The Use of Darbepoetin to Stimulate Erythropoiesis in Anemia of Chronic Kidney Disease in Cats: 25 Cases

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Background: Anemia is present in 30-65% in cats with chronic kidney disease (CKD) and few long-term treatment options exist. Darbepoetin is effective in treating anemia of kidney disease in humans and may be used in cats.

Hypothesis/Objective: To evaluate the use of darbepoetin, a recombinant analog of human erythropoietin, to stimulate erythropoiesis, and to effectively treat anemia of kidney disease in cats.

Animals: Twenty-five of 66 cats that received ≥2 doses of darbepoetin at the Animal Medical Center between January 2005 and December 2009 were included in this study.

Methods: Cats were included in the study if they received darbepoetin and follow-up data were available for at least 56 days and had CKD as a primary clinical diagnosis. Cats were excluded if they were treated with darbepoetin but did not have kidney disease. Response to treatment was defined as reaching or exceeding a target packed red blood cell volume or hematocrit of 25%.

Results: Fourteen of 25 cats responded. Thirteen of those 14 cats received a dosage of 1 µg/kg/wk or higher. Presumptive adverse effects included vomiting, hypertension, seizures, and fever.

Conclusions and Clinical Relevance: Darbepoetin is effective for treatment of anemia of kidney disease in cats. Pure red cell aplasia appears to be less common with darbepoetin than with epoetin usage.

Key words: Chronic renal disease; Erythropoietin; Pure red cell aplasia.

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nemia caused by kidney disease has been well characterized in both humans and companion animals.1-8 Erythropoiesis is mainly controlled by production of the hematopoietic growth factor erythropoietin (EPO) in response to anemia.7,9 EPO is predominantly produced in the peritubular interstitial cells of the inner cortex and outer medulla of the kidney.7,9,10 The main stimulus for EPO synthesis is renal hypoxemia, and the rate of production of EPO is inversely proportional to the oxygen-carrying capacity of blood.7,9 The hormone’s main site of action is the bone marrow, where it binds to its receptor expressed on the surface of erythroid progenitor cells and leads to erythropoiesis.10

As chronic kidney disease (CKD) progresses, there is loss of renal cells capable of producing EPO. Anemia develops, which may be exacerbated by blood loss and shortened red blood cell lifespan because of uremic syndrome.8-11 The development of human recombinant forms of EPO (epoetin) and other erythropoiesis stimulating agents (ESA) such as darbepoetin has dramatically transformed the management of renal anemia in people and companion animals since epoetin was introduced more than 2 decades ago.

Darbepoetin alfa, a hyperglycosylated recombinant human EPO analog, was developed in the early 1990s and contains 5 N-linked carbohydrate chains.12,13 The development of the molecule was based on the hypothesis that adding additional N-linked carbohydrate chains, thus increasing the amount of sialic acid residues, would result in a molecule with a longer circulating half-life.14,15 The proportion of human patients achieving a satisfactory hemoglobin concentration after treatment with darbepoetin was similar to patients on epoetin (93% darbepoetin versus 92% epoetin).13 The main advantage in humans is decreased dosing frequency, because darbepoetin has been successfully used with weekly to every 4 weeks treatment protocols with effective hemoglobin targets met.15

The use of ESAs is associated with a number of complications, such as iron deficiency, hypertension, cutaneous abnormalities, arthralgia, vomiting, diarrhea, nausea, polycythemia, and pure red cell aplasia (PRCA). PRCA is caused by the production of neutralizing anti-EPO antibodies that cross-react with all ESAs, including endogenous EPO.16-18 PRCA is characterized by severe, nonregenerative anemia with severely decreased bone marrow red blood cell precursors. The duration of antibody persistence in the serum is variable, and patients become transfusion dependent.
for the treatment of their anemia. Antibody-mediated PRCA is an extremely rare occurrence in humans, with fewer than 300 cases reported worldwide, and the majority associated with use of epoetin. In contrast, PRCA is an important concern in companion animals using human recombinant ESAs. The amino acid sequence of feline EPO is 83% homologous to human epoetin. Because anti-EPO antibodies are directed against the protein backbone, this lack of complete homology is thought to be the cause of increased rate of PRCA in animals compared with humans. The prevalence of PRCA is 25–30% in cats treated with epoetin. Because of this high prevalence, researchers have attempted to find alternatives for stimulating erythropoiesis in cats with CKD. Recombinant feline EPO also has been developed, but a recent study demonstrated that the PRCA prevalence was not substantially decreased in cats.

