Epoetin Alfa Use in Patients With ESRD: An Analysis of Recent US Prescribing Patterns and Hemoglobin Outcomes

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• ***Background:*** **It is unknown to what degree physicians adjust erythropoietin doses to achieve hemoglobin levels (11.0 to 12.0 g/dL [110 to 120 g/L]) recommended by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) for patients with end-stage renal disease receiving hemodialysis. Our objective is to examine epoetin alfa prescribing patterns for achieving the target hemoglobin level range in this population.** ***Methods:*** **Monthly hemoglobin levels and epoetin alfa doses from 2 large databases were retrospectively analyzed. One data set comprised 31,267 patients from the Fresenius Medical Care–North America (FMC-NA) database, and the other comprised 128,761 patients based on claims for Medicare services.** ***Results:*** **Longitudinal evaluation of the FMC-NA data set showed that hemoglobin levels in patients administered epoetin alfa cycled in and out of the NKF-K/DOQI hemoglobin target range, and doses were decreased in 98.8% of patients with persistent hemoglobin levels greater than 12.0 g/dL (>120 g/L). Hemoglobin levels in patients from the Medicare data set that initially were outside the target range migrated into the range with epoetin alfa dose titration. FMC-NA patients with a 3-month average hemoglobin level less than 11.0 g/dL (<110 g/L) were administered significantly greater epoetin alfa doses than those with average hemoglobin levels greater than 12.0 g/dL (>120 g/L; 21,838 versus 13,503 U/wk; $P < 0.0001$). Less than 0.4% of patients administered epoetin alfa were persistently anemic (hemoglobin < 11.0 g/dL [<110 g/L]) and were administered persistently high doses (>30,000 U/wk), but failed to respond with a 0.5-g/dL or greater (≥5-g/L) increase in hemoglobin levels.** ***Conclusion:*** **In these analyses, few hemodialysis patients experienced persistent anemia while being administered high epoetin alfa doses. Physicians appeared to appropriately adjust doses to achieve hemoglobin levels recommended by the NKF-K/DOQI guidelines.** ***Am J Kidney Dis*** **46:481-488.**

INDEX WORDS: Anemia; hemodialysis (HD); end-stage renal disease (ESRD); epoetin alfa; erythropoietin; hemoglobin; Medicare; reimbursement.

ANEMIA DEVELOPS during the course of chronic kidney disease (CKD), primarily as a result of insufficient erythropoietin production by the diseased kidneys. The severity of anemia is related directly to the severity of CKD.[1,2] Even before progression to end-stage renal disease (ESRD), nearly 40% of patients with CKD have hemoglobin levels less than 11.0 g/dL (<110 g/L).[2,3] Anemia is a nearly ubiquitous comorbidity in patients with ESRD. As of December 2002, 308,910 patients with ESRD in the United States were undergoing hemodialysis.[4]

The negative consequences of anemia in patients with ESRD are well documented and include decreased oxygen delivery and utilization,[5-7] impaired cognition and decreased mental acuity,[8] and worsened cardiovascular function.[9-12] In addition, anemia adversely affects long-term survival[13-15] and increases hospitalizations.[13-16] Patients with ESRD who achieve target hemoglobin levels experience improvement in health-related quality-of-life measures, including energy and activity levels, sleeping and eating behaviors, sexual function, and health and life satisfaction.[17-20] For these reasons, anemia management has been a central part of ESRD care to improve patient well-being.

The introduction of recombinant human erythropoietin (epoetin alfa) in 1989 marked a significant advance in anemia treatment in hemodialysis patients, of whom more than 90% in the United States were being administered epoetin alfa therapy as of 2004.[21] Mean monthly hemo-

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globin levels in hemodialysis patients increased from 9.7 g/dL (97 g/L) in 1991 to 11.7 g/dL (117 g/L) in 2002. Increased hemoglobin levels were accompanied by an increase in mean weekly epoetin alfa dose from 6,000 to 17,000 units.[4] During this same period, the percentage of prevalent hemodialysis patients with hemoglobin levels less than 11.0 g/dL (<110 g/L) decreased from approximately 85% to 25%.[4]

A hemoglobin value of 11.0 g/dL (110 g/L) is a significant benchmark because the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Anemia of CKD recommend a target hemoglobin level between 11.0 and 12.0 g/dL (110 and 120 g/L) in hemodialysis patients administered epoetin alfa.[22] The Centers for Medicare and Medicaid Services (CMS) has incorporated the NKF-K/DOQI guidelines for target hemoglobin level into its epoetin alfa reimbursement policy and its ESRD Clinical Performance Measures (CPM) project. The CPM project provides comparative data to providers to assist them in assessing and improving the care of patients with ESRD.

