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ESAs in Dialysis Patients: Are You a Hedgehog or a Fox?

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The philosopher Isaiah Berlin[1] divides authors and perhaps people in general into two categories: Hedgehogs, who view the world through the lens of one defining idea, and foxes, for whom the world cannot be boiled down to a single idea. Looking at erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in chronic kidney disease (CKD), should there be a single conclusion about the safety of ESAs?

In a previous editorial, I discussed the use of ESAs in nondialysis patients.[2] Here, I consider their continued use for the anemia of dialysis patients. ESAs have proved effective in correcting anemia in patients with ESRD. No one relishes blithely turning the clock back to the pre-ESA era, when dialysis patients were treated with repeated blood transfusions, iron therapy, anabolic steroids, and other maneuvers; however, mortality and the rate of cardiovascular complications in the dialysis population remain high, and reducing risk would be important in improving outcomes.

Randomized, controlled trials (RCTs) demonstrate there is increased risk in correcting anemia with ESAs in all patients with CKD–both dialysis and nondialysis. In the recently published Trial to Reduce Cardiovascular Endpoints with Aranesp Therapy (TREAT),[3] a placebo-controlled, double-blind, randomized study comprising 4038 nondialysis patients, there was a significantly higher rate of strokes in patients who were treated with darbepoetin (hazard ratio 1.92; $P < 0.001$) as well as higher rates of thromboembolism and cancer-related deaths. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study,[4] the risk was a higher rate of mortality and cardiovascular complications in nondialysis patients targeted to a hemoglobin (Hb) level of 13.0 g/dl with epoetin-alfa (hazard ratio 1.34; $P = 0.03$). A higher rate of death or myocardial infarction (MI) or vascular access thrombosis was also observed in the Normal Hematocrit study.[5]

Meta-analyses have reached similar conclusions.[6,7] In the meta-analysis by Phrommintikul *et al.*,[6] nine RCTs were selected on the basis of quality, sample size, and follow-up and viewed together for a total sample of 5143 patients, including both dialysis and nondialysis CKD trials. There was a higher risk for all-cause mortality (risk ratio [RR] 1.17; 95% confidence interval [CI] 1.01 to 1.35; $P = 0.031$) and arteriovenous access thrombosis (RR 1.34; 95% CI 1.16 to 1.54; $P = 0.0001$) in the higher Hb target group compared with the lower Hb target group. In a National Kidney Foundation (NKF) meta-analysis, published as a part of the revised 2007 NKF anemia guidelines,[7] dialysis and nondialysis patients with CKD were evaluated separately. Four studies and 2391 patients were included in the NKF analysis of dialysis patients. The NKF reported increased risk with anemia correction, despite the use of a random-effect rather than a fixed-effect model. The point estimate for risk with the study by Phrommintikul *et al.*[6] was 1.17 (95% CI 1.01 to 1.35; $P = 0.031$), whereas with the NKF study, the hazard ratio was 1.12 (95% CI 0.91 to 1.37).

Some in the academy will argue that because both the CHOIR study and TREAT enrolled nondialysis patients with CKD, these studies are not generalizable to the dialysis population; however, results of two RCTs of dialysis patients counter this assertion. The Normal Hematocrit study[5] is the largest anemia correction RCT of dialysis patients. It tested the hypothesis that the correction of anemia with Epogen in hemodialysis patients with clinical evidence of congestive heart failure or ischemic heart disease would improve outcomes. The primary end points were length of time to death or a first nonfatal MI. The study was halted at the third interim analysis on the recommendation of the Data Safety Monitoring Committee. At 29 months, there were 183 deaths and 19 first nonfatal MIs in the group with a normal hematocrit level and 150 deaths and 14 nonfatal MIs in the low hematocrit group (RR 1.3; 95% CI 0.9 to 1.9). Even though these differences did not reach the prespecified statistical stopping boundary, the study was halted for safety reasons. In addition, the incidence of thrombosis of vascular access sites was higher in the normal hematocrit group compared with the low-hematocrit group (243 [39%] *versus* 176 [29%] patients; $P = 0.001$). Unpublished data from the Normal Hematocrit study, archived by the Food and Drug Administration (FDA),[8] showed that the incidence of nonfatal MI was 3.1 and 2.3% in the normal and low hematocrit groups, respectively. The incidences of vascular thrombosis (39 *versus* 29%) and all other thrombotic events (22 *versus* 18%) were also higher in the normal hematocrit group (of note, there was no significant difference in the rate of stroke: 7% in normal and 6% in normal hematocrit group, respectively; personal communication from David Goodkin). The risk for thrombotic events is consistent with the TREAT data. With respect to patient-reported quality-of-life determinations, only one category of eight showed improvement in quality of life with higher Hb concentrations, but between-group comparisons (high *versus* low Hb) for quality of life were not reported.

