[haematologica reports]
2006;2(10):90-95

Darbepoietin alpha: pharmacokinetics and clinical use in neonates

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A B S T R A C T

Many hyporegenerative anemias in adults result from insufficient erythropoietin production, and the administration of recombinant human erythropoietin effectively stimulates red cell production. A biologically modified erythropoietic protein with a significantly longer half-life, darbepoetin alfa (Aranesp®), was developed by Amgen to allow for less frequent dosing. Studies in adults showed that darbepoetin alfa increased hemoglobin using once weekly to once every three week dosing. Studies evaluating the effectiveness of darbepoetin in treating other hyporegenerative anemias in adults and children are ongoing. Single dose pharmacokinetics have been determined in preterm infants, and phase II neonatal studies are in progress.

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Development of a long-acting erythropoietin

Erythropoietin (Epo) is a 165 amino acid protein with 3 N-linked carbohydrates and 1 O-linked carbohydrate post-translationally attached. Hyperglycosylated analogues of Epo were created to evaluate the effects of additional carbohydrates on biologic activity and half life.[1] Studies evaluating a variety of Epo isoforms modified to contain different numbers of carbohydrate binding sites showed that increasing the number of binding sites resulted in an increased half life, although receptor binding activity decreased with increasing carbohydrate sites.[1,2] When these isoforms were tested in mice, the biologic activity increased in proportion to the half life, despite the decreased receptor binding activity. Darbepoetin alfa (darbepoetin) contains 5 N-linked carbohydrate chains and up to 22 sialic acid residues. The half-life is more than twice that of recombinant human Epo (rHuEpo), and in vivo biologic activity that is significantly greater.[1,2] The potency of darbepoetin was determined by administering equal amounts of each drug either three times weekly or once weekly to CD-1 mice. Darbepoetin was 3.6 times more potent than three times weekly rHuEpo. Compared with once weekly dosing of rHuEpo, once weekly dosing of darbepoetin was 13 to 14 times more potent.[1-3]

Pharmacokinetic studies in adults

Clinical studies were initially performed to determine the pharmacokinetics of darbepoetin.[4] Single-dose pharmacokinetics of darbepoetin compared with equimolar doses of rHuEpo were performed in 11 adult patients with end stage renal disease (ESRD) who were undergoing peritoneal dialysis. The half-life of darbepoetin following intravenous (IV) injection was 25.3±2.2 hours, compared to 8.5±2.4 hours with rHuEpo. The half-life of darbepoetin was 48.8 hours when administered subcutaneously (SC). The two erythroid growth factors had similar volumes of distribution.

Darbepoetin pharmacokinetics were also determined after multiple IV or SC doses administered to patients with non-myeloid malignancies undergoing multicycle chemotherapy.[5] Fifty-six patients received weekly darbepoetin alpha 2.25 μg/kg administered either IV (n=27) or SC (n=29) during chemotherapy. Darbepoetin was cleared slowly after IV administration, resulting in a terminal half-life of 38.8 hours. Similar results were observed after single and multiple IV and SC doses. Importantly, no evidence of accumulation and no changes in pharmacokinetic profiles after repeated administration were observed for either IV or SC dosing.

Clinical studies in adults

Numerous randomized, multicentered clinical studies involving thousands of patients have been published evaluating the efficacy of darbepoetin in two general disease states: adults with ESRD, and those with a variety of malignancies. We previously reviewed studies published before 2004.[6]

Study designs varied in the dose, scheduling, and comparison groups. Doses were administered either IV or SC, and ranged from 0.075 to 2.5 μg/kg every one to two weeks. The outcome for the studies was determined by hematopoietic response, defined as either an increase in hemoglobin (Hgb) of 1-2 gm/dL, or maintenance of Hgb within a specified range, usually 9 to 13 gm/dL. Transfusion requirements were also determined. All of the studies evaluated patients for the development of anti-erythropoietin antibodies, a rare but significant side effect reported in adult rHuEpo patients, but not in pediatric patients.[7,8]

In ESRD patients, there were no differences between darbepoetin and rHuEpo in common side effects, or in the less common but more serious side effects of cerebro-vascular disorders, seizures, myocardial infarction, vascular access thromboses, transient ischemic attacks, or death (13.6% darbepoetin versus 11.1% rHuEpo).[6] Side effects of darbepoetin and rHuEpo are listed in Table 1. None of the deaths occurring in these renal studies were attributed to either darbepoetin or rHuEpo. In addition, no antibodies to Epo developed in the 1,706 renal patients receiving at least one dose of darbepoetin. This side effect is now thought to be explained by organic compounds leached from uncoated rubber stoppers in prefilled syringes containing polysorbate 80.[9] The incidence of anti-Epo antibodies resulting in pure red cell aplasia has now dramatically decreased.