Darbepoetin dosages of 0.45 and 0.75 µg/kg SC or IV per week have been demonstrated to provide optimal responses (defined as 1–3 g/dL increase in hemoglobin concentration over 4 weeks) in 60–70% of human patients. There are no recognized effective dosages for companion animals, and to the authors’ knowledge, there is only 1 peer-reviewed veterinary manuscript describing the use of darbepoetin in a dog. Ross described converting the total weekly epoetin dose (in international units [IU]) to a darbepoetin dose (in µg) by dividing the epoetin dose by 200. Thus, the purpose of this study was to retrospectively evaluate a population of cats with anemia of CKD treated with darbepoetin, including clinical outcome and observed adverse effects.

Materials and Methods

Selection of Cases

Medical records of cats treated with darbepoetin at the E & M Bobst Hospital of the Animal Medical Center between January 2005 and December 2009 were reviewed. The decision to treat with darbepoetin for clinical signs of renal anemia was at the discretion of the clinician. Initially, a starting dosage of 0.45 µg/kg SC once weekly was prescribed. In 2007, most clinicians used a starting dosage of 1 µg/kg SC once weekly, based on the perceived need for a dosage increase in many cats started at 0.45 µg/kg SC once weekly. Cats were included in the study if they had either CKD or an acute exacerbation of CKD as a primary clinical disease and follow-up data were available for at least 56 days. Cats were excluded if they were treated with darbepoetin but did not have CKD, had acute kidney injury, died within 2 months of receiving darbepoetin, or were lost to follow-up before 56 days. The choice of 56 days was based on the authors’ clinical experience that treatment results, failures, and complications would be seen in this time frame using this drug. Cats were not excluded if they received a whole blood or packed red blood cell transfusion.

Data Collection

The following information was collected from patients’ medical records immediately before darbepoetin administration: darbepoetin dosage, route of administration, iron supplementation, concurrent illnesses, packed red blood cell volume (PCV) or hematocrit (HCT), aggregate reticulocyte count, serum creatinine concentration (mg/dL), serum iron parameters, systolic blood pressure (BP; mmHg), rectal temperature (°F), and presence of vomiting. Follow-up data were noted during the entire time cats received darbepoetin treatment for darbepoetin dosage changes, iron supplementation, PCV or HCT, reticulocyte count, serum creatinine concentration, BP, rectal temperature, presence of vomiting, other physical examination changes possibly related to treatment, and date of death or date of last contact. An increased BP on ultrasonic Doppler blood pressure monitor was defined as >160 mmHg.

Data Analysis

Cats were defined as responsive to darbepoetin treatment if they reached or exceeded a target PCV or HCT of 25% within 56 days of initiating darbepoetin treatment and maintained a PCV or HCT ≥ 25% through day 56. This target value was chosen based on the authors’ clinical observations that animals have few clinical signs of anemia at or above these values. For the purposes of this study, PCV and HCT were regarded as similar values. Patients were considered to have adequate reticulocytosis if they had >60,000/µL reticulocytes. The mean time to reach target PCV or HCT was calculated for responder cats by calculating the time (in days) it required from initial darbepoetin administration to reach target PCV or HCT, which was generally monitored weekly.

Darbepoetin was administered SC, once a week until reaching target PCV or HCT. Once the target PCV or HCT was reached, either the initial frequency or dose administered was decreased according to clinician preference.

Statistical Analysis

Statistical analyses were performed using standard statistical software. A Mann-Whitney test was used to determine if there was a difference in pretreatment PCV, serum creatinine concentration, or maximum dose between responders and nonresponders. Cats that initially reached target PCV or HCT but then failed to maintain that response until day 56 were classified as nonresponders.

