

Treatment of Anemia in Patients with Chronic Heart Failure

STUART D. KATZ, MD,¹ DONNA MANCINI, MD,² ANA SILVIA ANDRONE, MD,¹ AND KATARZYNA HRYNIEWICZ, MD¹

New Haven, Connecticut; New York, New York

ABSTRACT

Anemia occurs frequently in chronic heart failure (CHF) patients and is associated with increased morbidity and mortality risk. Clinical trials with recombinant human erythropoietin in patients with chronic kidney disease and concomitant structural heart disease have demonstrated beneficial effects on ventricular remodeling but variable effects on clinical outcome. Preliminary clinical trials in patients with CHF demonstrate that erythropoietin therapy is well-tolerated and associated with short-term clinical benefits. The optimum target hemoglobin, erythropoietin dosing regimen, and role of iron supplementation in patients with CHF are not known. Darbepoetin alfa is a glycosylated derivative of erythropoietin with a prolonged half-life that may allow less frequent dosing in CHF populations. Additional studies are needed to determine the safety and efficacy of long-term erythropoietic therapy in CHF patients.

Key Words: Erythropoietin, heart failure, blood volume, exercise, vascular resistance.

Anemia is common in patients with chronic heart failure (CHF) and is independently associated with increased mortality risk (see review in this supplement). This report will review the results of clinical trials of erythropoietic therapy in patients with CHF with and without concomitant chronic kidney disease (CKD).

Erythropoietin Pharmacology

Current knowledge of the clinical pharmacology of recombinant human erythropoietin (rHuEpo) as a therapeutic agent for correction of anemia is largely derived from studies in patients with CKD. The recombinant therapeutic agent was first synthesized in 1985, only 2 years after the erythropoietin gene was cloned, and was approved for clinical use in 1988.¹ Initial studies in end-stage CKD populations indicated that a dose of 150–200 U·kg⁻¹·wk⁻¹ (administered via intravenous or subcutaneous routes in 1 to 3 divided doses per week) was sufficient to increase hemoglobin levels to between 10 and 12 g/dL in 83% to 90% of patients.^{1–4} Plasma half life after intravenous dosing is 6 to 8 hours.^{1,5} Administration of rHuEpo increases red blood cell mass by inhibition of apoptosis of erythroid precursors in the bone marrow with

subsequent increased proliferation and differentiation of erythroid cells.^{1,6} The action of erythropoietin is mediated by specific receptors expressed on bone marrow erythroid precursors that are coupled to cytoplasmic and nuclear events via activation of the JAK2/STAT5 signal transduction pathways.⁷ Erythropoietin may have physiologic and pharmacologic effects beyond stimulation of red blood cell production; erythropoietin receptors have been detected in many tissues including heart, vascular endothelium, retina, and brain.^{8,9} Laboratory studies and preliminary human studies indicate that stimulation of erythropoietin receptors inhibits apoptosis and may be cytoprotective in settings of ischemic or hypoxic tissue injury.^{9–11}

rHuEpo Treatment Trials in Patients With CKD and Concomitant Heart Disease

The use of rHuEpo in the treatment of chronic anemia was first applied on a large scale in patients with anemia resulting from end-stage CKD.^{1–4} In anemic patients with end-stage renal disease on dialysis, erythropoietin therapy has been associated with regression of left ventricular hypertrophy and reduction in left ventricular end-diastolic volume.^{12–14} Comparable beneficial effects of erythropoietin therapy on cardiac remodeling have also been demonstrated in predialysis anemic patients with CKD and concomitant structural heart disease.^{15,16}

Despite 15 years of clinical experience, the optimal hemoglobin target in CKD populations has not been well-established. In a multicenter, randomized, open-label trial of erythropoietin therapy in 1233 end-stage CKD patients on

From ¹Department of Internal Medicine, Yale University College of Medicine, New Haven, CT, and ²Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY.

Reprint requests: Stuart D. Katz, MD, Yale University School of Medicine, 135 College Street, Suite 301, New Haven, CT 06510.