Hertel and colleagues recently conducted a multicenter 52-week study to assess the efficacy of SC darbepoetin administered every 2 weeks to 524 patients with chronic renal disease (but not on dialysis) who were previously receiving once weekly rHuEpo dosing.[10] Darbepoetin doses were initially determined using a conversion table, and titrated to maintain hemoglobin concentrations ≤12 gm/dL. Initial doses averaged approximately 50 μg every other week. Baseline Hgb concentrations were 11.2±1.3 gm/dL, and remained similar (11.4±0.04 gm/dL) at the time of evaluation between 20 and 32 weeks into the study.

Randomized trials in patients with malignancy-associated anemia have been summarized previously.[6] A wide range of doses and dosing schedules were evaluated, and were generally higher than doses used in patients with ESRD. Dosing schedules included doses administered as infrequently as every three weeks.[11]

Bohlius and colleagues performed a meta-analysis of 57 oncology-related studies involving 9353 patients.[12] The analysis included randomized controlled trials comparing rHuEpo or darbepoetin plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent chemotherapy. Treatment with either red cell growth factor reduced the risk for red blood cell transfusions (relative risk = 0.64, 95% CI = 0.60-0.68; 42 trials and 6510 patients) and improved hematologic response (relative risk = 3.43, 95% CI = 3.07-3.84; 22 trials and 4307 patients). However, treatment increased the risk of thromboembolic events (RR = 1.67, 95% CI = 1.35 to 2.06; 35 trials and 6769 patients).

Table 1. Side effects.

Side effect	*rHuEpo*	*Darbepoietin*
Hypertension	25%	28%
Hypotension	25%	35%
Edema	19%	20%
Diarrhea	21%	17%
Headache	17%	19%
Nausea	26%	23%
Myalgia	28%	30%
Fever	12%	10%
Fatigue	12%	132%
Pruritis	6%	12%
Death	7%	8%
Antibody formation	0%	0%

Modified from Ohls, RK and Dai A. Clin Perinatol 2004;31:77-89.

Canon and colleagues (The 20030231 Study Group) recently published a controlled study in which 705 anemic patients with nonmyeloid malignancy from 110 European centers were randomized to one of two doses and schedules: 500 μg darbepoetin once every three weeks, or 2.25 μg/kg once a week for 15 weeks.[13] A total of 672 patients remained in the study at week 5. Fewer patients in the every-3-week group than in the weekly group received blood transfusions from week 5 to the end of the study (23% versus 30%), and equal numbers of patients achieved a target Hgb of ≥11 gm/dL (84% in the every 3 week group, 77% in the weekly group). The frequency of cardiovascular/thrombo-embolic adverse events was 8% in both groups, and the safety was comparable. None of the patients developed antibodies to Epo. The authors concluded that every three week dosing of darbepoetin was as safe and effective as weekly dosing. Because many chemotherapy regimens occur once every three weeks, this will likely become a common dosing schedule for oncology patients receiving darbepoetin.

Pharmacokinetic studies in pediatrics

One pharmacokinetic study has been published in pediatric patients.[14] Twelve patients 3-16 years of age with chronic renal disease were randomized to receive a single 0.5 μg/kg IV or SC dose of darbepoetin. Following a 2 week period, the same patients received a 0.5 μg/kg dose by the alternative route. The half life of darbepoetin in pediatric patients was similar to that