Survival curves were generated using the Kaplan-Meier product limit method, and log-rank analysis was used to determine whether there was a significant difference in survival time between animals that responded to darbepoetin treatment and those that did not respond, as defined above. Survival time was defined as the time from start of treatment with darbepoetin until death. Cats were censored for survival analysis if they were still alive at the time of data collection or were lost to follow-up. A P value of ≤ .05 was considered significant for all statistical tests.

Results

A total of 66 cats received ≥ 2 doses of darbepoetin. Of those, 25 cats met the inclusion criteria. One cat was being treated with intermittent hemodialysis. Forty-one cats were excluded from the study. Of these, 28 animals did not survive for 56 days, 10 were lost to follow-up, and 2 had acute kidney injury. One cat was started on darbepoetin for bone marrow failure with no evidence of renal disease. Of the 28 cats that were excluded because they failed to survive for 56 days after the start of treatment, the majority (24) were euthanized with a median survival time of 8 days because of deterioration in quality of life suspected to be a result of the renal disease.
Fourteen of 25 (56%) cats responded to darbepoetin treatment and 11 of 25 cats (44%) failed to respond, including 5 cats that initially reached or exceeded the target PCV of 25% but failed to maintain a PCV of >25% (nonsustained response; Fig 1). Median PCV at the start of darbepoetin was 19% (range, 13–26%) in the cats that responded, and 17% (range, 13–21%) in the nonresponder cats \( (P = .08) \). In the 14 responder cats, median serum creatinine concentration at the start of darbepoetin treatment was 5.7 mg/dL (range, 1.6–8.9 mg/dL) and in the 11 nonresponders, median serum creatinine concentration was 5.3 mg/dL (range, 2.1–8.7 mg/dL). There was no significant difference between serum creatinine concentrations of responders compared with nonresponders \( (P = .72) \).

Seven cats (5 responders and 2 nonresponders) received iron dextran (50 mg per cat, IM) within 1 day before starting darbepoetin. One nonresponder received iron dextran 3 weeks before and 3 responders received iron dextran at 3, 15, and 20 days, respectively, after starting darbepoetin. Eleven cats received iron dextran at a median of 41 days after starting darbepoetin, including 3 cats that had received a transfusion at the start of darbepoetin treatment and 1 cat that did not receive any iron product until iron dextran was administered at day 40. Three cats received more than 2 doses of iron dextran at a median interval of 28 days.

Thirteen cats (6 responders and 7 nonresponders) received a blood transfusion within 1 day before starting darbepoetin treatment. No cats received a transfusion within the 1st week of treatment. Three cats (all nonresponders) received transfusions after starting darbepoetin. Two cats suspected of gastrointestinal bleeding each received 2 transfusions, starting at days 20 and 22 after starting darbepoetin. Despite transfusion, the PCV never reached 25% in these 2 cats and they were classified as nonresponders. A third cat (nonresponder) received a transfusion at day 70. Five cats that received transfusions before darbepoetin had a decrease in PCV within 4 weeks of starting darbepoetin, compared with 4 cats receiving iron dextran that had a decrease in PCV within 4 weeks.

