vs* 29% among those on epoetin).[19]

Another conversion study, conducted at centres in Australia and Europe, demonstrated that darbepoetin alfa can effectively maintain target Hb concentrations over a treatment period of up to 12 months, regardless of the route of administration or dialysis modality.[20] This open-label investigation involved 703 adult patients with CKD.

TOLERABILITY AND SAFETY

Darbepoetin alfa is a well tolerated drug, based on analyses of an integrated safety database of more than 9000 patients with CKD who have received either darbepoetin alfa or epoetin in clinical studies; more than 8700 of these patients received darbepoetin alfa, and at least 1152 for more than 48 weeks.[8,11,16] These analyses revealed a similar rate of treatment discontinuation due to adverse events in both darbepoetin alfa and epoetin recipients. In all studies, the adverse events observed among darbepoetin alfa recipients were similar in frequency and severity to those associated with epoetin therapy and consistent with those expected for patients with CKD.[8,11,16,21]

Table 4 Incidence of adverse events following administration of darbepoetin alfa and epoetin (incidence > 10%)

Adverse event	Darbepoetin alfa ($n = 1578$)	Epoetin ($n = 591$)
Hypertension	23%	26%
Hypotension	22%	25%
Myalgia	20%	27%
Headache	16%	18%
Diarrhoea	15%	21%
Vomiting	15%	20%
Upper respiratory infection	14%	23%
Nausea	14%	24%
Dyspnoea	12%	18%
Abdominal pain	12%	17%
Arthralgia	11%	13%

Note: These data come from both open-label and blinded studies.

In clinical trials, the most frequently reported adverse events among recipients of darbepoetin alfa have been hypertension, hypotension and myalgia[25] (Table 4); those most commonly considered to be treatment-related have been hypertension and injection site pain. Although the reported incidence of hypotension has been relatively high among recipients of darbepoetin alfa (22%) and epoetin (25%), most hypotensive events appear to have been related to the dialysis procedure and not to the erythropoietic agent. Subcutaneous injection site pain has been reported in 7% of darbepoetin alfa recipients; this pain was generally mild and transient in nature, occurring predominantly after the first injection.[1,11,21] Serum accumulation of darbepoetin alfa is negligible.[20]

Despite the theoretical risk of immunogenicity, there has been no evidence of antibody formation to darbepoetin alfa. As of May 2002, darbepoetin alfa has been used to treat approximately 70 000 patients, including 11 726 patients enrolled in the clinical trial programme. Of the 11 726 clinical trial patients, 8720 were specifically enrolled within the nephrology programme. This total clinical trial experience translates to 6000 patient years of exposure. Tests for antibody formation were performed in a total of 3119 patients during the clinical trial programme for the purpose of gathering safety information. Antibodies were not found in any of the patients tested.

CONCLUSION

Clinical trials have demonstrated that darbepoetin alfa is an effective alternative to conventional epoetin for the treatment of anaemia in patents with CKD. The available data show that darbepoetin alfa can restore and/or maintain target Hb concentrations as effectively as epoetin, regardless of its route of administration or patients' dialysis modality. They also reveal that darbepoetin alfa therapy is very well tolerated and presents no additional risk to patients, compared with epoetin.

Due to its significantly longer serum half-life, equivalent doses of darbepoetin alfa can be administered less frequently than epoetin (i.e. once per week or once every second week) without compromising therapeutic efficacy. Current clinical practice guidelines reflect this difference in clinical utility, which offers a potential benefit to both patients and health-care providers alike. In summary, darbepoetin alfa has:

- Longer serum half-life than epoetin, enabling less frequent dosing;
- Can be given once per week or once every 2 weeks;
- Similar dose requirements for i.v. and s.c. administration;
- Similar adverse event profile to epoetin; and
- Maintains target Hb concentrations in patients switched from epoetin.

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