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Original Investigation

Spectrum and Burden of Erythropoiesis-Stimulating Agent Hyporesponsiveness Among Contemporary Hemodialysis Patients

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Background: Hemodialysis patients with erythropoiesis-stimulating agent (ESA) hyporesponsiveness have been a topic of active research. However, there have been no studies of ESA hyporesponsiveness among US patients following the dramatic change in anemia management that resulted from the 2011 changes in ESA product labeling and bundling of dialysis remuneration.

Study Design: Retrospective observational study.

Setting & Participants: We studied prevalent hemodialysis patients treated at a large dialysis organization in calendar years 2012 to 2013 (N = 98,972).

Predictor: ESA hyporesponsiveness, defined as 2 consecutive hemoglobin measurements < 10 g/dL (every other week) with contemporaneous ESA dose > 7,700 U/treatment. Patients with ESA hyporesponsiveness were identified during the first quarter of 2012 and followed up through 2013 using intention-to-treat principles.

Outcomes: Associations between the study exposure (ESA hyporesponsiveness) and mortality, missed hemodialysis treatments, ESA and iron use, and hemoglobin levels were determined using generalized estimating equations adjusting for imbalanced baseline covariates.

Results: At baseline, 12,361 (12.5%) patients were identified as having ESA hyporesponsiveness. The mean hemoglobin level among patients with ESA hyporesponsiveness was ~1 g/dL lower than in patients without ESA hyporesponsiveness at baseline, narrowing over follow-up to 0.4 g/dL. Initially, mean ESA use was approximately 3-fold greater for patients with ESA hyporesponsiveness than for those without ESA hyporesponsiveness, decreasing to 2-fold greater at study end; iron use and missed hemodialysis treatment rates were also greater among patients with ESA hyporesponsiveness throughout. ESA hyporesponsiveness was associated with enhanced mortality risk versus non–ESA hyporesponsiveness: adjusted incidence rate ratios were estimated at 2.24 (95% CI, 1.93-2.60) in the second quarter, gradually decreasing to 1.48 (95% CI, 1.18-1.84) by study end.

Limitations: It is possible that an alternative ESA hyporesponsiveness definition may be optimal. As such, the associations we observed may be conservative estimates of true relationships.

Conclusions: When using a contemporary definition at one point in time, ESA hyporesponsiveness was potently and persistently associated with greater mortality, greater iron and ESA use, and lower hemoglobin levels compared to non–ESA hyporesponsiveness.

INDEX WORDS: Anemia; erythropoiesis stimulating agent (ESA); ESA dosing; hyporesponsiveness; hemoglobin; iron utilization; hemodialysis; end-stage renal disease (ESRD).

Kidney disease–related anemia is highly prevalent among patients with end-stage renal disease and is associated with significant and debilitating morbidity, as well as increased risk for mortality.[1] In patients with end-stage renal disease who undergo hemodialysis, kidney disease–related anemia is typically treated with both erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron.[2,3] These treatments have been the standard of care for decades.

A significant proportion of patients with kidney disease–related anemia undergoing hemodialysis do not respond as anticipated: either they cannot achieve the targeted hemoglobin value or they require persistently high ESA doses to achieve targets. The mechanisms for reduced ESA responsiveness are not entirely delineated, but evidence indicates mediating roles of inflammation, iron deficiency (absolute or functional), inadequate vitamin D,[4] and underlying illnesses or infections.[5] Past studies have shown that greater ESA hyporesponsiveness is associated with poor survival,[6,7]

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and other studies have indicated that high ESA doses may contribute to poor patient outcomes.[2,3,8-11] Although prior studies of hyporesponsiveness did not conform to a single consensus definition (no such definition exists), all based ESA hyporesponsiveness on ESA doses and/or hemoglobin levels, each evaluated with respect to population distributions.

In 2011, there were marked changes in ESA dosing practices among US hemodialysis patients. During that year, there were changes to both US dialysis remuneration policy for injected drugs for dialysis patients and ESA product labeling, resulting in marked ESA dose reductions for the treatment of kidney disease–related anemia.[12-14] In parallel, the distribution of hemoglobin levels shifted downward in the US dialysis population. Because ESA hyporesponsiveness is defined with respect to ESA dose and hemoglobin levels, it is unclear whether findings from these prior studies pertain in contemporary nephrology anemia treatment practice: even recently published studies of ESA hyporesponsiveness have considered data from prior to 2011.[15]

We undertook the present study to identify a definition of ESA hyporesponsiveness that is relevant in today's ESA dosing environment and to use that definition to examine the prevalence of ESA hyporesponsiveness and the association of ESA hyporesponsiveness with clinical (hemoglobin concentrations, mortality and missed hemodialysis treatment rates) and health care utilization (cumulative ESA and iron use) outcomes.

