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Identifying Factors Associated with Hyporesponsiveness to Epoetin Alfa: The Anemia in Heart Failure with a Preserved Ejection Fraction Study

Erythropoiesis-Stimulating Agents (ESAs), approved for the treatment of anemia resulting from chronic kidney failure in 1989, have revolutionized the management of anemia and become blockbuster biologic therapies with annual sales in excess of $3 billion. The applications of ESAs to cardiovascular disease have not been as successful. In patients with chronic kidney disease, type 2 diabetes, and anemia, darbepoetin alfa not only failed to reduce the risk of death or a cardiovascular event, but was associated with increased risk of stroke (Pfeffer et al., 2009). An additional study demonstrated that subjects who were poor responders to ESAs (e.g. had a low percent change in hemoglobin levels after two doses) constituted a cohort with higher rates of death and cardiovascular events with ESAs (Solomon et al., 2010). Hypo-responsive subjects were older adult women with obesity, cardiac disease, higher hemoglobin values, higher CRPs and taking aldosterone receptor antagonist. These data, coupled with the findings of higher target hemoglobin being associated with an increased risk of death and MI during therapy with ESAs (Besarab et al., 1998; Singh et al., 2006) have raised concerns about their use in subjects with cardiovascular disease.

Among patients with systolic heart failure, meta-analysis of ESAs has shown improvements in exercise capacity, NYHA class and reductions in hospitalizations (Kotecha et al., 2011). For patients with heart failure with a normal ejection fraction (aka diastolic heart failure), for whom effective therapies remain elusive, a phase II randomized double blind safety/efficacy study was recently completed by our group with support from NIH (NCT00286182) and analysis is ongoing. Unique aspects of these data include: (1) a majority of the recruited subjects have characteristics of ESA hypo-responsiveness and indeed 36% were ESA hypo-responsive, and (2) subjects had measures of blood volume and its components (red cell and plasma volume) at baseline and after 24 weeks of therapy. Previous data has suggested that a hemodilutional anemia is common in subjects with systolic heart failure (Androne et al., 2003). Accordingly, we have a unique opportunity to explore whether ESA hypo-responsiveness is associated with blood volume measures.

In summary, our data suggests that a significant portion of subjects enrolled in the HFNEF anemia trial randomized to receive ESA were in fact hypo-responsive. We now propose to perform a case control study to evaluate for characteristics that differ between older adult subjects with HFNEF who are responsive versus hypo-responsive to ESAs. The hypothesis to be tested is subjects who are unresponsive to ESAs will have significantly higher plasma volumes and lower red cell deficits (characteristics of a hemodilutional anemia) when compared to subjects who are responsive to ESAs.

The proposed research will contribute to an emerging body of literature regarding the proper administration of ESAs. My goal is to advance my understanding of cardiovascular physiology and use such knowledge to practically address the application of ESA administration. Because ESAs are expensive, this work may prompt the development of alternative dosing strategies and provide support for the use of blood volume analysis to facilitate appropriate administration. In doing this work, I will learn

the scientific approach, develop my ability to formulate an appropriate hypothesis, and obtain exposure to important cardiovascular clinical research and analysis. I will garner expertise in the measurement of blood volumes and the analysis of data generated and analyzed with a critical eye toward measurement issues.