AJKD

Original Investigation

Erythropoiesis-Stimulating Agent Use Among Non–Dialysis-Dependent CKD Patients Before and After the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) Using a Large US Health Plan Database

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Background: In a landmark study, TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) examined the use of erythropoiesis-stimulating agent (ESA) therapy to treat anemia among patients with chronic kidney disease (CKD) and found no benefit compared to placebo.

Study Design: A retrospective observational design was used to determine the impact of TREAT on clinical practice.

Setting & Participants: A large US health plan database with more than 1.2 million claims for patients with non–dialysis-dependent CKD stages 3 and 4.

Factor: ESA prescribing 2 years before and after publication of TREAT.

Outcomes: Rate of ESA prescribing for ESA-naive and -prevalent cohorts.

Measurements: (1) Monthly ESA prescribing in the 2 years before and after publication of TREAT (ordinary least squares regression), (2) adjusted likelihood of prescribing ESA after TREAT (clustered logistic regression), and (3) probability of receiving ESA therapy based on anemia status (χ^2 test).

Results: For patients with CKD stage 3, the proportion prescribed ESA therapy declined from 17% pre-TREAT to 11% post-TREAT (a 38% decline), and for those with CKD stage 4, from 34% to 27% (a 22% decline). Prescribing of ESA therapy was declining even before TREAT, but the decline accelerated in the post-TREAT period (stage 3: change of slope, −0.08 [$P < 0.001$]; stage 4: change of slope, −0.16 [$P < 0.001$]). ESA prescribing declined after TREAT regardless of anemia status; among patients with hemoglobin levels < 10 g/dL, only 25% of patients with CKD stage 3 and 33% of patients with stage 4 were prescribed ESAs 2 years after TREAT, a notable 50% decline. After adjusting for all covariates, the probability of prescribing ESAs was 35% lower during the 2-year period after versus before publication of TREAT (OR, 0.65; 95% CI, 0.63-0.67).

Limitations: The cumulative effect of adverse safety concerns in the period before TREAT also influenced physician prescribing of ESA therapy and could not be separated from the influence of TREAT.

Conclusions: TREAT appears to be a watershed study that was followed by a marked decline in ESA prescribing for patients with CKD.

INDEX WORDS: Erythropoietin-stimulating agent (ESA); epoetin (EPO); darbepoetin; predialysis chronic kidney disease (CKD); TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy); hemoglobin; anemia; prescribing patterns; Choose Wisely campaign; Thomson Reuters; MarketScan.

Erythropoiesis-stimulating agents (ESAs), such as epoetin alfa (erythropoietin), were first approved by the US Food and Drug Administration (FDA) in June 1989 to treat the anemia associated with kidney disease. However, not until October 2009 was the first placebo-controlled ESA trial in patients with chronic kidney disease (CKD) with hard outcomes published. TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) examined the effect of correcting the anemia of CKD with darbepoetin in patients with diabetes mellitus.[1] It found that treatment with darbepoetin was not beneficial in reducing mortality or attenuating cardiovascular or renal events, but resulted in a 2-fold higher rate of stroke and thromboembolic complications and a higher rate of cancer deaths among patients with a history of cancer, suggesting that the placebo arm (rescue when hemoglobin level < 9 g/dL) should be

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Received January 31, 2014. Accepted in revised form May 13, 2014.

Because an author of this article is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Thomas A. Depner, MD) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Editorial Policies.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2014.05.013

considered as the preferred management strategy for patients with non–dialysis-dependent CKD, although this strategy may require higher levels of blood transfusions.[2,3] After publication of the TREAT results, the FDA revised its ESA labeling and clinical guidelines[4] in June 2011 and, in the widely publicized Choose Wisely campaign[5] (disseminated in April 2012), use of the lowest ESA dose to reduce the need for blood transfusions was recommended. To determine the impact of the TREAT results, we undertook a study using a large US health plan claims database to describe ESA prescribing before and after publication of TREAT.

METHODS

Data Source

This analysis was based on retrospective administrative data from the Thomson Reuters MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database, which represent the health care experiences of more than 20 million individuals annually who obtain health care insurance from large private employers or government-funded Medicare health care insurance plans. Health care in the MarketScan database is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans (including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations) and is one of the largest collections of patient data in the United States. The elderly also are well represented through the inclusion of groups covered by Medicare. Enrollment records provide health plan enrollees' demographics, including age, sex, region of residence, and health insurance plan characteristics. MarketScan databases also provide detailed cost, use, and outcomes data for health care services performed in both inpatient and outpatient settings. The inpatient and outpatient medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique encrypted beneficiary identifiers. MarketScan databases have been used in a number of diverse health research studies. MarketScan research databases meet or exceed requirements of the US Health Insurance Portability and Accountability Act of 1996. Detailed data description can be found at http://marketscan.truvenhealth.com/marketscanportal/.