Suspected reasons for failure to achieve or maintain the target PCV were varied. Two of the nonresponders had increased reticulocyte counts and were suspected to have chronic gastrointestinal bleeding (one had documented melena). A bone marrow aspirate in one of these cats indicated a myeloid to erythroid \( (M : E) \) ratio of 6 : 1. Another nonresponder was receiving hemodialysis 3 times weekly, developed sepsis, and died 63 days after starting darbepoetin treatment. Of the 5 cats that had a nonsustained response, 2 cats responded within 2–3 weeks, but the PCV slowly decreased after decreasing the darbepoetin dose. Both cats were euthanized 9–12 weeks after starting treatment because of deteriorating clinical condition, worsening azotemia, and poor quality of life. The 3rd cat with a nonsustained response developed pleural effusion suspected to be a consequence of heart failure. Despite iron supplementation, iron parameters remained markedly decreased (serum iron concentration, 9–11 µg/dL; reference range, 33–134 µg/dL) in this cat. The 4th cat that did not sustain a response was strongly suspected to have developed feline infectious peritonitis (FIP) after renal transplantation and immunosuppression. This cat had received darbepoetin for 3 weeks before renal transplantation and responded adequately within 2 weeks. Darbepoetin was discontinued immediately after transplantation. The cat remained mildly anemic for 9 months and then anemia progressively worsened. Darbepoetin treatment was restarted (along with a packed red blood cell transfusion) 11 months after transplantation at a HCT of 15%. This cat was euthanized 31 days after restarting darbepoetin, when pleural fluid analysis and other clinical parameters were strongly suggestive of FIP. One nonresponder had primary bone marrow failure diagnosed before starting darbepoetin treatment and reached the target PCV after 7 weeks of treatment but redeveloped anemia by week 8 and required a transfusion at day 70. This cat was included in the study because it had longstanding CKD before developing bone marrow disease. Three cats reached and maintained a PCV or HCT \( \geq 25\% \) through day 56 but subsequently redeveloped anemia. One cat redeveloped anemia at day 78 after a decrease in dose. Another developed heart failure at day 105. A decrease in PCV occurred simultaneously with initiation of repeated thoracocentesis of serosanguinous fluid, which continued until euthanasia at day 126. At necropsy, \( M : E \) ratio was 2 : 1. The 3rd cat developed anemia at day 132 after a dose reduction. The dose was not increased, and the cat died at day 144 because of severe acute gastrointestinal bleeding.

Seven of 25 (28%) cats received a median starting dosage of 0.5 (range, 0.45–0.71) µg/kg SC once weekly, and 17 (68%) received a median starting dosage of 1.0

![Fig 1. Mean weekly \((\pm3\text{ days})\) packed red blood cell volume for responders (diamonds) versus nonresponders (circles). Error bars indicate standard deviation.](image-url)
(range, 0.78–1.19) μg/kg SC once weekly, and 1 cat received a starting dosage of 1.8 μg/kg SC once weekly. Of the 7 cats that received an average starting dosage of 0.5 μg/kg SC once weekly, only 1 responded without a dosage increase, 2 responded with a dosage increase to 1.0 μg/kg SC once weekly within the first 21 days of treatment, and the remaining 4 cats did not respond despite a dosage increase to 1.0 μg/kg SC once weekly. In these nonresponders, 1 cat initially began to respond but then failed to continue to respond. At the 1.0 μg/kg SC once weekly average starting dosage, 10 of 17 (59%) responded without a dosage increase, 5 did not respond and did not receive a dose increase, and 2 did not respond despite a dosage increase to 2.0 μg/kg SC once weekly within 21 days of starting treatment. In the nonresponders at this initial dosage, 4 initially began to respond but then failed to continue to respond. The 1 cat that received a starting dosage of 1.8 μg/kg SC responded. The median of the highest administered dosage was 1.1 (range, 0.47–2.13) μg/kg SC once weekly, and there was no difference between responders and nonresponders (P = .3).

For the 14 cats responding to darbepoetin treatment, the average time to response (target PCV or HCT of 25% or higher) was 1 week in 2 cats, 2 weeks in 3 cats, 3 weeks in 2 cats, 4 weeks in 4 cats, 5 weeks in 2 cats, and 6 weeks in 1 cat. The median time to adequate response for all cats was 21 days (range, 7–47 days). The median PCV or HCT increase from initial darbepoetin administration to target PCV or HCT in the 14 responder cats was 8%. Nine cats had at least 1 reticulocyte count >60,000/μL during treatment. Reticulocyte numbers at the start of treatment and once target PCV or HCT was reached were available for 6 cats. Median reticulocyte count increase was 12,510/μL (range, 10,600–96,230/μL).

Data were available for 9 serum iron evaluations in 8 cats (Table 1). Serum iron indices were submitted based on clinicians’ discretion before or during darbepoetin treatment. All cats with measured iron parameters had received either an iron dextran injection or a blood product transfusion before or at the time of initiating darbepoetin treatment.