In addition to recommending target hemoglobin levels, the practice guidelines also address the means of achieving the recommended levels, including appropriate adjustments in epoetin alfa dosing, management of iron deficiency, and reduced use of catheters for vascular access. The guidelines appear to be viewed as a positive development by physicians and reimbursement agencies. However, it is unknown how successful dialysis facilities, acting under the order of physicians, are in achieving the recommended hemoglobin levels and associated dosing of epoetin alfa. An examination of this question is important because of the ongoing scrutiny of Medicare reimbursement for erythropoietin therapy in hemodialysis patients. The goal of the retrospective analyses reported here is to examine physician practice patterns and understand the relationship among hemoglobin levels, epoetin alfa dose, and epoetin alfa dosing decisions. We performed cross-sectional and longitudinal evaluations of 2 large patient databases. These databases offer a unique opportunity to understand variability in epoetin alfa dosing and hemoglobin levels in large cohorts of hemodialysis patients.

METHODS

This is a 3-part retrospective analysis. The first part is a cross-sectional analysis of the distribution of hemoglobin levels in a population of patients with ESRD from the Fresenius Medical Care–North America (FMC-NA) database who were receiving hemodialysis. In the second part of the analysis, we examine the longitudinal relationship between hemoglobin levels and epoetin alfa dosing patterns by using data from records of claims submitted to the CMS for services provided to patients with ESRD at the Minneapolis Medical Research Foundation. In the third part, we again use the FMC-NA database to examine persistency rates for low hemoglobin levels and high epoetin alfa doses.

Distribution of Hemoglobin Levels: FMC-NA Data Set

Data for 31,267 patients from the FMC-NA database were analyzed for May through December 2001 to determine the distribution of mean hemoglobin values in prevalent hemodialysis patients. Rolling averages were calculated for each of six 3-month periods, ending in July, August, September, October, November, and December 2001. Several monthly records of predialysis hemoglobin levels and epoetin alfa doses were obtained for each patient. For consistency with data captured on Medicare claims, the hemoglobin value used for purposes of this analysis was the last value of the month. Missing hemoglobin values were imputed by the last-observation-carried-forward method. A weekly average epoetin alfa dose was calculated for each patient by dividing total dose for the month by number of days in the month and multiplying by 7. Doses missed because of hospitalization or missed hemodialysis treatments were not captured in the analysis; therefore, actual epoetin alfa doses administered may have been underestimated. Epoetin alfa doses were compared by using a simple *t*-test with log-transformation. A monthly cross-sectional analysis of the distribution of FMC-NA patients in the hemoglobin level categories also was conducted during the 2-year period from July 2000 through June 2002.

Relationship Between Hemoglobin Levels and Epoetin Alfa Doses: CMS Data Set

The prevalent cohort in the analysis of hemoglobin levels and epoetin alfa doses consisted of all hemodialysis patients who were alive for the 6-month period from April through September 2001 and had Medicare as primary payor. A total of 128,761 patients representing 3,516 dialysis facilities were included in this analysis. Facilities were grouped according to mean hemoglobin levels of their patients in April 2001 (<11.0 g/dL [<110 g/L], 11.0 to 12.5 g/dL [110 to 125 g/L], and >12.5 g/dL [>125 g/L]). The upper limit of 12.5 g/dL (125 g/L), measured during a 3-month period, was selected because it is the audit trigger used by the CMS for reimbursement decisions. The CMS data set very likely included patients from the FMC-NA data set. As with the FMC-NA data set, missed doses may have resulted in underestimation of the actual epoetin alfa dose administered.