METHODS

Data and Patient Cohort

Data for our retrospective study were abstracted from the electronic health record of a large dialysis organization. The large dialysis organization data set contains information about patient demographics, disease history, comorbid conditions, dialysis-specific information for each treatment session, laboratory results such as hemoglobin levels, and IV anemia medications administered at dialysis sessions (ESAs and iron).

Patients eligible for the analysis were 18 years or older, were not Veterans Affairs beneficiaries (contractual stipulation), received in-center hemodialysis at the large dialysis organization, and had a dialysis vintage of 6 months or longer to allow for stabilization of ESA dose following dialysis therapy initiation. In a majority of patients, ESA and iron dosing followed one of the large dialysis organization's clinical protocols: for each, 3 protocols of varying intensity are in place; physicians may choose among these or treat off-protocol. In rare cases in which patients were treated with agents other than epoetin alfa (eg, darbepoetin alfa) or other dosing frequencies were used, ESA dose units were converted based on manufacturer recommendations.[16]

For descriptive analyses, we considered the point prevalent cohort of eligible patients at the start of each of 8 consecutive calendar quarters from quarter 1 (Q1), 2012, through Q4, 2013 (Fig 1). Within each cohort, we calculated the point prevalence of ESA hyporesponsiveness using each of 5 candidate definitions: (1) 2 most recent hemoglobin measurements, separated by 14+ days, both <10 g/dL; (2) 2 most recent hemoglobin measurements, separated by 14+ days, both <9.5 g/dL; (3) ESA dose > 7,700 U/treatment (this corresponds to the 80th percentile for dose among the cohort and is approximately equivalent to a dose of 23,100 U/wk); (4) meets criteria for definitions 1 and 3; and (5) meets criteria for definitions 2 and 3. Point prevalence was defined as the number of patients affected on the first date of the quarter divided by the number of patients in total.

For associative analyses, we considered the point prevalent cohort of eligible patients at the start of Q1 in 2012. Exposure status was assigned as ESA hyporesponsiveness or non–ESA hyporesponsiveness based on whether the patient met definition 4 of ESA hyporesponsiveness at any point during Q1 in 2012 (Fig 1). Patients were followed forward in historical time until the earliest of death, loss to follow-up (transfer of care, transplantation, or withdrawal from dialysis therapy), or end of study (December 31, 2013).

Baseline patient characteristics for the associative analysis (eg, demographics and comorbid conditions) were determined as of the start of Q1 2012; described as means, standard deviations, medians, interquartile ranges, counts, and proportions; and compared using *t* tests, Wilcoxon rank sum tests, and χ^2 tests, as dictated by data type. Continuous patient baseline variables and mean medication dosages were determined using data available up to 90 days prior to January 1, 2012 (study initiation). In rare instances for which patient data were not available in the prior quarter, January 2012 data were used to capture baseline variables. During follow-up, ESA use was analyzed on a monthly basis as mean dose administered per dialysis session, considering all attended dialysis treatments (ie, opportunities to receive ESA) so as to account for treatments with zero dose. However, extra dialysis treatments (including isolated ultrafiltration sessions) were not considered because ESA is not administered during these. Hemoglobin level was calculated on a monthly basis during follow-up as the mean of all measurements made during the month (typically 2). On a monthly basis during follow-up, IV iron use was considered as the cumulative dose administered during the month. Deaths were

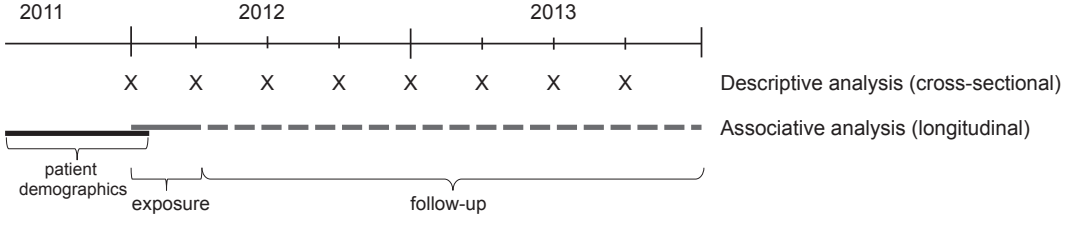

Figure 1. Study schematic. For the descriptive portion of the analysis (presented in Table 1), the point prevalence of erythropoiesis-stimulating agent (ESA) hyporesponsiveness according to 5 candidate definitions was considered at the beginning of 8 calendar quarters (indicated by Xs). For the associative analysis (presented in Tables 2 and 3 and Figs 2 and 3), patient demographic information was collected in the 90 days leading up to January 1, 2012 (through January 30 if required; black line). Patients were ascribed ESA hyporesponsiveness status if they met definition 4 at any time during quarter 1 2012 (solid grey line). Outcomes were assessed through December 31, 2013 (dashed grey line).