Table 2. Pediatric studies of darbepoetin alfa administration

Author and Year	*Study Design*	*Results*
De Palo 2004 (15)	7 children ages 7-15 years on hemodialysis; patients switched from rHuEpo to darbe, starting doses 0.45 to 3.6 µg/kg/week	6 of 7 patients had increased Hgb within 1 month; doses decreased to average of 0.51 µg/kg/week by third month of study; 2 patients developed worsening hypertension
Geary 2005 (16)	33 children with chronic renal failure on peritoneal or hemodialysis; starting dose 0.45 µg/kg/week, dose adjusted to maintain Hgb 10-12.5 gm/dL	23 patients completed the study; 91% achieved Hgb >10gm/dL; 87% receiving darbe less than once a week by end of study; 8/14 children reported injection site pain
Warady 2006 (17)	124 children aged 1-18 years on stable rHuEpo treatment, randomized 1:2 to continue rHuEpo or switch to darbe; doses titrated to maintain Hgb 10-12.5 gm/dL	rHuEpo and darbe were equivalent in maintaining Hgb during 28 week evaluation period; darbe "non-inferior" to rHuEpo
Durkan 2006 (18)	6 infants 3-8 kg, ages 1-8 months, never on rHuEpo; started on 0.45 mg/kg once a week; hemoglobin and iron studies measured every 2-4 weeks	3 of 6 infants achieved target hemoglobin of 10-11 grams/dL; 3 of 6 infants did not achieve target hemoglobin despite increasing dose to 1.2 µg/kg/week

Study reference numbers listed to the right of the author; darbe: darbepoetin alfa; IV; intravenous; SC subcutaneous; rHuEpo: recombinant human erythropoietin

found in adult patients with ESRD.[4] Doses administered SC had a terminal half-life of approximately 43 hours (compared with approximately 49 hours in adults), while those administered IV had a half life of 22 hours (25 hours in adults). The authors concluded that the pharmacokinetic profile of darbepoetin was similar in pediatric patients, although subcutaneous absorption appeared to be slightly more rapid.

Clinical studies in pediatrics

Four clinical studies have been published in pediatric patients, summarized in Table 2. De Palo and colleagues enrolled 7 children ages 7 to 15 undergoing hemodialysis for over 1 year and being treated with rHuEpo for at least 6 months.[15] Patients were switched to darbepoetin at starting doses ranging 0.45 to 3.6 µg/kg once a week. The starting dose was determined by taking the weekly rHuEpo dose and dividing by 200 (conversion estimate: 200 units rHuEpo is approximately equivalent to 1 µg darbepoetin). Six of 7 patients had a significant increase in Hgb within 1 month. Doses of darbepoetin were then decreased in order to maintain Hgb concentrations between 11 and 13 gm/dL, eventually decreasing to 0.51±0.18 µg/kg once a week by the third month of treatment. All patients tolerated the change from rHuEpo to darbepoetin. Two patients developed worsening hypertension that required adjustment of their antihypertensive medication. The authors concluded that once weekly dosing of darbepoetin could be effective and beneficial for pediatric patients and the clinicians caring for them.

Geary and colleagues[16] evaluated the efficacy and safety of darbepoetin in children with chronic renal failure on peritoneal dialysis or hemodialysis. Initial dosing was 0.45 µg/kg/week, which was adjusted to maintain Hgb response within a target range of 10.0-12.5 gm/dL. Hgb assessments were measured between 8-12 and between 20-28 weeks. Of the 23 patients remaining in the study for both measurements, Hgb was 11.8 and 11.4 between weeks 8 and 12 and 20 and 28, respectively. Ninety seven percent of patients achieved a Hgb response greater than 10 gm/dL between 8-12 weeks, and 91% achieved this Hgb response by weeks 20-28. One patient developed worsening hypertension during the study, thought to possibly be related to darbepoetin, and over half of the patients enrolled considered the injection to be more painful than rHuEpo. By the end of study, 87% were receiving darbepoetin less than once weekly. The authors concluded that starting doses of 0.5 µg/kg/week of darbepoetin effectively treats anemia in children with chronic renal failure. In addition, doses may be administered every other week for many patients.

