Dialysis Facility Ownership and Epoetin Dosing in Hemodialysis Patients: A US Physician Perspective

Together with the other articles in this section, the following is a commentary on Thamer M, Zhang Y, Kaufman J, Cotter D, Dong F, Hernan MA: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis. JAMA 297:1667-1674, 2007

Even before there were randomized controlled trials (RCTs), it was evident that erythropoiesis-stimulating agents (ESAs) increase hemoglobin and reduce the need for blood transfusions in hemodialysis patients. Hence, in 1989, the US Food and Drug Administration (FDA) approved ESAs for use in hemodialysis patients to reduce the need for blood transfusions (Table 1). Since then, the FDA has widened the target hemoglobin range to 10 to 12 g/dL (100 to 120 g/L), and the Centers for Medicare and Medicaid Services (CMS) has periodically revised reimbursement criteria to pay for ESAs given to maintain hemoglobin levels that were higher than the FDA-recommended target range. This culminated in a CMS policy adopted in April 2006 that reimbursed ESAs regardless of hemoglobin, with the only restriction being that the dose should be reduced by 25% in the month after a hemoglobin level greater than 13 g/dL (130 g/L) was recorded. Thus, the CMS was clearly paying for ESAs administered at hemoglobin levels above the target set by the FDA.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES: WHY WAS THE TARGET RECOMMENDED BY THE FDA NOT FOLLOWED?

One argument was that the FDA was wrong, and outcomes would be better if the target was higher. The 1997 National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) clinical practice guidelines[9] reflected this belief by recommending that the hemoglobin target be 11 to 12 g/dL (110-120 g/L), rather than 10 to 12 g/dL (100-120 g/L) as suggested by the FDA. However, at the time that these guidelines were published, there were no large RCT results supporting the belief that a target higher than the FDA's target improved outcomes (Table 1). The first RCT to test this hypothesis, published in 1998, was stopped early when the data safety monitoring board, observing a trend toward increased mortality in the group targeting hemoglobin 14 g/dL (140 g/L) versus 10 g/dL (100 g/L), considered it futile to continue.[5] Despite this mortality finding, it remains argued that quality of life is better at higher than recommended hemoglobin levels. However, the reporting of quality of life in these studies has been seriously flawed by a lack of masking, selective reporting of components that were different between groups (without statistical adjustment for multiple comparisons), and the use of different quality of life instruments. It is no surprise that quality of life results have varied between studies.

Another argument for not following FDA recommendations was that fluctuations in hemoglobin levels made it impossible to maintain hemoglobin in a narrow target range, such as the targets suggested by the FDA or even DOQI.[10,11] Implicit in this argument was the assumption that it was better to err too high rather than too low. However, there are no data from RCTs to support this hypothesis either.

The most plausible argument for not following FDA recommendations is the financial benefits inherent with targeting higher hemoglobin levels. The best evidence that the administration of ESAs to hemodialysis patients has been influenced by financial motives comes from several analyses of registry data comparing ESA use in for-profit and not-for-profit dialysis units. In 2006, Thamer et al reported that the most frequent use of subcutaneous ESAs, known to require lower doses and reduce cost, was in dialysis units not affiliated with for-profit chains.[12] Similarly, Collins et al reported that the administration of ESAs to patients whose hemoglobin levels exceeded recommendations was more common in for-profit chain facilities than in not-for-profit facilities.[13] In the 2006 US Renal Data System Annual Data Report,[14] there were marked differences between dialysis providers in the proportion of patients with hemoglobin of at least 12 g/dL (120 g/L). The nonprofit provider, Dialysis Clinic, Inc, had only 20% of the 2004 prevalent population

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Table 1. Timeline of Evidence and Recommended Hemoglobin Targets at the Time of Each Study in the United States for Hemodialysis Patients