Four of 14 responders had concurrent illness noted (pulmonary neoplasia, urolithiasis, lymphoma, suspected pancreatitis). Seven of 11 nonresponders had concurrent illnesses noted (2 with pleural effusion, and 1 each with FIP, jejunal mass and seizures, lymphoma and heart disease, lymphoma and bone marrow failure, and pyelonephritis and sepsis).

Potential adverse reactions included vomiting in 9 cats, although it could not be determined if vomiting was because of darbepoetin or uremia. Systolic blood pressure was evaluated before treatment in 12 cats and during treatment in 22 cats. Four of those 12 cats were hypertensive before treatment, 3 remained hypertensive, and 1 was not hypertensive at any point after starting treatment. Three of the 8 cats that were normotensive before treatment became hypertensive. Three additional cats were hypertensive during treatment, but no pretreatment measurements were available for comparison. The median increase in blood pressure (from pretreatment to the highest recorded blood pressure measurement) was 30 (range, −80 to 115) mmHg. Six cats had a blood pressure >180 mmHg during treatment. In 3 cats, the increase was not repeatable and no antihypertensive medication was prescribed. Blood pressure decreased to <180 mmHg in 2 cats after starting amlodipine. One cat was receiving amlodipine before darbepoetin, and blood pressure remained high but stable. There was no discernable pattern relating rapidity of response or absolute increase in PCV between hypertensive and normotensive cats. Three of the 4 cats with seizures or acute neurologic events were hypertensive. Of the 3 cats with fever, 1 became septic, 1 developed hyperthermia during a blood transfusion, and another was suspected of having FIP and was febrile only on its last examination before being euthanized. One cat was recorded to have signs consistent with either arthralgia or weakness. Of the 11 nonresponders, PRCA was not clinically suspected in 9 cats because other conditions were present that adequately explained the poor response. PRCA was considered possible but unlikely in 2 cats. Neither cat was documented to have reached the target PCV, but insufficient information was available to determine if other conditions were present. Twelve cats (48%) had 1 or more potential adverse events noted.

Survival data were available for all 25 cats in the study. Two cats were lost to follow-up at 65 and 86 days and 2 cats were still alive at the time of data collection. Overall, median survival for all cats was

| Table 1. Serum iron parameters in 8 cats (1 cat had 2 measurements). |
|----------------------|----------------------|----------------------|----------------------|
|                     | Responders           | Nonresponders        |
|                     | Iron ± SD            | Iron ± SD            | Ferritin ± SD        | Ferritin ± SD        | TIBC ± SD | TIBC ± SD | % Sat ± SD | % Sat ± SD |
| Mean ± SD           | 48 ± 72              | 25 ± 16              | 148 ± 47             | 333 ± 150            | 235 ± 25 | 331 ± 102 | 22 ± 32%   | 5 ± 2%     |
| Median              | 10                   | 24                   | 148                  | 277                   | 223      | 304        | 5%         | 5%         |
| N                   | 3                    | 6                    | 2                    | 4                     | 3        | 4          |            |            |
| Reference range     | 33–134 μg/dL         | 33–134 μg/dL         | 31–144 ng/dL         | 31–144 ng/dL         | 169–325 μg/dL | 169–325 μg/dL |
136 days. Median survival time for responders was 238 days compared with 83 days for nonresponders. This difference was statistically significant \( (P = .0005; \text{Fig 2}) \). Darbepoetin treatment was discontinued in 4 of the 14 responders at a median of 80 days after initiating treatment. One cat with acute-on-chronic disease recovered sufficiently after acute decompensation to maintain a PCV of 25% without darbepoetin. In 1 cat, darbepoetin was discontinued after 5 months, and the cat maintained a nearly normal PCV. One cat received a renal transplant and its anemia resolved. One cat with CKD received a very short course of darbepoetin starting immediately after diagnosis of CKD and responded well; transient causes of anemia were not excluded before starting treatment.