1071-9164/\$ - see front matter

© 2004 Elsevier Inc. All rights reserved.

doi:10.1016/j.cardfail.2004.01.002

chronic hemodialysis with concomitant history of cardiac disease (heart failure or coronary artery disease), raising hematocrit to a the normal range (target hematocrit 42%) was associated with a trend toward increased risk of death or nonfatal myocardial infarction (relative risk 1.3, 95% confidence interval 0.9–1.9) when compared with raising hematocrit to a subnormal range (target hematocrit 30%).¹⁷ However, within each treatment group, increasing hematocrit was associated with decreased mortality. Although nearly half of the patients had a history of CHF, normalization of hematocrit in that subset of patients was not associated with increased risk of hospitalization for heart failure or risk of death from heart failure when compared with the lower hemoglobin target group.

Subsequent smaller clinical trials of hemoglobin normalization in less severely ill patients with CKD have not corroborated the findings of the trial by Besarab and colleagues. In a randomized clinical trial of 146 patients with end-stage renal disease and concomitant left ventricular hypertrophy or left ventricular dilation, erythropoietin therapy adjusted to achieve a target hemoglobin of 13.5 g/dL was associated with improved quality of life and reduced fatigue without evidence of increased risk of adverse events or death when compared with a target hemoglobin of 10 g/dL.¹⁸ In another randomized trial of 416 patients with CKD (majority on dialysis) and a high prevalence of concomitant heart disease (38% ischemic heart disease or heart failure), erythropoietin therapy adjusted to achieve a normal hemoglobin level (13.5–15.0 g/dL in women, 14.5–16.0 g/dL in men) was associated with improved quality of life when compared with erythropoietin adjusted to hemoglobin level of 9.0 to 12.0 g/dL with no difference in mortality between the 2 groups during follow-up of approximately 1 year (13.4% versus 13.5%, $P = .98$).¹⁹

Silverberg and colleagues have reported a large nonrandomized clinical series of erythropoietic therapy in 179 patients with severe CHF, mild to moderate CKD (predialysis with mean serum creatinine 2.1–2.4 mg/dL) and coexisting anemia (hemoglobin 9.5–11.5 g/dL).²⁰ Nearly half of these patients also had type II diabetes mellitus. Patients received treatment with subcutaneous erythropoietin 4000 to 10,000 U/wk and intravenous iron sucrose 400 to 800 mg/mo (adjusted to achieve serum ferritin 500 μ g/L) with target hemoglobin of 12.5 g/dL over a mean duration of follow-up of 1 year. Hemoglobin increased significantly from baseline in both diabetic and nondiabetic subjects by a mean of 2.0 to 2.2 g/dL during follow-up. Erythropoietic therapy was associated with clinical improvements in both diabetic and nondiabetic subjects as evidence by increased functional capacity (New York Heart Association [NYHA] 3.89 ± 0.24 to 2.53 ± 0.42 in diabetics and 3.91 ± 0.24 to 2.55 ± 0.48 in nondiabetics, both $P < .05$ versus baseline), improved left ventricular ejection fraction ($34.8 \pm 13.5\%$ to $39.8 \pm 8.0\%$ in diabetics and $35.0 \pm 15.5\%$ to $37.6 \pm 11.7\%$ in nondiabetics, both $P < .05$ versus baseline), reduced hospitalizations, and evidence of slowing of progression of renal disease. One-year mortality rate in the study population with

severe CHF was a surprisingly low 10.1%. The lack of a suitable control group limits interpretation of these findings, but this report is consistent with previous randomized studies in predialysis CKD patients and suggests that erythropoietic therapy should be considered as a possible treatment option for the population of anemic patients with coexisting CHF and mild to moderate CKD.

