IN THE LITERATURE

Dialysis Facility Ownership and Epoetin Dosing in Hemodialysis Patients: An Overview

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

In April 2007, Thamer et al published a manuscript in the *Journal of the American Medical Association* that described an association between for-profit status of dialysis facilities and higher use of recombinant human erythropoietin (epoetin alfa) for treatment of anemia of kidney failure, suggesting that profit may have an influence on medical practice.[1] The manuscript by Thamer et al comes on the heels of 2 high-profile studies in earlier stages of chronic kidney disease that failed to show a benefit to targeting high hemoglobin levels (>13 g/dL) and new US Food and Drug Administration (FDA) warnings resulting from adverse effects of epoetin administration in cancer patients.[2-4] In the accompanying *JAMA* editorial,[5] Daniel Coyne asserts that "higher epoetin use was the goal, and targeting higher hemoglobin levels was the means to that goal." The authors of the manuscript themselves were more cautious in their interpretation, concluding that "reimbursement policy and clinical performance measures may provide incentives for dialysis facilities, in particular for-profit facilities, to target hematocrit levels exceeding those recommended by the clinical guidelines."[1]

To provide additional perspective on this important study, we solicited editorials from multiple perspectives in anemia care in hemodialysis, including a US physician, a physician in the United Kingdom practicing in a setting of capitation, medical economists, and medical officers of a large for-profit dialysis provider. In order to place these commentaries into context, this introductory editorial reviews both the history of epoetin utilization and reimbursement in the United States and the key findings of Thamer et al.[1]

ERYTHROPOIETIN FOR THE TREATMENT OF ANEMIA IN KIDNEY FAILURE

Since its introduction in 1989, epoetin has been a mainstay of dialysis care, dramatically decreasing transfusion requirements and potentially improving health-related quality of life.[6-8] Reflecting the fact that anemia was modifiable and the finding that patients with higher hemoglobin levels had better outcomes in observational studies, anemia management became a quality indicator for the Medicare End-Stage Renal Disease (ESRD) program.[9-11] As recently as October 2006, cohort data have demonstrated that meeting clinical performance targets in hemodialysis patients, including a target hemoglobin of at least 11 g/dL (110 g/L), was associated with a decrease in hospitalization and mortality rates.[12] An editorial on this manuscript, appearing in *AJKD*, stresses the limitations of this form of data analysis, stating that one cannot conclude that achievement of clinical performance targets (including hemoglobin) is the cause of the reduction in mortality and hospitalization. Rather, patients with fewer comorbid conditions or better overall health may more readily achieve clinical targets and have better outcomes, irrespective of the achieved level of hemoglobin.[13]

As utilization has continued to rise, erythropoiesis-stimulating agents have become Medicare's largest single pharmaceutical expense, costing about $2 billion in 2004, and represent a critical source of revenue for dialysis providers.[14] With the projected growth of the dialysis population in the next decade, federal expenditures for this program are likely to continue to grow.

DIALYSIS AND ERYTHROPOIESIS-STIMULATING AGENT REIMBURSEMENT

Medicare has struggled with reimbursing dialysis care since the implementation of the ESRD program in 1973, as, even at the outset, hemodi-

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Table 1. Centers for Medicare and Medicaid Services Reimbursement and Guidelines for Use of Epoetin to Treat the Anemia of Kidney Disease in Dialysis Patients in the United States

Year	Guideline	Hemoglobin Target (g/dL)	Epoetin Reimbursement
1989	FDA approval	10-11	$40/dose (additional $30 for >10,000 units)
1991	—	—	$11 per 1,000 units
1994	—	—	$10 per 1,000 units
1997	DOQI	11-12	$10 per 1,000 units
2000	KDOQI	11-12	$10 per 1,000 units
2006	KDOQI	>11*	$10 per 1,000 units
2007	KDOQI	11-12	$10 per 1,000 units

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

Abbreviations: FDA, US Food and Drug Administration; DOQI, Dialysis Outcomes Quality Initiative; KDOQI, Kidney Disease Outcomes Quality Initiative.

*The Anemia Workgroup concluded that there was "insufficient evidence to recommend routinely maintaining [hemoglobin] levels at 13.0 g/dL."[23]

alysis costs far exceeded expectations.[15] In 1983, Medicare implemented a composite rate, bundling reimbursement into a single payment of $130 per session.[15] Nearly 25 years later, per session reimbursement still remains near this level despite significant inflationary pressures that have reduced the value of this reimbursement to a fraction of its prior amount.[16]

