

Differences in Blood Volume Components Between Hyporesponders and Responders to Erythropoietin Alfa: The Heart Failure With Preserved Ejection Fraction (HFPEF) Anemia Trial

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ABSTRACT

Background: Hyporesponders to erythropoietin-stimulating agents (ESAs) have been associated with an increased subsequent risk of death or cardiovascular events. We hypothesized that subjects who are hyporesponsive to erythropoietin alfa would have higher plasma volumes and lower red cell deficits than subjects who are responsive to therapy.

Methods: As part of a prospective, single blind, randomized, placebo-controlled study comparing erythropoietin alfa with placebo in older adults ($n = 56$) with heart failure and a preserved ejection fraction (HFPEF), we performed blood volume analysis with the use of an indicator dilution technique with 131 iodine-labeled albumin. We evaluated differences in plasma volumes and red cell volumes in hyporesponders (eg, <1 g/dL increase in hemoglobin within the first 4 weeks of treatment with erythropoietin alfa) compared with subjects who were responders and controls.

Results: Nine of 28 subjects (32%) assigned to ESA were hyporesponders. Hyporesponders did not differ from responders nor control subjects by any baseline demographic, clinical, or laboratory parameter, including hemoglobin. Hyporesponders had a greater total blood volume expansion ($1,264.7 \pm 387$ vs 229 ± 206 mL; $P = .02$) but less of a red cell deficit (-96.2 ± 126 vs -402.5 ± 80.6 mL; $P = .04$) and a greater plasma volume expansion ($+1,360.8 \pm 264.5$ vs $+601.1 \pm 165.5$ mL; $P = .01$). Among responders, the increase in hemoglobin with erythropoietin alfa was associated primarily with increases in red cell volume ($r = 0.91$; $P < .0001$) as well as a decline in plasma volume ($r = -0.55$; $P = .06$).

Conclusions: Among older adults with HFPEF and anemia, hyporesponders to erythropoietin alfa had a hemodilutional basis of their anemia, suggesting that blood volume analysis can identify a cohort likely to respond to therapy. (*J Cardiac Fail* 2013;19:685–691)

Key Words: Anemia, erythropoietin alfa, heart failure, blood volume.

Erythropoietin-stimulating agents (ESAs) are approved for treatment of patients with significant anemia and chronic kidney disease with or without dialysis. More

recently, studies have documented that anemia is highly prevalent in patients with heart failure, strongly associated with morbidity and mortality, and often due to underlying chronic renal disease.¹ Accordingly, clinical trials have evaluated the use of ESAs in patients with heart failure.^{2–12}

Results from the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) demonstrated that administering an ESA (darbepoetin alfa) to achieve target hemoglobin of 13 g/dL was associated with an elevated risk of stroke and resulted in an issuance of a package insert for all ESA products.¹³ Subsequent analyses of these data identified that hyporesponders to darbepoetin alfa, defined as patients in the treatment group in the lowest quartile of change in hemoglobin level ($<2\%$ change), who had a median reduction in hemoglobin levels of 0.2 g/dL after the first 4 weeks of therapy, experienced an increased rate of

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death and cardiovascular events with ESA therapy.¹⁴ These data coupled with recently reported negative outcomes for patients with systolic heart failure treated with darbepoetin alfa in the Reduction of Events With Darbepoetin Alfa in Heart Failure (RED-HF) trial¹⁵ have dampened the interest in ESAs for use among patients with heart failure.^{2–12} Identifying the cohort of subjects who are hyporesponders to ESAs and may be at increased risk for adverse outcomes with their use may be essential for appropriately applying these therapies.

A significant percentage of the subjects with heart failure who are anemic have a hemodilutional basis of their anemia¹⁶ which can be identified by blood volume analysis.¹⁷ We analyzed data from a recently completed randomized clinical trial of erythropoietin alfa in older adult subjects with heart failure and a preserved ejection fraction¹² to determine if hemodilutional anemia is associated with an inadequate response to ESA. The hypothesis was that blood volume analysis would reveal significant differences in blood volume components (eg, higher plasma volume and lower red cell deficit differences) in subjects who are hyporesponsive to EPO compared with subjects who are responsive to EPO and control subjects.

