Erythropoiesis-Stimulating Agent Hyporesponsiveness Is Associated with Persistently Elevated Mortality among Hemodialysis Patients

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Introduction

• Anemia is highly prevalent among patients with end-stage renal disease (ESRD) and is associated with poor outcomes and mortality. Renal anemia in patients with ESRD receiving hemodialysis (HD) is typically treated with both erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron.

• Many HD patients with renal anemia do not respond optimally to ESA treatment (ie, are ESA-hyporesponsive [ESAhr]). ESA-hyporesponsive patients are unable to achieve their targeted hemoglobin (Hb) concentration or require chronic high ESA doses to achieve their targets.4

• Prior studies have examined the association between ESAhr and outcomes among HD patients.6–10

• However, none have been conducted following 2011 changes to the US ESA labels and reimbursement policy, using recent data and a definition of ESAhr that is relevant to contemporary practice.

Objectives

• To determine a contemporary definition of ESAhr that is relevant to current ESA dosing practices

• To study the association between ESAhr and mortality in HD patients

Methods

• Eligible patients were 18 years or older, non-veterans, receiving in-center HD at a large dialysis organization (LDO), and had a dialysis vintage of 6 months to ensure stable ESA use.

• Point prevalence for various definitions of ESAhr was determined at the beginning of each consecutive calendar quarter (Q) during the study period (01 Jan 2012 to 31 Dec 2013) by dividing the number of patients meeting the definition criteria by the total number of patients eligible at that time.

• For associative analyses, the point prevalent cohort of eligible patients at the start of Q1 2012 was considered. Exposure status was assigned as ESAhr or non-ESAhr based on whether the patient met the operative definition of ESAhr (ie, at any point during Q1 2012). Patients were followed until the earliest of death, loss to follow-up (transfer of care, temporary withdrawal of care, and/or beyond Q2), or end of study (Q1 2013).

• ESA utilization was calculated monthly as the mean administered per dialysis session. Hgb concentration was determined as the mean of all measurements during the month. Observations of missed dialysis treatments were assessed quarterly and expressed as rates (number of events during the quarter divided by cumulative time at risk).

• Associations of ESAhr status with ESA utilization and hemoglobin concentration were estimated using general estimating equation linear models with an identity link and Gaussian distribution. Models contained fixed effects terms for exposure group (ESAhr vs non-ESAhr) and exposure month (Q1 through Q8), and a random intercept for patient to account for differences in time over the association between exposure groups.

• Associations of ESAhr status with mortality and missed dialysis treatments were estimated using general estimating equation models using a log link and Poisson (normal) or negative binomial (missed treatments) distribution.

• Adjusted models contained fixed effects terms for covariates that differed significantly between exposure groups at baseline (P < 0.10).

• In cases where adjusted models did not converge, changes in covariate adjustments were necessary on a model-by-model basis, based on the variables presumed to have the least influence on the final estimates.

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Results

• The point prevalence of candidate definitions of ESAhr was assessed (Table 1). Definitions of ESAhr based on ≥ 700 U/treatment and consecutive Hb measurements (separated by at least 14 days) < 10 g/dL met the expected prevalence rate of approximately 10%4–6 and was used to define ESAhr in all subsequent analyses.

• Compared to non-ESAhr patients, ESAhr patients were younger, more likely to be African American, more frequently used central venous catheters, less frequently used arteriovenous fistulas, and were more frequently treated with antibiotics (Table 2).4

• ESAhr patients had significantly greater ESA and IV iron utilization (Figure 1A and 1B) and lower Hb concentrations (Figure 1C) compared to non-ESAhr patients at all times during follow-up.

• ESAhr was associated with a greater adjusted risk of mortality vs non-ESAhr in Q2 through Q8 of follow-up (Figure 2; Adjusted incidence rate ratios [IRDs; 95% CIs] ranged from 2.34 [1.93, 2.80] to 2.46 [2.32, 2.52] in Q2 of follow up to 1.48 [1.18, 1.84] in Q8).

• ESAhr was also associated with a greater rate of missed dialysis treatments compared to non-ESAhr. Adjusted incidence rate differences (IRDs; 95% CI) ranged from 2.46 (2.32, 2.52) in Q2 of follow up to 1.48 (1.36, 1.68) in Q8.

Conclusions

• We identified a definition of ESAhr that is relevant to contemporary clinical practice and expected disease prevalence.

• Using this definition we show that ESAhr is potentially and persistently associated with:

– Increased ESA and IV iron use
– Lower Hb concentrations
– Elevated rates of mortality and missed dialysis treatments

References


Acknowledgments

• We extend our sincere appreciation to the teammates in more than 2,000 DaVita clinics who work every day to take care of patients and also to ensure the availability of high-quality clinical research data.

• The authors also thank the patients and caregivers who participate in our research to advance the care of others.

• The authors thank the clinical investigators, research staff, and DaVita management teams who contributed to this research as evidenced by their involvement in the DaVita CRN, one of the clinical research networks sponsored by DaVita Clinical Research.