	Randomized Controlled Trials in Hemodialysis Patients				
Year	Reference	N	Hemoglobin Levels Targeted (g/dL)†	Higher Target Outcomes‡	Recommended Hemoglobin Target (g/dL)†
1989	Suzuki[1]	179	P *v* Low *v* High	---	FDA: 10-11 (12 max) CMS: 10-11
1991	Bahlmann[2]	129	P *v* 10-11.7	↓ TFN	---
1991	Laupacis[3]	118	P *v* 9.5-11 *v* 11.5-13	↑ BP	---
1993	Sikole[4]	38	C *v* 10-11.7	↓ LVH	---
1994	---	---	---	---	FDA: 10-12 CMS: 10-12
1997	---	---	---	---	DOQI: 11-12 CMS: 90-day mean 12.2
1998	Besarab[5]	1233	10 *v* 14	↑ Death (NS) ↓ TFN ↓ Kt/V ↑ Access thrombosis	CMS: 90-day mean 12.5
2000	Foley[6]	146	9.5-10.5 *v* 13.5-14.5	↓ Kt/V	KDOQI: 11-12
2003	Furuland[7]	416§	9-12 *v* 13.5-16	↓ TFN ↑ BP	KDOQI: 11-12
2005	Parfrey[8]	596	9.5-11.5 *v* 13.5-14.5	↑ CVD ↓ URR ↑ BP	KDOQI: 11-12
2006	---	---	---	---	KDOQI: ≥11
2006	---	---	---	---	CMS: ↓ ESA if >13 FDA alert issued
2007	---	---	---	---	KDOQI: 11-12

Note: To convert hemoglobin in g/dL to g/L, multiply by 10.

Abbreviations: BP, blood pressure; C, control (no erythropoiesis-stimulating agent); CMS, Centers for Medicare and Medicaid Services; CVD, cerebrovascular disorder; DOQI, Dialysis Outcomes Quality Initiative; ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; HD, hemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; LVH, left ventricular hypertrophy; NS, not significant ($P > 0.05$); P, placebo; TFN, blood transfusions; URR, urea reduction ratio.

†Hematocrit values were converted to hemoglobin in g/dL by dividing by 3.

‡Statistically significant differences high versus low (unless otherwise indicated); does not include quality of life scores.

§Included nondialysis patients with chronic kidney disease.

with hemoglobin greater than or equal to 12 g/dL (120 g/L), while a major for-profit provider, DaVita, had over 60% with hemoglobin of at least 12 g/dL (120 g/L). Most recently, an analysis of registry data led Thamer et al to likewise conclude that large for-profit chains targeted higher hemoglobin levels than not-for-profit dialysis facilities.[15]

The pattern from observational studies is clear. More ESA is used in for-profit facilities than in not-for-profit facilities. Of course, there may be nonfinancial explanations that could explain these results. However, careful statistical adjustment for differences in patient populations failed to provide a cogent, alternative explanation. This, combined with the fact that for-profit dialysis facilities (like other corporations) must show an increase in quarterly earnings to survive, provides a compelling argument that the quest to increase earnings has influenced the administration of ESAs to hemodialysis patients.

WHAT SHOULD PHYSICIANS DO?

Recent data from RCTs in nondialysis patients have shown that targeting hemoglobin levels higher than those recommended by the FDA can have adverse consequences.[16-18] There is little reason to believe that this would not also be the case for hemodialysis patients. Responding to these and other recent RCT results, the FDA issued an alert in November 2006. The FDA recommended that physicians should "[w]ithhold the dose of ESA if the hemoglobin exceeds 12 g/dL (120 g/L) or rises by 1 g/dL (10 g/L) in any 2 week period."[19] In the absence of RCT data to the contrary, perhaps we should heed the advice of the FDA.

In an editorial accompanying the study by Thamer et al, Daniel Coyne suggested that physicians should maintain hemoglobin levels between 10.5 (105 g/L) and 11.5 g/dL (115 g/L),

rarely initiate an ESA if hemoglobin is above 10 g/dL (100 g/L), change the ESA dose by approximately 25% monthly when the hemoglobin falls outside this range, and either reduce by 50% or stop the ESA when the hemoglobin level exceeds 12.5 g/dL (125 g/L).[20] This is very similar to the recommended protocol in our dialysis unit, although our protocol strictly follows the FDA recommendation targeting hemoglobin 10 to 12 g/dL (100-120 g/L), and withholding the ESA when the hemoglobin exceeds 12 g/dL (120 g/L). Of course, treating iron deficiency and other barriers to the effective use of ESAs should be included in the management paradigm.

