

Erythropoiesis-Stimulating Agent Hyporesponsiveness and Adverse Outcomes: Guilty as Charged?

Jay B. Wish



Although there is no consensus as to a definition of erythropoiesis-stimulating agent (ESA) resistance or hyporesponsiveness, ESA hyporesponsiveness often is described as a requisite threshold dose of ESA to maintain

Related article, p. 590

hemoglobin (Hb) level in the target range or failure to reach the target range despite such a dose. These thresholds are variably expressed as the actual ESA dose (per treatment based on 3-times-weekly administration or total weekly dose), the ESA dose per kg of body weight, or the ESA resistance index, which is weekly ESA dose per kg of body weight per g/L (not g/dL) of Hb level achieved.

Szzech et al,¹ in their secondary analysis of the Correction of Hemoglobin in the Outcomes in Renal Insufficiency (CHOIR) Study, defined “high” ESA dose as more than 20,000 units of epoetin per week and noted that such doses were associated with more major adverse cardiovascular event (MACE) outcomes irrespective of target or achieved Hb level. The 2006 KDOQI (Kidney Disease Outcomes Quality Initiative) Anemia Guidelines define ESA resistance as failure to increase Hb level to >11 g/dL despite an ESA dose equivalent to epoetin > 500 U/kg per week.² The US Food and Drug Administration–approved product information for epoetin alfa, revised in 2011, recommends a starting dose of 50 to 100 U/kg (based on 3-times-weekly dosing) with upward titration of dose by 25% at 4 and 8 weeks if inadequate Hb level response is achieved. If target Hb level is not achieved at 12 weeks (4 weeks after the second upward dose titration), no further dose increase is recommended.³ This would constitute a maximum epoetin dose of ~150 U/kg 3 times weekly or 450 U/kg per week, with failure to achieve Hb target constituting ESA hyporesponsiveness. A patient receiving epoetin, 450 U/kg per week, with Hb level of 100 g/L would have an ESA resistance index of 4.5.

ESA hyporesponsiveness is a therapeutic issue because it constitutes failure to achieve a desired Hb goal, increases the cost of care, and is associated with adverse outcomes. The only benefit of ESAs recognized by the US Food and Drug Administration is transfusion avoidance; ESA hyporesponsiveness leads to increased transfusions with the risk for allosensitization for future kidney transplants, as well as adverse dialysis provider public profile and payment in the United States. The association of ESA hyporesponsiveness with MACE and all-cause mortality has been documented in several observational studies,^{4–6} but confounding by comorbid conditions and indication cannot be completely excluded.

The causes of ESA hyporesponsiveness were reviewed by Ogawa and Nitta⁷ and are summarized in [Box 1](#). Iron deficiency, the most common cause of ESA hyporesponsiveness, can be absolute or functional. Absolute iron deficiency, most commonly defined as transferrin saturation (TSAT) < 20% and/or serum ferritin level < 200 ng/mL in a dialysis patient, is straightforward and its correction with intravenous (IV) iron generally leads to increased ESA responsiveness. Functional iron deficiency is usually due to an inflammatory state that may be apparent or occult, is characterized by TSAT < 20% and ferritin level > 200 ng/mL, and is more challenging to treat.

Our understanding of functional iron deficiency, an evolutionary mechanism to protect the body against infection by siderophilic pathogens, has been revolutionized by the discovery of hepcidin, the master regulator of internal iron distribution.⁹ Inflammatory cytokines, especially interleukin 6, stimulate liver synthesis of hepcidin, which by internalizing the ferroportin iron exporter on duodenal enterocytes and macrophages leads to decreased iron absorption by the gut and decreased iron release from storage sites in the liver and spleen. This results in less circulating iron available for erythropoiesis (represented by low TSAT) and increased storage iron (represented by high ferritin level). IV iron is variably effective in overcoming this “reticuloendothelial iron blockade” that leads to ESA hyporesponsiveness.

Although the association among inflammation, functional iron deficiency, ESA hyporesponsiveness, and poor patient outcomes is complex, the Proactive IV Iron Therapy in Hemodialysis Patients (PIVOTAL) Trial¹⁰ has shed some light on this issue. PIVOTAL randomly assigned 2,141 patients in the first year of maintenance hemodialysis (HD) to high-dose IV iron (400 mg monthly unless TSAT was >40% or serum ferritin was >700 ng/mL) or low-dose IV iron (0–400 mg monthly if TSAT was <20% or serum ferritin was <200 ng/mL) with a mean follow-up of 2.1 years. The primary end point was a composite of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure, assessed in a time-to-first-event analysis. Patients in the 2 arms had similar Hb levels, but patients in the high-dose IV iron arm had 19.4% reduction in ESA requirements and 15% reduction in primary events ($P = 0.04$ for superiority). These results suggest an association between high ESA doses and MACE that cannot be attributed to underlying inflammation or functional iron deficiency, although an independent beneficial effect of higher-dose IV iron cannot be excluded. In other words, ESA hyporesponsiveness, rather than being just a biomarker for