Five of the responders were euthanized for degrading quality of life presumed because of progressive CKD, 2 were euthanized because of cancer, 1 died acutely of unknown causes, 1 died with congestive heart failure and anemia, and 1 was euthanized during an acute gastrointestinal bleeding episode. Two responder cats were lost to follow-up and 2 were still alive. All nonresponder cats continued darbepoetin treatment until death. Of the nonresponders, 3 died or were euthanized because of degrading quality of life presumed to be due to progressive CKD, and 1 each died or was euthanized because of cancer, FIP, fluid overload, sepsis, and seizures. Three cats were euthanized with severe azotemia and anemia.

**Discussion**

The present study demonstrates that darbepoetin treatment can be effective at correcting anemia of CKD. Overall, 56% of cats in the present study responded to treatment by reaching the target PCV or HCT. A dosage of 1.0 \( \mu \)g/kg SC once weekly was more effective than 0.45 \( \mu \)g/kg SC once weekly, and more animals responded to this dosage compared with the lower dosage. However, because of the retrospective nature of this study and low number of animals observed, it is difficult to make dosage recommendations based on this study. The effective starting darbepoetin dosage for cats seems to be slightly higher than that for humans (0.45–0.75 \( \mu \)g/kg SC or IV once weekly), but only 60–70% of people respond to this dosage range and may need a higher dosage of darbepoetin to stimulate erythropoiesis.\(^\text{13,24}\) A regenerative reticulocyte response (ie, >60,000/\( \mu \)L) was inconsistently noted, even in patients that reached the target PCV or HCT. Reticulocyte counts typically were measured 7 days after the weekly darbepoetin injection, and an increase in reticulocytes may have occurred within days and thus not be detected using this monitoring protocol. Time to response varied among cats, with a median of 21 days and a median PCV or HCT increase of 8%. Two of 14 responders responded within the 1st week, which potentially could be too rapid an increase in PCV or HCT and may have harmful consequences such as hyperviscosity, cardiac overstimulation, cerebral vascular events, and hypertension as shown in studies of humans, although no evidence of this was detected in our study population.\(^\text{27,28}\)

There are multiple potential causes for failure to respond to darbepoetin treatment. Iron is a necessary component of hemoglobin formation. Iron deficiency can not only impair adequate erythropoiesis but also impair the ability of an ESA to function properly.\(^\text{23,29–32}\) Causes of low serum iron concentration include insufficient supplementation, iron loss from bleeding, and sequestration from inflammation. Although an increased ferritin concentration may indicate adequate to high iron stores, it may indicate the presence of acute or chronic inflammation, which may affect a substantial proportion of patients with kidney disease.

Gastrointestinal hemorrhage may contribute to failure to respond to darbepoetin treatment. Uremia can cause bleeding in renal failure patients.\(^\text{33–35}\) Continued loss of blood may worsen chronic anemia and make it relatively difficult for an ESA to correct anemia. In this study, 2 cats that failed to respond had probable gastrointestinal hemorrhage. Concurrent illnesses and chronic inflammatory conditions may also have contributed to failure to respond to darbepoetin treatment. Twenty-nine percent of cats that responded had a concurrent illness, whereas 64% of nonresponders had a reported concurrent illness. However, statistical analysis to determine a significant difference between concurrent illnesses and treatment outcome was not performed because of low numbers of cases.

In humans, darbepoetin has a similar adverse event profile to that of epoetin.\(^\text{13}\) Hypertension is reported in 23%, cerebrovascular disorders in <1%, seizures in 2%, and PRCA in <1%.\(^\text{13,36}\) In 1 study on the use of recombinant human EPO for management of anemia in cats and dogs with renal failure, hypertension was an adverse event to epoetin administration in 40% and 50% of dogs and cats, respectively.\(^\text{23,31}\) In the current study, 41% of cats were noted to be hypertensive during darbepoetin treatment. Seizures also are a known adverse event from ESA treatment, and in this study, 16% of cats receiving darbepoetin developed seizures.