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Because the Normal Hematocrit study recruited high-risk patients, it may not be generalizable to the dialysis population at large; however, consider the Canadian-European Normalization of Hemoglobin with Erythropoietin Trial,[9] which enrolled relatively healthy incident hemodialysis patients by excluding patients with symptomatic heart disease as well as those with left ventricular dilation at baseline. Patients were randomly assigned to higher *versus* lower Hb (13.0 *versus* 11.0 g/dl, respectively). The primary end point was a change in left ventricular volume index. Changes in parameters of heart failure, stroke, and quality of life were also measured. No significant benefit in either of the cardiac structural or functional parameters was observed in the high- *versus* low-Hb groups; however, there was a statistically significantly higher rate of stroke in the higher Hb group. Quality of life showed improvement in the vitality score in the high- *versus* low-Hb group, although the 6-minute walk test and two other measures of quality of life did not improve significantly.

The FDA has lumped together the major RCTs on anemia correction in patients with CKD.[10] The current FDA recommendation states a Hb goal of 10 to 12 g/dl for all patients with CKD, regardless of dialysis status.[10] From a safety perspective, there is some rationale for lumping the trials together: The risk of ESA exposure seems insensitive to the patient population. Data from RCTs of patients with CKD,[3,4,5,11,12] patients with cancer,[11,13] healthy individuals who underwent spine surgery,[14] and critically ill patients[15] all point to increased risk with ESA exposure.

In patients with CKD, data from both observational studies and secondary analyses of RCTs suggest that exposure to high dosages of ESA explains the higher risk for mortality and cardiovascular complications[16–19]; however, no study has proved causality so far, and the issue continues to be debated.[20] Confounding by indication and dosage-targeting bias have been raised as limitations in these analyses.[21,22] Furthermore, not all studies implicate ESA exposure in explaining risk; a recent study using marginal structural modeling failed to report an association between high ESA dosage and adverse outcome.[23] Conversely, a secondary analysis of the CHOIR study, using landmark analysis as a way to avoid some of the biases inherent in observational studies, demonstrated that high ESA dosage was an independent predictor of the combined end point of mortality, nonfatal MI, heart failure, and stroke.[17] In this analysis, targeting a higher Hb or lower Hb with higher dosages of ESA associates with poor outcomes, whereas achieving a higher Hb improves outcomes. A fair appraisal of the evidence is that, although additional studies will be needed to address causality, we should be concerned about the possibility of adverse effects from high ESA dosage.

Reducing ESA dosage in dialysis patients will probably result in a higher red cell transfusion rate. In the Normal Hematocrit study,[5] 129 (21%) patients in the normal hematocrit group received red cell transfusions compared with 192 (31%) patients in the low hematocrit group ($P < 0.001$). In the Canada-Europe study, transfusion rates were 9.1% with the high target *versus* 19.3% with the low target. In TREAT, nearly twice as many patients required blood transfusions when assigned to placebo *versus* darbepoetin (496 [24.5%] *versus* 297 [14.8%] patients, respectively; $P < 0.001$).