Box 1. Causes of ESA Hyporesponsiveness⁷

- Iron deficiency
- Chronic inflammation
 - Hemodialysis catheter
 - Diabetic vascular disease
 - Periodontal disease
 - Dialysate contamination
- Inadequate dialysis
- Hyperparathyroidism
- Renin-angiotensin system inhibitors
- Malignancy
- Other (rare)
 - Bone marrow disorders
 - Myelosuppressive drugs
 - Hemolysis
 - Hypersplenism
 - Malnutrition
 - L-Carnitine deficiency
 - Pure red blood cell aplasia
- Unknown (about 1/3)⁸

Abbreviation: ESA, erythropoiesis-stimulating agent.

underlying diseases with higher risk for adverse outcomes, is more likely a contributor to adverse outcomes itself.

In this issue of *Kidney Medicine*, Cizman et al¹¹ present a retrospective observational cohort study of US Medicare-participating maintenance dialysis patients with a minimum 6 months of continuous ESA use from 2012 to 2014. ESA hyporesponsiveness was defined ESA resistance index ≥ 2.0 units of IV epoetin (or therapeutically equivalent subcutaneous dose or alternate ESA) per kg/wk/g/L. ESA-hyporesponsive patients were subgrouped into isolated (2 consecutive months of hyporesponsiveness with no additional ESA hyporesponsiveness months during the study period), intermittent (ESA hyporesponsiveness $<75\%$ of months during the study period), and chronic (ESA hyporesponsiveness $\geq 75\%$ of months during the study period). Of patients meeting inclusion criteria, 43,416 were ESA hyporesponsive and 67,403 were normoresponders, and among patients with ESA hyporesponsiveness, 23% were chronic hyporesponders, 50% were intermittent hyporesponders, and 27% were isolated hyporesponders.

Irrespective of the pattern of hyporesponse, all patients with ESA hyporesponsiveness had shorter time to death ($P < 0.001$) than normoresponders. Patients with ESA hyporesponsiveness were younger, were more likely to be female and Black, and had lower body mass index, higher Charlson Comorbidity Index score, and higher incidence of hypertension, type 2 diabetes, hyperlipidemia, heart failure, coronary artery disease, arrhythmia, and valvular heart disease than normoresponders. A higher percentage of patients with ESA hyporesponsiveness had TSAT $< 20\%$ and parathyroid hormone level > 800 pg/mL, but serum ferritin levels were similar to normoresponders. Despite adjustment for population differences, patients with ESA hyporesponsiveness had higher hospitalization rates related

to heart failure, myocardial infarction, stroke, and thromboembolic events, as well as higher emergency department visits, inpatient stays, inpatient days, home health agency use, skilled nursing days, and hospice days.

Previously, Sibbel et al¹² differentiated acute ESA hyporesponsiveness (≤ 4 consecutive months) and chronic ESA hyporesponsiveness (4 consecutive months) from ESA normoresponders, and they also found that patients with ESA hyporesponsiveness more likely to be female, be Black, and have similar comorbid conditions to the Cizman et al study.¹¹ In the Sibbel et al¹² study, patients with chronic ESA hyporesponsiveness tended to have lower TSAT and higher serum ferritin values than those with acute ESA hyporesponsiveness, suggesting a greater degree of functional iron deficiency reflective of high hepcidin levels and an inflammatory state. Quarterly mortality was significantly higher among patients with chronic ESA hyporesponsiveness than acute ESA hyporesponsiveness and higher among patients with acute ESA hyporesponsiveness than normoresponders.

Because both the Cizman et al¹¹ and Sibbel et al¹² studies are retrospective, they are hypothesis generating and cannot establish a cause-and-effect relationship between either ESA hyporesponsiveness or ESA dose and adverse outcomes. Nonetheless, given the accumulation of evidence of this nature, it is reasonable to consider whether ESA-sparing strategies might lead to improved patient outcomes, as did the use of higher iron doses in the PIVOTAL study.¹⁰ One such approach is a new class of oral pharmaceutical agents that, through activating the oxygen sensors in the kidney by inhibiting hypoxia-inducible factor prolyl hydroxylase (HIF-PH), lead to endogenous production of erythropoietin at a more physiologic blood level than the spikes produced by exogenous ESAs.¹³ HIF-PH inhibitors also lead to transcription of genes to increase iron delivery to the bone marrow, including those that code for transferrin, transferrin receptor, duodenal cytochrome B, and divalent metal transporter 2, while leading to an indirect suppression of hepcidin production by the liver. Phase 2 studies of these agents have shown them to have comparable short-term safety and efficacy in achieving target Hb levels as ESAs.¹³ A 6-month phase 3 study of roxadustat, an HIF-PH inhibitor, in HD patients in China¹⁴ showed it to be superior to ESAs in achieving target Hb levels in patients with high C-reactive protein levels. Karaboyas et al¹⁵ have described an appreciable increase in ESA hyporesponsiveness prevalence within 3 months following an increase in C-reactive protein levels in HD patients. The results of global phase 3 long-term studies of HIF-PH inhibitors have been presented in abstract form, revealing no unexpected safety findings, but none of these studies has appeared in a peer-reviewed publication as of this writing.

