

The FDA's Perspective on the Risk for Rapid Rise in Hemoglobin in Treating CKD Anemia: *Quo Vadis*

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Clin J Am Soc Nephrol 5: 553–556, 2010. doi: 10.2215/CJN.00490110

The Trial to Reduce Cardiovascular Endpoints with Aranesp Therapy (TREAT) (1) has prompted the Food and Drug Administration (FDA) to reevaluate the use of erythropoiesis-stimulating agents (ESAs) in the treatment of chronic kidney disease (CKD) anemia (2). An FDA public advisory committee meeting in 2010 is anticipated. The TREAT study reported, against placebo, minimal benefit and increased risk of ESA therapy (1). Before TREAT, Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (3), Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) (4), and Normal Hematocrit (5) studies also demonstrated either no benefit or increased risk of targeting a higher hemoglobin (Hb) concentration. Consequently, attention has shifted from the benefits of ESAs to their risks (6). Most nephrologists will be eager to receive guidance from the convened FDA panel on how to interpret these trials in terms of clinical practice. In a recent *New England Journal of Medicine* Perspective article, Unger *et al.* (2) from the FDA reviewed the evidence from TREAT and the Normal Hematocrit and CHOIR studies. Unger *et al.* raised again, among several factors, the issue of too rapid an increase in Hb as being an important factor in determining clinical outcomes in patients who have CKD and anemia and are treated with an ESA. Here, I examine the strength of this evidence and evaluate the FDA's emphasis on the rate of increase of Hb in ESA treatment of CKD anemia.

The FDA's concern regarding the potential risk of too rapid an increase in Hb dates back to a review conducted by the Center for Biologics Evaluation and Research (CBER) in 2001 (7). The CBER performed exploratory safety analyses of the Aranesp licensing application and observed an association between Hb rate of rise >0.5 g/dl per wk and the risk for cardiovascular and thromboembolic events. This Aranesp review comprised 1598 patients with chronic renal failure (a mixture of predialysis, hemodialysis, and peritoneal dialysis patients) (7,8). The data showed a lower rate of adverse events with higher Hb concentration; however, the analysis also demonstrated increasing rates of adverse events with both an increasing and a decreasing rate in change of Hb concentration over time (*i.e.*, either a positive or a negative Hb-time slope). On

the basis of this review, a warning was added to the Aranesp package insert (PI) (9) and then subsequently into the Procrit/Epogen PI (10). In the warning section of the Aranesp PI, a statement follows concerns about increased cardiovascular risk: "A rate of rise greater than 1 g/dl over 2 weeks may also contribute to these risks." In the Procrit PI (9), the statement is more explicit: "The rate of hemoglobin increase should not exceed 1 g/dl in any two-week period."

After the publication of the CHOIR study and in preparation for the Cardiovascular and Renal Disease Advisory Committee in September 2007, the CBER analyzed data from both the Normal Hematocrit and CHOIR studies (11). Two approaches were used to consider cardiovascular risk by Hb concentration. In the first, risk was considered in a "static" manner: Risk was constant for each patient throughout the study as a function of the mean Hb concentration. Using this approach, Unger (11) reported a conclusion similar to the previous Aranesp analysis: Lower achieved Hb concentrations in both the Normal Hematocrit and CHOIR studies were associated with higher cardiovascular risk, whereas higher Hb concentrations were associated with lower risk. This conclusion has been confirmed by several observational studies (12–14) and by *post hoc* analysis of randomized trials (1,3,5) that evaluated *achieved* Hb rather than the *targeted* Hb concentration. In contrast, targeting of a higher Hb in the randomized trials (1,3–5) has been associated with either no benefit or an increased risk for mortality and cardiovascular complications. The second approach was similar to what was used for the Aranesp safety analysis and termed a "dynamic" analysis: Each interval between Hb assessments was viewed as time at risk for adverse events, and each period was associated with a particular Hb value and a rate of change of Hb preceding each visit. To calculate the rate of change of Hb, the slope of the preceding Hb-time relation was determined by linear regression. Negative and positive Hb slopes were then calculated. This approach was applied separately to data from the Normal Hematocrit study and the CHOIR study. A schematic representation of this analysis (adapted from the FDA) is depicted in Figure 1. There is an association between negative and positive Hb slopes and the rate of cardiovascular adverse events, respectively; however, the association was strongest for declining slopes of Hb concentrations and the rate of adverse events, compared with increasing slopes of Hb concentration.

