**Trials and Tribulations:**

**NHT, CHOIR, TREAT, PIVOTAL**

The balance between iron and ESA dose

By Lynda Szczek, MD, practicing nephrologist, Durham, NC

To boldly rote the obvious, trials in anemia have provided surprising, controversial, and dramatic, practice-changing results for the last 20 years. The latest key trial to add to our knowledge on how to treat the anemia of kidney disease is the PIVOTAL trial (1).

The PIVOTAL trial compared higher-dose, proactive IV iron (400 mg monthly) to lower-dose, reactive iron (0 to 400 mg if ferritin <200 μg/L or TSAT <20%) on the risk of the composite endpoint of death, myocardial infarction, stroke, and congestive heart failure. The higher dose proactive arm was found to have a (first) non-inferior association with cardiovascular outcomes of death, myocardial infarction (MI), stroke, and heart failure, and second, a superior effect on that composite. The Hazard Ratio (HR) for the high-dose as compared to the low-dose group was 0.85 (95% CI 0.35 to 1.05; p=0.04). When individual events were compared, it should be noted that the HRs all favored the high-dose group, but the point estimate for both congestive heart failure and MI were numerically lower than the point estimates for the other events in the composite.

To provide maximal benefit in the application of these findings to clinical practice, the potential mechanism for this benefit deserves careful scrutiny. First, the effect of each arm on hemoglobin should be considered. In the high-dose, proactive arm of the PIVOTAL trial, hemoglobin began to rise immediately after randomization. After only 3 months, hemoglobin was 0.6 g/dL higher than baseline. The curves of cumulative ESA dose by treatment arm in the supplemental material began to split immediately after randomization also, with the group in the high-dose, proactive arm receiving cumulatively less ESA. Patients in the lower dose reactive arm also saw a similar rise in hemoglobin. This change, however, occurred at a seemingly slower pace not maximizing until about 24 months of treatment. Multiple studies suggest that a higher hemoglobin target results in a greater risk of cardiovascular events (2, 3, 4). The Normalization of Hematocrit Trial demonstrated that randomizing to a normal target hematocrit of 42% caused a greater risk of MI and death than a hematocrit of 30%. The authors suggest in the discussion that this could be due to the increased IV iron that was required to attempt to achieve the 42% hematocrit because it was clear that higher achieved hemoglobin was associated with better outcomes. This hypothesis was subsequently supported by observational studies that fueled a controversy over the relative safety of IV iron (5). The CHOIR trial was published 8 years later, demonstrating that targeting a hemoglobin of 13.1 g/dL as compared to 11.3 g/dL in CKD patients resulted in a greater risk of death, MI, stroke, and heart failure. The TREAT trial subsequently demonstrated that in a population of patients with diabetes mellitus, targeting a hemoglobin of 13 g/dL as compared to placebo resulted in no significant change in overall cardiovascular risk (good or bad); however, the trial did note an increased risk of stroke when it was examined as a separate endpoint.

Following the relative consistency of outcomes among these trials, secondary analyses of both CHOIR and TREAT were undertaken to attempt to discern the mechanism of the risk identified. These analyses supported the hypothesis that there is a relationship between ESA dose and cardiovascular risk with patients receiving the highest doses at the greatest risk (6, 7, 8).

So it is not unreasonable to hypothesize that the potential benefit seen in the PIVOTAL trial could be at least in part due to the decreased ESA doses that occurred sooner and to a greater extent in the higher proactive iron arm. In these observational trials, higher achieved hemoglobin was associated with better outcomes and the risk of targeting higher hemoglobin seemed to be mediated through higher doses among those patients who failed to respond to ESAs and whose hemoglobin didn’t achieve target.

It is important, however, to consider the implications of the immediate increase in hemoglobin in PIVOTAL. In the high-dose proactive arm, hemoglobin rose and ESA dose was reduced immediately after beginning treatment with similar changes occurring later in the lower dose reactive arm. In that functional iron deficiency has been defined as a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores (9), does the immediate increase in hemoglobin suggest that erythropoiesis was previously limited by iron availability in both arms?

If so, could it be that what was really being tested was quicker iron repletion (or the ability of supplemental iron to overcome functional iron deficiency) as compared to slower iron repletion?

This should be interpreted in the context of studies that assess the effect of iron supplementation on cardiovascular outcomes. Most notably, a trial by Anker et al. randomized patients with congestive heart failure and iron deficiency to receive 200 mg of IV iron (ferric carboxymaltose) versus placebo (10). Patients treated had a greater likelihood of improving their heart failure functional class and had greater improvements in functional outcomes such as the 6-minute walk test. These results suggested that the cardiovascular performance of congestive heart failure patients (even those without a dedicated history of chronic kidney disease) benefited from the presence of adequate and available iron. Interpreting PIVOTAL in the setting of the randomized trial by Anker et al. suggests a potential role for iron repletion/availability of adequate iron in cardiac function. This is an important consideration in the potential mechanism in PIVOTAL.

In that patients who are inflamed are likely to have a functional iron deficiency due to increased levels of hepcidin with the subsequent sequestration of iron in the reticuloendothelial system, the totality of this literature also seems to point to this as a key feature of anemia management that has not been fully investigated. The pieces of the puzzle are different trials of different sizes, treatments, and populations, but they all seem to fit together. They point to the treatment of anemia being far more complex than only increasing hemoglobin. The importance of having iron truly available to the bone marrow, not just adequate levels of TSAT and ferritin, and iron’s relationship to the...
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cardiovascular system should be our next focus if we really want to maximize patient outcomes.

Disclosure: Lynda Szczech, MD, is an employee of FibroGen, Inc., a company developing treatments for anemia.

References:

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