Although the FDA review cited a low rate of transfusion-related complications in the current era, it is unlikely that repeated blood transfusions will be without risk.[11] Iron use will also rise with aggressive attempts to reduce ESA dosage. Exposure to large amounts of intravenously administered iron, over the long-term, raises safety concerns,[24] although observational studies have been reassuring.[25]

In the absence of additional RCTs, clinicians are faced with making decisions on what to do with managing anemia in dialysis patients. Maintaining dialysis patients on the lowest possible dosage of ESA, above a Hb threshold of >9 g/dl, is commensurate with the placebo arm of TREAT. This Hb threshold is also consistent with the lower Hb arm of the Normal Hematocrit study. For some patients, this strategy will be well tolerated and should be the goal. These patients probably will be healthier and have less laboratory evidence of inflammation, normal iron stores, well-controlled metabolic bone disease parameters, and good dialysis adequacy; however, a Procrustean one-size-fits-all approach to treating anemia in dialysis patients has its own problems, because dramatically decreasing the ESA dosage in some patients, perhaps the majority, will result in a precipitous fall in Hb concentration, long-term complications of repeated blood transfusion, and intolerable fatigue. In these patients, engaging in a discussion about the risks and benefits of ESA therapy, as well as individualizing goals of therapy, will be important. A computerized "generic" anemia protocol will not do for these patients. Maneuvers that lower ESA dosage but prevent a concomitant drop in the Hb concentration should be aggressively pursued. These include using intravenous iron therapy to keep the patient iron-replete, even when the patient has a high ferritin level.[26,27] Switching to subcutaneous ESA will also result in one-third lower ESA dosage use,[28] and patients may be willing to trade the discomfort of subcutaneous ESA for greater safety.[29] Optimizing adequacy of dialysis or switching patients to alternative modalities, such as peritoneal dialysis[30] or nocturnal[31] hemodialysis, may also result in lower ESA dosage. Treating inflammation either with drugs, such as pentoxyfilline[32] or a statin,[33] or treating an underlying infection or treating hyperparathyroidism also seem effective in reducing ESA dosage without causing the Hb to fall. For some patients who are waiting for a kidney allograft, long-term ESA therapy will be necessary because blood transfusion must be avoided to minimize the risk for sensitization. Conversely, avoiding ESAs should be considered for patients who are within 2 years of a diagnosis of a malignancy or are actively undergoing chemotherapy.

In conclusion, there is increased risk in targeting a higher Hb level in dialysis patients. Aiming for an Hb level of >9 g/dl is commensurate with the placebo arm of TREAT but also the lower Hb arm of the Normal Hematocrit study; however, a higher rate of red cell transfusion will probably be necessary

with such a strategy. The key to ESA therapy in dialysis patients will be individualization of risk and benefit. In seventh century BC, the Greek soldier-poet Archilochus[34] wrote, "The fox knows many things but the hedgehog knows one big thing." In CKD anemia, the one big thing is using the lowest possible dosage of ESA because of safety concerns; however, reducing exposure to ESA and individualizing therapy will require "many things" and undeniably the smarts of a fox.

DISCLOSURES

A.K.S. was principal investigator of the CHOIR study and a member of the Executive Committee for TREAT. He presented to the FDA Cardiovascular Disease and Renal Advisory Committee in September 2007 and to the US Congress House of Representatives Ways and Means Committee in December 2006 and June 2007. He has received consulting fees from Amgen, Johnson and Johnson, Fibrogen, and Watson and has received grant support from Amgen, Johnson and Johnson, and Watson.

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Round 2 at *JASN*

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To become the second editor of *JASN* was not an easy road traveled. My competition consisted of two highly visible and extremely well-published nephrologists from prestigious institutions with extensive editorial experience, each of whom had served the American Society of Nephrology (ASN) in many capacities, including president. Before and immediately after my interview with the search committee at the time of the 1995 ASN Annual Meeting in San Diego, I had serious doubts that I would be selected; however, on the final day of the annual meeting, I learned that I would be the next editor of *JASN*.

After a very brief period of euphoria, I began to feel like the old hound that loved to chase cars but after finally catching one was uncertain what to do next. I quickly recovered and immediately asked Kirsten M. Madsen and R. Tyler Miller to serve as my deputy editors, and together we set about the task of organizing a new staff in preparation for taking on the editorial responsibilities of *JASN* in July 1996.