These static and dynamic exploratory analyses have several

Published online ahead of print. Publication date available at www.cjasn.org.

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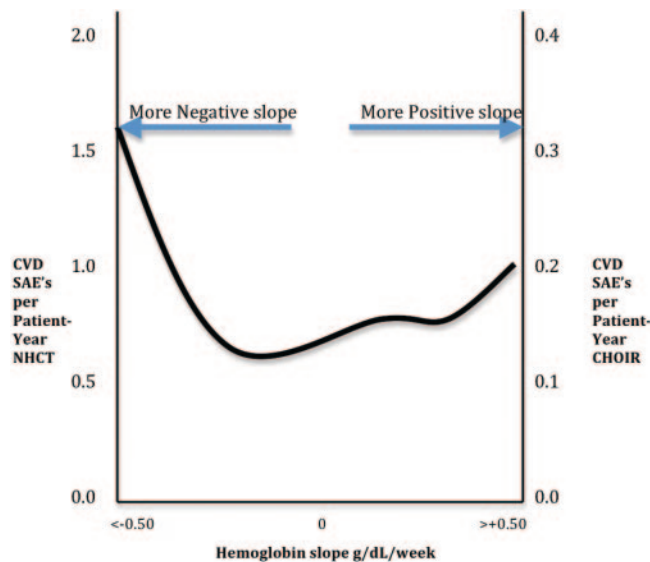


Figure 1. Relationship between cardiovascular serious adverse events (SAEs) and rate of change in Hb concentration over time (g Hb/wk) for the Normal Hematocrit Study (NHCT; left vertical axis) and the CHOIR study (right vertical access). Adapted from reference (11).

limitations. Some limitations are common to most *post hoc* analyses and are reviewed elsewhere (15). The sample in the Aranesp safety analysis comprised predialysis, hemodialysis, and peritoneal dialysis patients who were variously treated or not treated with ESAs. This heterogeneity could have influenced the results. For example, in hemodialysis patients, major changes in Hb concentration over time are more likely because of fluid removal during dialysis and subsequent fluid accumulation after dialysis, resulting in marked hemoconcentration or hemodilution, respectively. Hb fluxes may vary from patient to patient and from study to study. Because the hemodialysis population has a higher rate of adverse events, there is likely to be an association between Hb fluxes and outcome that is influenced by treatment modality and within the treatment modality by intrinsic patient factors. The more recent analyses by the FDA (11) of the Normal Hematocrit and CHOIR studies present a stronger case for the importance of rate of change in Hb (Figure 1); however, it is unclear whether all of the enrolled patients in the Normal Hematocrit and CHOIR studies were used for the analysis or some patients were excluded. There is also limited information on how missing data were handled. In the FDA analyses of both the CHOIR and Normal Hematocrit studies, rather than using independently adjudicated clinical event data, serious adverse event data were re-coded and used. It is widely accepted that adjudicated end-point data are more reliable and less prone to bias. Adverse event data are at best a crude estimate of risk. Last, in the exploratory FDA analyses of both the Normal Hematocrit and CHOIR studies, no statistical testing was presented and no models that adjusted for confounding factors were included (11).

The importance of confounding factors in influencing the FDA analyses should not be underestimated. In fact, even if

multivariable models had been constructed, the effect of untested confounders cannot be completely eliminated, but at least presenting these models would have provided some insights into the magnitude of confounding. It is possible that an association between rate of change of Hb and adverse clinical events might represent the effect of acute illness or recovery from acute illness or the effect of various comorbidities. The effect of comorbidities on clinical outcome was recently reported by us with respect to the CHOIR study (16). Statistical techniques that might mitigate the effect of confounding (*e.g.*, propensity matching, marginal structural modeling) are now established and should have been considered. Properly designed large randomized trials would be the ideal solution, but none is currently ongoing.