Study Sample

We used the most recent MarketScan data, 2007 through 2011, to identity CKD stages 3 and 4 claims for this study. CKD diagnosis claims were the unit of analysis and were identified as follows. All CKD stage 3 (*International Classification of Diseases, Ninth Revision* [*ICD-9*] diagnosis code 585.3) and 4 (*ICD-9* diagnosis code 585.4) claims identified from November 2007 through October 2011 (2 years before and after TREAT published in October 2009) were eligible for inclusion. All claims were required to have at least 6 months of previous enrollment coverage for purposes of baseline information and 3 months postenrollment coverage to examine prescription of ESA therapy. To ensure confirmation of a definitive CKD diagnosis (rather than a rule-out diagnosis), we also required that each identified claim had at least one CKD diagnosis code within the previous 6 months. In our analysis of ESA therapy by anemia status, we used laboratory results for hemoglobin or hematocrit from a sample of the MarketScan data (5% of all claims). All laboratory results had at least one CKD stage 3 or 4 code in the previous 6 months and we allowed for 3 months after a laboratory test to ascertain any ESA prescribing. For a laboratory result with missing hemoglobin values but for which hematocrit data were available, hematocrit levels were converted to hemoglobin levels by dividing by 3. Hemoglobin levels were assessed in 2 categories: indicating anemia (< 10 g/dL) or nonanemia (≥ 10 g/dL).

ESA Administration

We defined ESA therapy by the receipt of darbepoetin alfa or epoetin alfa. For each eligible CKD claim, we extracted ESA claims data (medical encounters and pharmacy) in the 3 months following a CKD diagnosis by using Healthcare Common Procedure Coding System (HCPCS) codes for the outpatient setting and National Drug Code (NDC) numbers for outpatient pharmacy claims (see Item S1, available as online supplementary material, for a complete list of HCPCS and NDC codes). We restricted our analysis to the outpatient setting because ESA therapy usually is administered during a patient's outpatient visit by subcutaneous injection and cannot be determined in the inpatient setting because it usually is bundled with other inpatient treatments.

The study CKD claims were disaggregated by ESA-prevalent and ESA-naive claims as follows. ESA-naive CKD claims were those without evidence of ESA use in the prior 6 months, and ESA-prevalent CKD claims were those with evidence of ESA prescribing in the prior 6 months. We conducted analyses of both ESA-prevalent and -naive claims for each calendar month in the 2-year pre- and post-TREAT periods. Recipients of a red blood cell transfusion in either the inpatient or outpatient setting were identified using *Clinical Procedural Terminology* (*CPT*) 4 code, HCPCS code, or *ICD-9, Clinical Modification* (*ICD-9-CM*) procedure codes (Item S1).

Statistical Analysis

Patient characteristics were measured during the 6-month period prior to each study claim and compared by 2-year pre- and post-TREAT study periods separately for CKD stages 3 and 4 diagnosis. Data for patient demographics included sex (male or female), age (< 65 or ≥ 65 years), insurance status (commercial or Medicare), region of residence (Northeast, North Central, South, and West), Charlson Comorbidity Index[6] score (0, 1-3, and > 3), and involvement of a nephrologist (≥ 1 visit in the previous 6 months). The presence of comorbid conditions, based on *ICD-9* codes in claims data, including diabetes, ischemic heart disease, congestive heart failure, cancer, and hypertension, also was examined. Receipt of ESA therapy in the 3 months after each study claim was analyzed by pre- and post-TREAT period and by CKD stage using χ^2 tests.

For each month, we determined whether a study claim was associated with ESA use and/or a blood transfusion as follows. To assess the monthly rate of use of ESAs and blood transfusion in the 2 years before and after TREAT, those with availability of 1 or more days' supply of ESA (or receipt of ≥ 1 blood unit) within a given month were considered ESA or blood transfusion users in that month (entered in the numerator). A trend evaluation was performed using ordinary linear regression analysis and the slopes in each of the 2 periods (pre- vs post-TREAT) by CKD stage for all CKD claims, ESA-prevalent CKD claims, and ESA-naive CKD claims separately using ordinary least squares regression. ESA prescribing based on anemia status during pre- and post-TREAT periods was analyzed and compared by χ^2 tests. A clustered logistic regression model using generalized estimating equation methodology (to account for repeated measurement from the same patient) was used to identify predictors of ESA use adjusting for variables influencing ESA prescribing. These variables included age, sex, insurance status, region of residence, Charlson Comorbidity Index score, involvement of nephrologist, presence of comorbid conditions, and CKD stage. An indicator for the post-TREAT period also was included. All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc) with a 2-sided $\alpha = 0.05$ for statistical significance.