In summary, ESA hyporesponsiveness is a challenging clinical problem that is not uncommon and is associated with adverse outcomes and increased health care use. The more sustained the ESA hyporesponsiveness the worse the outcome, but even short periods of ESA hyporesponsiveness appear to be of concern. It is unresolved whether ESA

hyporesponsiveness is merely a marker for the pernicious underlying conditions that produce it or whether the high ESA doses administered in patients with ESA hyporesponsiveness are directly toxic. It is hoped that carefully designed clinical trials of ESA-sparing strategies, such as HIF-PH inhibitors, in patients with ESA hyporesponsiveness will resolve this issue in the near future.

ARTICLE INFORMATION

Author's Full Name and Academic Degree: Jay B. Wish, MD.

Author's Affiliation: Indiana University Health and Division of Nephrology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN.

Address for Correspondence: Jay B. Wish, MD, Division of Nephrology, Indiana University Hospital, 550 N University Blvd, Ste 6100, Indianapolis, IN 46260. E-mail: jaywish@earthlink.net

Support: None.

Financial Disclosures: Dr Wish is a consultant to AstraZeneca (roxadustat), Akebia (vadadustat and ferric citrate), Vifor (iron sucrose and ferric carboxymaltose), and Rockwell Medical (ferric pyrophosphate citrate) and is on the speakers bureau for AstraZeneca (roxadustat) and Akebia (ferric citrate).

Peer Review: Received July 27, 2020, in response to an invitation from the journal. Direct editorial input by the Editor-in-Chief. Accepted in revised form August 3, 2020.

Publication Information: © 2020 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). Published online August 25, 2020 with doi [10.1016/j.xkme.2020.08.002](https://doi.org/10.1016/j.xkme.2020.08.002)

REFERENCES

1. Szczech LA, Bernhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin- α dose and achieved hemoglobin outcomes. *Kidney Int.* 2008;74(6):791-798.
2. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47(suppl 3):S11-S145.
3. Amgen. Highlights of prescribing information for Epogen (epoetin alfa). Accessed July 17, 2020, https://www.pi.amgen.com/~ /media/amgen/repositorysites/pi-amgen-com/epogen/epogen_pi_hcp_english.pdf.
4. Luo J, Jensen DE, Maroni BJ, et al. Spectrum and burden of erythropoiesis-stimulating agent hyporesponsiveness among contemporary hemodialysis patients. *Am J Kidney Dis.* 2016;68(5):763-771.
5. Nisho A, Chhatkuli BP, Ma JZ, et al. Higher doses of erythropoietin-stimulating agents and hyporesponsiveness to their effect are associated with increased mortality among prevalent hemodialysis patients. *Blood Purif.* 2013;36(1):29-36.
6. Bae MN, Kimn SH, Kin YO, et al. Association of erythropoietin-stimulating agent responsiveness with mortality in hemodialysis and peritoneal dialysis patients. *PLoS One.* 2015;10(11):e0143348.
7. Ogawa t, Nitta K. Erythropoiesis-stimulating hyporesponsiveness in end-stage renal disease patients. *Contrib Nephrol.* 2015;185(1):76-86.
8. Gillespie IA, Macdougall IC, Richards S, et al. Factors precipitating erythropoiesis stimulating agent responsiveness in a European haemodialysis cohort: case-crossover study. *Pharmacoeconom Drug Saf.* 2015;24(4):414-426.
9. Agarwal AK, Yee J. Hepcidin. *Adv Chronic Kidney Dis.* 2019;26(4):298-305.
10. Macdougall IC, White C, Anker S, et al. Intravenous iron in patients undergoing maintenance dialysis. *N Engl J Med.* 2019;380(5):447-458.
11. Cizman B, Smith HT, Camejo RR, et al. Clinical and economic outcomes of erythropoiesis-stimulating agent hyporesponsiveness in the post-bundling era. *Kidney Med.* 2020;2(5):590-600.
12. Sibbel SP, Koro CE, Brunelli SM, et al. Characterization of chronic and acute ESA hyporesponse: a retrospective cohort study of hemodialysis patients. *BMC Nephrol.* 2015;16:144.
13. Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv Chronic Kidney Dis.* 2019;26(4):253-266.
14. Chen H, Hao C, Liu B-C, et al. Roxadustat for treatment of anemia in patients undergoing long-term dialysis. *N Engl J Med.* 2019;381(11):1011-1022.
15. Karaboyas A, Mogenstern H, Fleisher NA, et al. Inflammation and erythropoiesis-stimulating agent response in hemodialysis patients: a self-matched longitudinal study of anemia management in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Med.* 2020;2(3):286-296.