![Kaplan-Meier survival curves comparing cats that were nonresponders (solid line) versus responders (dotted line). The difference is significant \( (P = .0005) \).](image-url)
or an acute neurologic event without a prior history of a seizure disorder. Seizures were reported previously in 2 of 11 cats receiving epoetin.23 In our study, 3 of the 4 cats with seizures were hypertensive, which could have contributed to seizure prevalence, by cerebral vascular accidents or hypertensive encephalopathy. All of the animals with seizures had moderate to severe azotemia (International Renal Interest Society [IRIS] Stage 3 or 4). The development of hypertension and seizures did not seem to be related to how quickly an animal reached target PCV or HCT from initiation of treatment. It is unclear if seizures and hypertension were caused by treatment or the underlying CKD, and a prospective, randomized clinical study may help to determine which cause was responsible.

It is difficult to attribute vomiting solely to darbepoetin treatment because patients with CKD can manifest this clinical sign. The majority of animals (>90%) were noted to have inappetence or vomiting before darbepoetin treatment. Fever was noted in 12% of cats, and a plausible infectious cause of fever unrelated to darbepoetin administration was detected in all cases.

The lack of a definitive test for PRCA impairs our ability to confidently determine its prevalence in this study. A presumptive diagnosis of PRCA is made by presence of suggestive clinical parameters and exclusion of other factors that may cause a failure to respond to ESA treatment. In a study by Cowgill et al,23 5 of 7 cats and 2 of 3 dogs followed for ≥ 90 days developed refractory anemia attributed to anti-epoetin antibodies. Antibodies directed against native EPO formed in approximately half of healthy dogs receiving epoetin, but clinically apparent anemia developed in only 33% of the dogs that developed antibodies. An antibody test is not commercially available for cats or dogs. Assays for antiardarbepoetin antibodies have been developed in human medicine.37 The cytological definition of PRCA varies substantially in the veterinary literature, from M : E ratios of 8 : 1 to ratios of 49 : 1, 71 : 1, and 92 : 1.23,31,38,39 Neither of the nonresponders in this study that had bone marrow cytology analyzed had ratios that approached these values. It may be that these values overestimate M : E ratios of animals with PRCA. Two nonresponders that never reached the target PCV had insufficient evaluation to determine a likely cause of their failure to respond.

Survival for cats responding to darbepoetin treatment was a median of 238 days, which is comparable to published survival data of cats in IRIS stage 4 CKD.40 There was a significant difference in responder survival compared with nonresponders, with responders having longer survival. Therefore, it is possible that darbepoetin treatment, by improving anemia, increases survival time for animals with renal disease. However, a controlled, randomized study would be necessary to prove this hypothesis. Correcting anemia can improve quality of life in humans and animals.23,41

Over half of the cats that received darbepoetin were excluded from this study, which may have biased the results. We chose to include only patients with at least 56 days of follow-up to include a sufficient treatment period to determine if an adequate response was present (typically 3–5 weeks in cats) and to determine if complications would develop.20 PRCA, one of the most serious complications of epoetin, has been reported to occur after 5–38 weeks of treatment, with a median of 14.5 weeks.20,23 We included patients with at least 8 weeks of observation to avoid inappropriately excluding cases that developed complications. Twenty-eight cats were excluded because they were euthanized or died within 56 days after starting darbepoetin. Most of those cats were euthanized because of deteriorating quality of life from their CKD. Two cats not included in the study merit further comment. One cat developed self-limiting vomiting and diarrhea the day after darbepoetin administration on 2 occasions. The owner discontinued administration and that cat was immediately lost to follow-up. An additional cat was euthanized at 5 weeks during an acute episode of gastrointestinal bleeding.

**Conclusion**

Darbepoetin administration in cats with CKD is effective at stimulating erythropoiesis and aids in correcting anemia of renal disease. A starting dosage of 1.0 μg/kg SC once weekly seems to provide a better response than lower dosages, and iron supplementation is strongly recommended during darbepoetin treatment.

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**Footnotes**

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**References**

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19. MacLeod JN. Species-specific recombinant erythropoietin preparations for companion animals. Paper presented at 2001 ACVIM Veterinary Medical Forum, Denver, CO.