Currently and historically, epoetin is reimbursed outside the composite rate and represents a critical source of dialysis provider revenue (Table 1). In 1989, the FDA approved erythropoiesis-stimulating agents for use in hemodialysis patients to reduce the need for blood transfusions, with a recommended target hemoglobin concentration of 10 to 11 g/dL (100 to 110 g/L) and maximum achieved hemoglobin concentration not to exceed 12 g/dL (120 g/L). Accordingly, on June 1, 1989, Medicare began reimbursing dialysis providers for epoetin administered in dialysis facilities. Medicare's initial policy set a flat fee of $40 per dose (equivalent to the wholesale price for 4,000 units) with a $30 additional payment for any dose of greater than or equal to 10,000 units.[17] Because this policy resulted in lower than expected epoetin utilization, particularly by for-profit providers,[18] it was updated effective January 1, 1991 to set the reimbursement rate for epoetin at $11 per 1,000 units and revised again in 1994 to $10 per 1,000 units.[16] For most dialysis providers, this reimbursement level exceeds acquisition costs for epoetin. As demonstrated in a study by the Department of Health and Human Services Office of the Inspector General evaluating 2003 data, epoetin acquisition costs were on average 12% lower than Medicare reimbursement at the 4 largest dialysis providers and 5% lower than reimbursement at a random sample of smaller providers.[19] This may be attributable to (1) utilization of overfill (whereby there is often slightly more epoetin in a vial than stated) and (2) rebates and discounts for high-volume purchasing.[19]

ANEMIA MANAGEMENT GUIDELINES

Following the introduction of recombinant human erythropoietin, anemia treatment became an attractive therapeutic target for the dialysis community as hemoglobin level was readily modifiable in most patients. The general sentiment, albeit not supported by strong evidence, was that by treating anemia, dialysis patients would feel better and potentially live longer. Critically, in a time where there were major concerns about contamination of the blood supply with emerging infectious diseases, transfusions could also be limited. The 1997 National Kidney Foundation Dialysis Outcome Quality Initiative (DOQI) recommended target hemoglobin of 11 to 12 g/dL (110 to 120 g/L) for dialysis patients,[20] and the first update to these guidelines in 2000 maintained this recommendation.[21] Subsequent literature emphasized the difficulty of keeping individual patients' hemoglobin values within a 1 g/dL (10 g/L) range and demonstrated that variability in hemoglobin concentration may be associated with worse outcomes.[22,23] Therefore, in 2006 the National Kidney Foundation released updated KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines that recommended

a minimum hemoglobin target of 11 g/dL (110 g/L) without specifying a maximum target level in order to avoid fluctuations to hemoglobin levels below the recommended target.[24] Revised KDOQI anemia guidelines published in this month's *AJKD* reflect the results of newer clinical trials and reinstate the maximum target level at 12 g/dL (120 g/L) (Table 1).[25]

Critically, there are no data on how to best achieve hemoglobin targets, and the KDOQI guidelines are unable to offer more than a loose framework of opinion-based guidance for epoetin administration and utilization. In the absence of this data, epoetin dosing has been left to the physician. In the setting of limited physician and nurse time and increasingly complex epoetin reimbursement guidelines, many dialysis facilities have developed anemia management protocols to guide epoetin dosing. Currently, the 3 largest dialysis providers in the United States, Fresenius Medical Care (now comprising chains 1, 4, and 6 in the Thamer et al article), DaVita (now comprising chains 2 and 3 in the Thamer et al article), and Dialysis Clinic, Incorporated (the not-for-profit chain 5 in the Thamer et al article) all have anemia management protocols available for use by physicians.

WHAT DID THIS IMPORTANT STUDY SHOW?

In their April 2007 publication, Thamer et al used data from the US Renal Data System to evaluate epoetin use in for-profit and not-for-profit dialysis facilities.[1] They took a snapshot of epoetin use for in-center hemodialysis in November and December 2004, evaluating: (1) weekly mean epoetin administered in December 2004 and (2) dose adjustments from November to December 2004. The authors focused on the 6 largest chains that provided dialysis care in 2004. All but dialysis chain 5 are for-profit organizations. It should be noted that, in the ensuing 2 years, there has been considerable consolidation within the industry such that chains 1, 4, and 6 are now part of a single provider while chains 2 and 3 comprise a second provider.

Mean hematocrit level (approximately 3 times the hemoglobin concentration) was slightly lower in not-for-profit facilities than in for-profit facilities (35.6% versus 36.2%, test for significance not reported), and for-profit facilities had more patients exceeding the target of 36% while not-for-profit facilities had a higher proportion of patients with hematocrit levels both below the minimum target level of 33% and at the target level of 33% to 36%. The primary finding was that weekly mean epoetin administered in December 2004 was significantly greater in for-profit hemodialysis facilities than in not-for-profit hemodialysis facilities. Although all of the for-profit chains had higher epoetin use than chain 5, epoetin use by chain 2 was particularly high during this study (Fig 1, upper panel). The secondary finding was that for-profit facilities, particularly chain 2, responded to hematocrit levels below 36% with a far more substantial increase in epoetin dose than not-for-profit facilities (Fig 1, lower panel). These findings are similar to those reported by Collins et al,[26] also using US Renal Data System data, and remained robust in multiple sensitivity analyses, including those that explored other time periods during 2004. Critically, both Thamer et al and Collins et al relied on mean epoetin dose, despite the fact that epoetin use is typically not normally distributed and should be analyzed with a nonparametric test that accounts for median dose. The parametric statistical approach used in the Thamer article could potentially result in more impressive differences between for-profit and not-for-profit facilities than truly exist, whereas an analysis relying on median values and nonparametric analyses would likely yield less significant differences.