Warady and colleagues conducted a 28-week open label study comparing the efficacy of darbepoetin with that of rHuEpo in pediatric subjects with chronic renal disease.[17] One hundred twenty four patients aged 1-18 who were receiving stable rHuEpo treatment were randomized in 1 to 2 fashion to either continue receiving rHuEpo or convert to darbepoetin. Doses were titrated to achieve and maintain Hgb levels 10.0-12.5

gm/dL. The adjusted mean change in Hgb between the baseline and the evaluation period for the rHuEpo and darbepoetin groups was -0.16 gm/dL and 0.15 gm/dL, respectively, with a difference of 0.31 gm/dL (95% CI: -0.45, 1.07) between the means. The authors concluded that darbepoetin was similar (*non-inferior*) to rHuEpo in the treatment of anemia in pediatric patients with chronic renal disease.

Durkan and colleagues evaluated darbepoetin administration in six infants less than 8 kg with chronic renal impairment.[18] Infants were started on 0.5 µg/kg per week of darbepoetin, and laboratory evaluations were performed every 2-4 weeks. Infants weighed between 3 and 8 kg, were 1-8 months of age at the start of treatment, and had not received rHuEpo. Three of the infants enrolled were medically stable, and achieved target Hgb between 10 and 11 gm/dL. Their doses were decreased and dosing intervals increased to maintain Hgb within this range. The other three infants did not reach target Hgb, despite increasing the dose to 1.2 Ìg/kg per week. The authors determined that darbepoetin could be administered successfully to infants by individually tailoring dosing schedules.

Neonatal anemia

Neonates also experience hyporegenerative anemias, the most common of which is the anemia of prematurity. This normocytic, normochromic anemia occurs in preterm infants less than 32 weeks gestation, and is due primarily to inadequate Epo production. The administration of rHuEpo, given three to seven times weekly, has been shown to significantly increase reticulocyte counts and decrease transfusion requirements. Given the success of darbepoetin in adults that allowed extended dosing periods, darbepoetin might stimulate erythropoiesis in neonates to the same extent in order to allow similar extended dosing schedules.

In vitro studies in neonates

Prior to performing pilot studies in infants with the anemia of prematurity, we evaluated the ability of darbepoetin compared to rHuEpo to stimulate colonies derived from erythroid progenitors isolated from fetal liver, marrow, and cord blood.[6] We found that, similar to adult bone marrow,[19] fetal progenitors appeared more sensitive to rHuEpo, with maximum stimulation occurring at doses that were the protein-equivalent of 5 to 10 ng/mL of darbepoetin. However the stimulation curves were similar, and comparable numbers of colonies were produced at maximal stimulation for both growth factors.

Pharmacokinetic studies in neonates

We performed single dose pharmacokinetics in preterm infants to determine half life and clearance.[20]

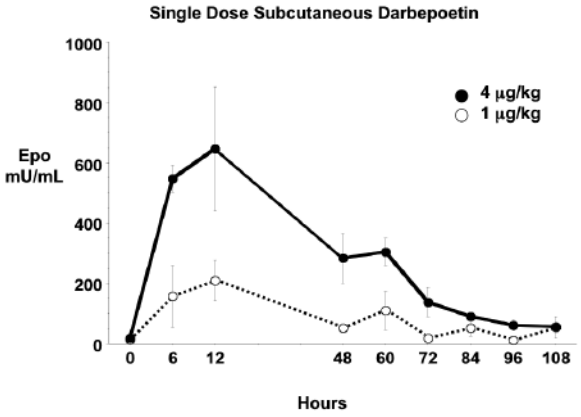

Figure 1. Erythropoietin concentrations before (time 0) and after a single dose of darbepoetin. The solid circles represent 4 µg/kg dose, and the open circles represent the 1 µg/kg/dose (modified from reference 20).

Preterm infants <32 weeks gestation at birth with a birth weight <1500 g were eligible for participation if they were at least 21-days-old and had a Hgb ≤10.5 gm/dL. Infants were randomized to receive a single SC dose of darbepoetin, either 1 or 4 µg/kg. Epo concentrations and reticulocyte counts were measured serially just prior to, and at various times following the dose. Twelve infants (1129±245 grams birth weight, 29.2±1.2 weeks gestation, 4±12 days old, Hgb 9.6±1.0 gm/dL) were enrolled. Absolute reticulocyte counts increased after a single dose. The highest recorded concentrations of drug occurred 6 to 12 hours after administration (Figure 1). The half-life was 26 hours (range 10 to 50; Table 3). These preliminary findings suggested that darbepoetin dosing in neonates would require a higher unit dose/kg and a shorter dosing interval than generally used for anemic adults.