The discussion about rate of increase in Hb in the recent article by Unger *et al.* on behalf of the FDA does not completely describe the relationship between Hb change and outcome. The data demonstrate that there is an association between both negative and positive Hb slopes and adverse outcome but that negative Hb slopes (*i.e.*, rapid decreases in Hb) have a stronger relationship with adverse clinical outcome than positive Hb slopes; therefore, the terms “rate of change in Hb,” “Hb flux,” and “Hb variability” are more appropriate terms than “rate of increase” and “rate of rise.” The effect of intrinsic patient factors, hyporesponsiveness to ESAs however defined, and the potential effect of ESA dosage need to be more robustly incorporated into the analyses. In the FDA reanalysis of the CHOIR and Normal Hematocrit studies, dosage was analyzed but without adjustment for confounding and was separately considered from the analysis of rate of increase of Hb (11). There are now several analyses that suggest an effect of ESA dosage on adverse clinical outcome in the treatment of CKD anemia (17–19). This issue is reviewed more extensively elsewhere (20).

Besides the limitations of these unpublished FDA analyses, even if one considers Hb fluxes or Hb oscillations under the broad heading of Hb variability, a phenomenon that is now well characterized (21,22), the evidence to support an association with outcomes is limited. Although some studies reported an association of Hb variability with increased mortality (23–26), a more recent analysis by Brunelli *et al.* (27), studying a more contemporaneous cohort of hemodialysis patients failed to demonstrate such an association. In the study by Brunelli *et al.* (27), 6644 incident patients between 2004 and 2005 were evaluated. Hb variability was defined for each patient as the residual standard deviation of a linear regression model of time on Hb. No association between Hb variability and all-cause mortality was observed. Furthermore, there was no significant interaction with Hb variability and mortality on the basis of age ($P = 0.22$), arterial disease ($P = 0.45$), Hb slope ($P = 0.68$), or mean Hb ($P = 0.78$).

In summary, the association between the rate of change in Hb and adverse outcome is an exploratory analysis by the FDA and should be considered “hypothesis testing.” Adding a “caution” in the ESA label is of course appropriate absent data from prospective studies or randomized, controlled trials and is in the direction of placing a high priority on patient safety; however, one should not assume that there is a causal relationship

between rate of increase of Hb and adverse outcome. Randomized trials do not lend support to Hb as a valid surrogate marker for clinical outcome, and it is likely that “rate of change of Hb” and “Hb variability” will not be ones either. Incorporating strategies to limit the rate of increase in Hb either in designing clinical trials (as the FDA purported to do with respect to TREAT [2]) or in developing anemia treatment algorithms (2,11) are surely premature. No randomized trial or prospective study has confirmed the FDA analysis and as the Unger article emphasized, these are necessary; however, important and more immediate questions about treating CKD anemia need to be addressed by the FDA: Should patients with CKD continue to receive treatment with ESAs? Which types of patients with CKD should receive ESA? What are the benefits of ESA treatment? Is there a specific Hb threshold for treating individual patients with CKD? What is a safe ESA dosage if an ESA is used? These questions have some answers on the basis of data from TREAT and the other anemia trials that preceded it. These questions should be the focus of the FDA public advisory panel.

Disclosures

A.K.S. was principal investigator of the CHOIR study and a member of the Executive Committee for the TREAT and presented to the FDA Cardiovascular Disease and Renal Advisory Committee in September 2007. A.K.S. also testified to the US Congress Ways and Means Committee in December 2006 and June 2007. He has received consulting fees from Ortho Biotech Clinical Affairs/Johnson & Johnson, Fibrogen, Amgen, and Watson and lecture fees from Ortho Biotech Clinical Affairs/Johnson & Johnson; has served on advisory boards for Ortho Biotech Clinical Affairs, AMAG, and Amgen; and has received grant support from Ortho Biotech Clinical Affairs, Roche, Watson, Johnson & Johnson, AMAG, and Amgen.

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