Methods

Study Design

This is a retrospective analysis of a recently completed prospective, single blind, randomized, placebo-controlled, 24-week, phase 2 study that used blinded end point analysis. The details of the study and its primary results have been reported.¹² In brief, 56 eligible patients were randomly assigned in a 1:1 ratio to receive erythropoietin alfa (starting dose 7,500 units) or placebo administered subcutaneously every week with a prespecified dosing algorithm for a total of 24 weeks.¹⁸ In this analysis, we evaluated the number of subjects who were hyporesponders to erythropoietin therapy (as defined below) and compared the demographic/clinical characteristics and blood volume analysis of hyporesponders with those of responders and control subjects to determine if differences exist.

Blood Volume Analysis

Blood volume was calculated by standard indicator dilution technique. After intravenous administration of ¹³¹I-iodine-labeled albumin (Volumex; Daxor Corp, New York, New York) and sufficient time for circulation and equilibration (ie, 12 minutes), venous samples from at least 3 of 5 samples drawn at 6-minute intervals (ie, 12, 18, 24, 30, and 36 minutes after injection) were obtained. Each sample was centrifuged and pipetted to obtain 2 measures of spun hematocrit on each specimen and 2 1,000- μ L samples of plasma. Plasma radioactivity of each sample was measured in a semiautomated counter (BVA-100 Blood Volume Analyzer; Daxor Corp, New York, New York) and plasma volume was determined as the zero-time volume of distribution of the radiolabeled albumin with the use of semilogarithmical techniques.¹⁹ Blood volume and red blood cell volumes were calculated from the plasma volume measurement and compared with ideal values for age, sex, height, and weight based on the patient's ideal weight.¹⁶ To evaluate the true hematocrit, controlling for plasma

volume expansion, we calculated the normalized hematocrit as the peripheral hematocrit multiplied by the ratio of total blood volume to ideal blood volume.

Statistical Analyses

Results are expressed as mean $\pm$ standard deviation unless otherwise noted. We defined responders as those who were randomized to receive erythropoietin alfa and who had a rate of hemoglobin rise ≥ 1 g/dL within the first 4 weeks of treatment, whereas hyporesponders also were randomized to receive erythropoietin alfa but had a change in hemoglobin of < 1 g/dL within the first 4 weeks of treatment. These 2 cohorts were compared with control subjects who received saline injections during the course of trial. We compared the clinical, demographic, laboratory, and echocardiographic characteristics of the 3 cohorts to identify any clinical characteristics that might differ among the cohorts and thus facilitate identification of nonresponders at baseline. The primary focus was on blood volume measures. Differences between cohorts were evaluated with a chi-square with Fisher exact test for dichotomous variables and Wilcoxon rank test for continuous variables given the nonnormal distribution of the data. Additionally, we evaluated changes in blood volume components from baseline to 24 weeks of therapy among responders, hyporesponders, and control subjects. Finally, to determine the underlying mechanism of observed increases in hemoglobin with erythropoietin alfa therapy, we correlated changes in hemoglobin with changes in blood volume components (eg, plasma volume and red cell volume). SAS for Windows (version 8.0; SAS Institute Inc, Cary, North Carolina) was used for all analyses.

Results

Of the 56 people enrolled in the trial, most were older adults (mean 77 years of age), women (68%), and with comorbidities common in HFPEF (ie, hypertension, obesity, coronary artery disease, and chronic renal disease). Based on the definition of hyporesponsiveness to erythropoietin alfa administration (ie, change in hemoglobin of < 1 g/dL within the first 4 weeks of treatment), 33% of patients in the treatment group were nonresponders. The changes in hemoglobin values during the course of the trial were significantly different in responders compared with hyporesponders and control subjects (Fig. 1).

Hyporesponders did not differ significantly from responders to erythropoietin alfa therapy in any demographic, clinical, laboratory, or echocardiographic characteristics (Table 1). Notably, hyporesponders tended to be younger than responders ($P = .06$) and to have larger body surface areas ($P = .07$). The type of diuretics employed, their dose, and the number of changes in dose during the course of the trial did not differ between responders and nonresponders. However, there were significant differences in blood volume components at baseline between hyporesponders and responders/controls (Table 2). Specifically, total blood volume of hyporesponders was significantly higher than responders and controls ($P = .03$), both in absolute terms and when indexed for body size ($P = .02$). The excess blood volume in hyporesponders was attributable to the

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