There is a need for additional RCTs in hemodialysis patients. Trials should address not only outcomes, but how to achieve those outcomes in the most cost effective manner possible. For example, how long should ESAs be withheld when the target is exceeded? When should the hemoglobin be retested? How should iron replacement best be integrated with ESA dosing? There is also a need for the CMS to revisit its reimbursement policy for ESAs. In 2003, Congress asked the CMS to submit a report on how a bundled payment system for end-stage renal disease could be designed and to carry out a demonstration project. This has not yet occurred. Finally, ethics in industry need not be an oxymoron. Dialysis providers and the pharmaceutical industry should both consider how they could improve not only next quarter's earnings, but also long-term patient outcomes. The incidence rate for end-stage renal disease has been slowing in the United States, and the best way for the industry to increase earnings in the future may be to increase the longevity of hemodialysis patients. This is a goal that we can all profit from.

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REFERENCES

1. Suzuki M, Hirasawa Y, Hirashima K, et al: Dose-finding, double-blind, clinical trial of recombinant human erythropoietin (Chugai) in Japanese patients with end-stage renal disease. Research Group for Clinical Assessment of rhEPO. Contrib Nephrol 76:179-192, 1989

2. Bahlmann J, Schoter KH, Scigalla P, et al: Morbidity and mortality in hemodialysis patients with and without erythropoietin treatment: a controlled study. Contrib Nephrol 88:90-106, 1991

3. Laupacis A: A randomized double-blind study of recombinant human erythropoietin in anaemic hemodialysis patients. Canadian Erythropoietin Study Group. Transplant Proc 23:1825-1826, 1991

4. Sikole A, Polenakovic M, Spirovska V, Polenakovic B, Masin G: Analysis of heart morphology and function following erythropoietin treatment of anemic dialysis patients. Artif Organs 17:977-984, 1993

5. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339:584-590, 1998

6. Foley RN, Parfrey PS, Morgan J, et al: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 58:1325-1335, 2000

7. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant 18:353-361, 2003

8. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol 16:2180-2189, 2005

9. National Kidney Foundation: NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. Am J Kidney Dis 30:S192-S240, 1997 (suppl 3)

10. Berns JS, Elzein H, Lynn RI, Fishbane S, Meisels IS, Deoreo PB: Hemoglobin variability in epoetin-treated hemodialysis patients. Kidney Int 64:1514-1521, 2003

11. Lacson E Jr, Ofsthun N, Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis 41:111-124, 2003

12. Thamer M, Zhang Y, Kaufman J, Stefanik K, Cotter DJ: Factors influencing route of administration for epoetin treatment among hemodialysis patients in the United States. Am J Kidney Dis 48:77-87, 2006

13. Collins AJ, Ebben JP, Gilbertson DT: EPO adjustments in patients with elevated hemoglobin levels: provider practice patterns compared with recommended practice guidelines. Am J Kidney Dis 49:135-142, 2007

14. United States Renal Data System: USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD, National Institutes of

Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007, pp 191-204

15. Thamer M, Zhang Y, Kaufman J, Cotter D, Dong F, Hernan MA: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis. JAMA 297:1667-1674, 2007

16. Drueke TB, Locatelli F, Clyne N, et al: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 355:2071-2084, 2006

17. Singh AK, Szczech L, Tang KL, et al: Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 355:2085-2098, 2006

18. Phrommintikul A, Haas SJ, Elsik M, et al: Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 369:381-388, 2007

19. US Food and Drug Administration and Center for Drug Evaluation and Research: Information for Healthcare Professionals: Erythropoiesis Stimulating Agents (ESA). Available at: http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Accessed June 14, 2007

20. Coyne DW: Use of epoetin in chronic renal failure. JAMA 297:1713-1716, 2007