In the following series of editorials, the impact and interpretation of the manuscript by Thamer et al is examined from multiple perspectives in the dialysis community. In the first editorial, Dr Bertram Kasiske presents the perspective of a US dialysis physician. In the second editorial, Dr Iain MacDougall presents an international perspective from the capitated system of the United Kingdom. In the third editorial, Drs Joshua Cohen and Peter Neumann, both medical economists, present the payer perspective and analyze the influence of Medicare reimbursement strategies on epoetin use. In the final editorial, Drs Michael Lazarus and Ray Hakim of Fresenius Medical Care present the perspective of a large for-profit dialysis provider.

As expected, there is some inconsistency and redundancy when multiple authors give their interpretation of the same article. The authors have not seen one another's editorials before publication. We believe each viewpoint has value,

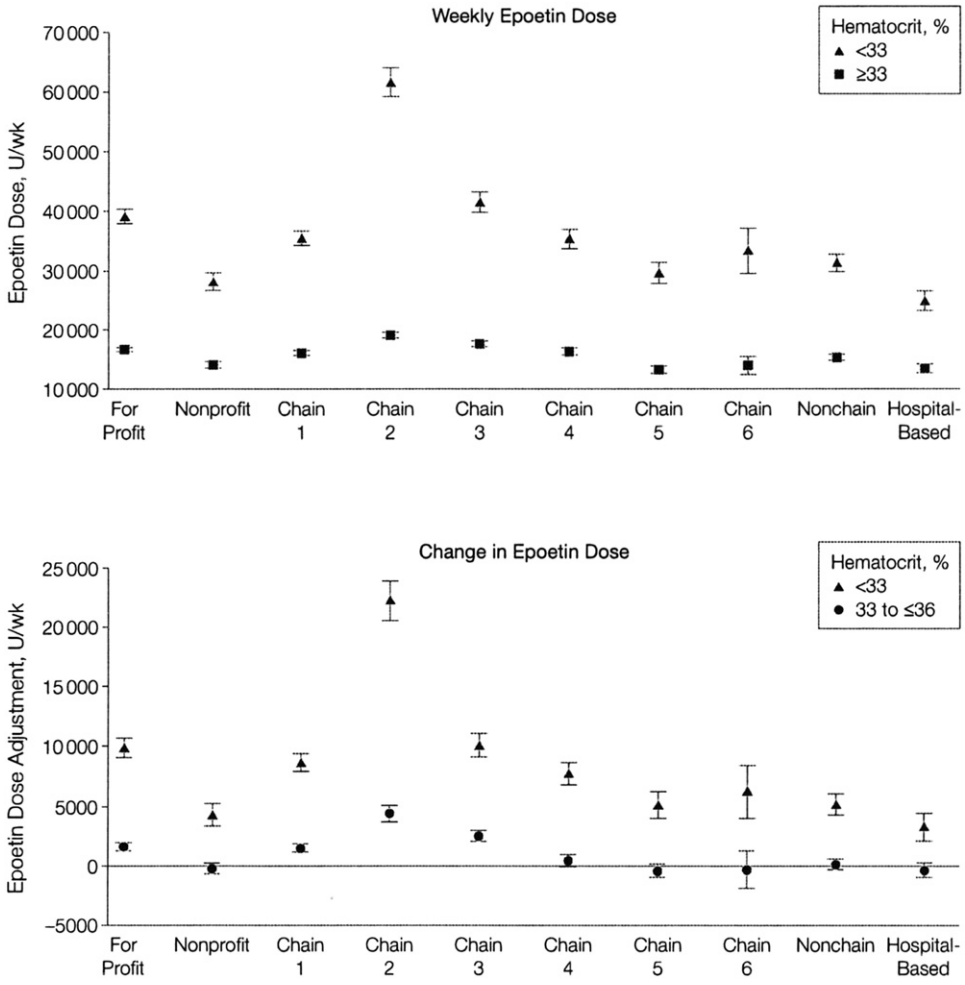

Figure 1. Epoetin dose by facility status and chain. (A) The adjusted mean weekly epoetin dose in December 2004. (B) The adjusted change in epoetin dose between November and December 2004. Chains 1, 2, 3, 4, and 6 are for-profit. Error bars indicate 95% confidence intervals. Depicted patients are the subpopulation of white men residing in the Southeast, aged greater than or equal to 65 years, with diabetes, cardiovascular disease, and other comorbid conditions. Reprinted with permission from Thamer et al.[1]

and invite those with other viewpoints to join the debate by submitting letters to the editor.

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