Pharmacokinetic evaluations were repeated using a single IV dose of darbepoetin, 4 µg/kg, administered over 4 hours.[21] Patients in this study included both term and preterm infants, and ages ranged 3 to 28 days. The half-life of darbepoetin was 10.1 hours (range 9.0–22.7; Table 3), and the volume of distribution and more rapid clearance than reported in children. These results also suggested that darbepoetin dosing in neonates would require a higher unit dose/kg and a shorter dosing interval than that used in either adults or children.

Clinical studies in neonates

There are no clinical studies published evaluating multiple doses of darbepoetin administered to neonates. We are currently performing a randomized, masked, dose response study of darbepoetin adminis-

Table 3. Darbepoetin half life in adults, children and neonates.

Half Life (hours)	*SC*	*IV*
Adults	49	25
Children	43	22
Neonates	26 (range: 10-50)	10.1 (range: 9-22.7)

IV; intravenous; SC subcutaneous

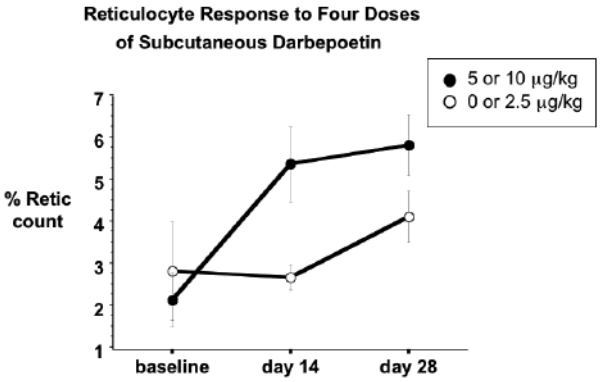

Figure 2. Changes in percent reticulocyte count after 4 weeks of darbepoetin. The open circles represent infants receiving 0 or 2.5 µg/kg darbepoetin for 4 doses, and the solid circles represent infants receiving 5 or 10 µg/kg for 4 doses.

tered to preterm infants. Eligible infants are ≤1500 grams birth weight, at least 10 days of age, have not received rHuEpo, and have informed consent. Once enrolled, infants are randomized to 0, 2.5, 5, or 10 µg/kg/week of darbepoetin, administered SC for 4 consecutive weeks. The 10 preterm infants enrolled thus far averaged just over 900 grams birth weight, were approximately 28 weeks gestation, and were enrolled by 15 days of age. Their reticulocyte response (0 and 2.5 µg/kg doses combined; 5 and 10 µg/kg doses combined) is shown in Figure 2 (unpublished data). No adverse events thought to be related to study drug have been reported, and the study is ongoing. Based on these preliminary observations and the previous pharmacokinetic studies in neonates, a multicenter study of darbepoetin administration has been designed. Infants will be followed throughout hospitalization for transfusion requirements and morbidities, and at 18-22 months corrected age to determine neurodevelopmental outcomes.

Summary and future prospects

Darbepoetin is a biologically modified erythroid growth factor with a half life at least 3 times that of rHuEpo, and with excellent efficacy in adults with ESRD or malignancies. Pediatric and neonatal studies are underway. Given the differences in pharmacokinetics between neonates and adults, it seems likely that higher doses of darbepoetin will be required to obtain a sustained hematopoietic response. Preterm infants have a much greater volume of distribution and greater clearance, necessitating doses that are three to four times greater than those used in children or adults.[22] We speculate that in neonates, darbepoetin may prove to be as effective as rHuEpo for the treatment of the anemia of prematurity, as well as for other hyporegenerative anemias, while significantly decreasing the number of doses required. In addition to the hematopoietic properties of erythropoietin, animal studies evaluating erythropoietin as a neuroprotective factor have shown positive effects,[23,24] and neonatal observations have also shown promise.[25] With its extended half-life, it is possible that a single dose of darbepoetin at birth in extremely low birth infants could be administered as a perinatal neuroprotectant. Further study is required to test the safety and efficacy of darbepoetin in anemic term and preterm infants.

Acknowledgments

Supported by a grant from the National Institutes of Health M01 RR 00997.

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