rHuEpo Treatment Trials in CHF

Initial experience of recombinant human erythropoietin therapy in patients with CHF was reported by Silverberg and colleagues in 2 sequential studies.^{21,22} In an open-label, nonrandomized study design, 26 patients with NYHA class III-IV CHF and hemoglobin <12 g/dL were treated with subcutaneous rHuEpo (mean dose 5277 U/wk) and intravenous iron sucrose (mean dose 185 mg/mo) adjusted to achieve a target hemoglobin of 12 m/dL over a mean follow-up duration of 7 months. The mean hemoglobin increased from 10.2 to 12.1 g/dL. Erythropoietin therapy was associated with improved function class (3.66 ± 0.47 at baseline to 2.66 ± 0.70 , $P < .05$), increased left ventricular ejection fraction ($27.7 \pm 4.8\%$ at baseline to $35.4 \pm 7.6\%$, $P < .001$), and reduced need for oral and intravenous furosemide.²¹ After completion of this pilot trial, the same group of investigators performed a randomized open-label trial to compare the effects of partial correction of anemia with subcutaneous rHuEpo and intravenous iron sucrose therapy versus usual care in 32 patients with NYHA class III-IV CHF and hemoglobin <11.5 g/dL.²² Patients randomized to erythropoietic therapy received subcutaneous rHuEpo (4000 U 1–3 times weekly) and intravenous iron sucrose (200 mg every 2 weeks) adjusted to achieve a target hemoglobin of 12.5 g/dL over a mean follow-up duration of 8 months. Hemoglobin significantly increased in response to rHuEpo therapy when compared with usual care (10.3 to 12.9 g/dL versus 10.9 to 10.8 g/dL, $P < .0001$). Erythropoietin therapy improved functional class (3.8 ± 0.4 to 2.2 ± 0.7 active treatment versus 3.5 ± 0.7 to 3.9 ± 0.3 usual care, $P < .0001$) and decreased days in hospital (13.8 ± 7.2 to 2.9 ± 6.6 days active treatment versus 9.9 ± 4.8 to 15.5 ± 9.8 days usual care, $P < .0001$).

Based on the promising findings of these pilot trials, Mancini and colleagues conducted a single-blind, randomized, placebo-controlled trial of erythropoietin therapy in 26 patients with advanced CHF, hematocrit $<35\%$, and serum creatinine <2.5 mg/dL.²³ Patients received subcutaneous rHuEpo 5000 3 times weekly adjusted to raise hematocrit to $>45\%$ for 3 months or a single subcutaneous injection of saline (2:1 randomization ratio). Patients treated with erythropoietin also received oral iron supplementation 325 mg daily and supplemental folate 1 mg daily. Erythropoietin therapy was associated with significant increases in hemoglobin (11.0 ± 0.5 to 14.3 ± 1.0 g/dL, $P < .05$), peak oxygen uptake (11.0 ± 1.8 to 12.7 ± 2.8 mL \cdot min $^{-1}\cdot$ kg $^{-1}$, $P < .05$), and exercise duration (590 ± 107 to 657 ± 119

seconds, $P < .004$) when compared with the placebo group. The increase in hemoglobin levels was significantly associated with the increase in peak oxygen uptake ($r = .53$, $P < .02$). In a subgroup of 15 patients (9 erythropoietin-treated and 6 placebo-treated), blood volume analysis was performed with injection of ^{131}I -albumin. Hemodilution (expanded plasma volume with normal red blood cell volume) was identified as the cause of anemia in 4 of the 9 patients receiving erythropoietin therapy. In these patients, erythropoietin therapy was associated with increased red blood cell volume and substantial compensatory reduction in plasma volume with no net change in total blood volume. The observed reduction in plasma volume occurred without change in diuretic use and is consistent with the previous report of reduced diuretic requirements during rHuEpo therapy by Silverberg and colleagues.

Erythropoietin Resistance

Three of the 15 patients in the study by Mancini and colleagues randomized to erythropoietin therapy did not respond to the initial dose of erythropoietin injections but did manifest a rise in hemoglobin when the dose was increased to 10,000 U 3 times weekly. Poor responsiveness to the usual therapeutic doses of rHuEpo occurs in approximately 10% of patients with CKD and is most often attributable to iron deficiency, underdialysis, or concomitant inflammatory conditions.²⁴ Patients with end-stage renal disease on hemodialysis often have iron deficiency from chronic blood loss and intravenous iron supplements are routinely used to promote erythropoiesis in this setting.^{1,2,6} In predialysis patients with CKD, parenteral iron may not be necessary during rHuEpo therapy.²⁵ Resistance to erythropoietin therapy has also been reported in 40% to 50% of patients with cancer-associated anemia.²⁶ The incidence of erythropoietin resistance and the role of adjunct intravenous iron supplementation in anemic CHF patients remains to be determined.