Critical to our effort was convincing Ms. Bonnie O'Brien, then current managing editor of *JASN* (founding editor Jared Grantham's right-hand person) and a native of Kansas City, to relocate with *JASN* to Gainesville and the University of Florida. I believe the fact that she was an avid and very skilled tennis player and that tennis is enjoyed outdoors the year around in Gainesville was a major factor in her successful recruitment. The transition from the old to the new editorial team was virtually seamless, in large part because of the professionalism displayed by the very successful founding editor, Jared Grantham, and the presence of Bonnie. Interestingly, although the journal editorship has moved twice since leaving Gainesville, first to Seattle under William Couser and now in Nashville with Eric Neilson, Bonnie and the managing editor's office have remained in Gainesville, a true testimonial to the power of the internet and tennis!

I was extremely fortunate to enjoy the support of an outstanding group of associate editors that included Corinne Antignac, Alfred K. Cheung, Mark Knepper, Alan M. Krensky, Richard P. Lifton, William E. Mitch, Giuseppi Remuzzi, and Eberhard Ritz. These individuals manifested an incredible wealth of knowledge and experience in their respective areas of expertise, which was especially important to this newly minted editor. Indeed, their contributions along with those of Kirsten Madsen, who was later appointed senior deputy editor, to the quality of the editorial process were immeasurable. Also, I would be remiss in not acknowledging the extremely important role of the members of the editorial board and the dozens of additional referees who day in and day out provided thoughtful, well-written, and detailed reviews of manuscripts submitted to *JASN*. Their outstanding efforts maintained the integrity and quality of the peer-review process.

An initial mini-crisis involving *JASN* arose somewhat unexpectedly at the ASN Spring Council meeting in 1996. The editor's report included an artist's rendering of a proposed new style and color for the cover. Furthermore, the editor proposed that greater emphasis be placed on "nephrology" in the title so that gradually, over the course of approximately 3 years, the journal might become known simply as "NEPHROLOGY" rather than *JASN*. Eventually, the cover would have read, "NEPHROLOGY, the official publication of the American Society of Nephrology." The council did not accept the proposal, and, as they say, "the rest is history." We will never know whether NEPHROLOGY could have replaced *JASN* in name recognition. The deep red or burgundy color was found acceptable and, incidentally, matched the color of the editor's pick-up truck.

A new feature introduced with the January 1997 issue was the "Milestones in Nephrology" series. We are indebted to Mark Knepper, who served as the feature editor. Our intent was to reprint scientific articles from any journal source that had provided

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CORRECTION

Erratum for Singh: ESAs in Dialysis Patients: Are You a Hedgehog or a Fox? *J Am Soc Nephrol* 21: 543–546, 2010. In the original published version of this article, the references were incorrectly numbered. In the reference list, reference 32 should have been listed as reference 31, reference 33 should have been listed as reference 32, and reference 34 should have been listed as reference 33. Reference 31 should have been omitted.

Also, the following text was incorrect: "The incidences of stroke (39 *versus* 29%) and all other thrombotic events (22 *versus* 18%) were also higher in the normal hematocrit group. The risk for stroke and thrombotic events is consistent with the TREAT data." The text should have read: "The incidences of vascular thrombosis (39 *versus* 29%) and all other thrombotic events (22 *versus* 18%) were also higher in the normal hematocrit group (of note, there was no significant difference in the rate of stroke: 7% in normal and 6% in normal hematocrit group, respectively; personal communication from David Goodkin). The risk for thrombotic events is consistent with the TREAT data."

We apologize for these errors.

A corrected version of this manuscript has been posted online.

CORRECTION

Erratum for Berl *et al.*: Oral Tolvaptan Is Safe and Effective in Chronic Hyponatremia. *J Am Soc Nephrol* 21: 705–712, 2010. There is an error in the affiliation line. Although Dr. Quittnat-Pelletier is presently at the Renal Division, University of Toronto, Toronto, Ontario, Canada, her contribution to this manuscript was made when she was at the Division of Nephrology, Department of Medicine III, Universitätsklinikum C.G.Carus, Dresden, Germany.

We apologize for this error.

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