Clinical Trials of Darbepoetin Alfa in CKD

Darbepoetin alfa is a long-acting N-linked glycosylated derivative of erythropoietin that has been used in the treatment of anemia in patients with chronic renal disease.²⁷ Despite the change in structure from the native erythropoietin glycoprotein, darbepoetin alfa retains strong affinity for erythropoietin receptors. Because of its long half-life (48 hours), darbepoetin alfa may be administered subcutaneously at intervals of 1 to 2 weeks during maintenance therapy.²⁷ In 122 anemic patients with end-stage CKD not previously treated with erythropoietin, once-weekly darbepoetin alfa administered at a dose of 0.45 to 0.75 $\mu\text{g}/\text{kg}$ intravenously or subcutaneously raised hemoglobin 1 g/dL in 60% to 80% of patients within 4 weeks.²⁸ In an open-label study of 341 patients with end-stage renal disease chronically treated with rHuEpo, darbepoetin alfa was substituted at a regimen based on the frequency and number of units of

rHuEpo dosing (200 U rHuEpo = 1 μg darbepoetin alfa, patients with 2–3 times weekly rHuEpo dosing received darbepoetin alfa once weekly and patients with once-weekly rHuEpo dosing received darbepoetin alfa once every other week).²⁹ The route of administration of rHuEpo (subcutaneous or intravenous) was maintained for darbepoetin alfa administration. There were no clinically important changes from baseline hemoglobin after 24 weeks of follow-up, although the intravenous darbepoetin alfa was associated with a statistically significant increase of hemoglobin of 0.58 g/dL ($P < .05$ versus baseline).

Conclusions

Preliminary studies indicate that erythropoietin therapy is well-tolerated and associated with short-term clinical benefit in patient with CHF. The optimal target hematocrit, erythropoietin dosing regimen, and iron supplementation regimen for anemic patients with CHF remain to be determined. Based on currently approved indications and the results from studies in CKD populations, some CHF patients with relatively severe anemia (Hgb levels < 11 g/dL) and concomitant moderate to severe CKD could be considered as potential candidates for erythropoietic therapy.

References

1. Winearls CG. Recombinant human erythropoietin: 10 years of clinical experience. *Nephrol Dial Transplant* 1998;13(Suppl 2):3–8.
2. Erslev AJ. Erythropoietin. *N Engl J Med* 1991;324:1339–44.
3. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73–8.
4. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. *Ann Intern Med* 1989;111:992–1000.
5. McMahon FG, Vargas R, Ryan M, Jain AK, Abels RI, Perry B, et al. Pharmacokinetics and effects of recombinant human erythropoietin after intravenous and subcutaneous injections in healthy volunteers. *Blood* 1990;76:1718–22.
6. Macdougall IC. Meeting the challenges of a new millennium: optimizing the use of recombinant human erythropoietin. *Nephrol Dial Transplant* 1998;13(Suppl 2):23–7.
7. Leyland-Jones B. Evidence for erythropoietin as a molecular targeting agent. *Semin Oncol* 2002;29:145–54.
8. Magnanti M, Gandini O, Giuliani L, Gazzaniga P, Marti HH, Gradilone A, et al. Erythropoietin expression in primary rat Sertoli and peritubular myoid cells. *Blood* 2001;98:2872–4.
9. Sterin-Borda L, Barcelo AC, Bozzini CE. Erythropoietin improves cardiac contractility in post-hypoxic mice. *Br J Haematol* 2003;121:180–6.
10. Ehrenreich H, Hasselblatt M, Dembowski C, Cepek L, Lewczuk P, Stiefel M, et al. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med* 2002;8:495–505.
11. Becerra SP, Amaral J. Erythropoietin—an endogenous retinal survival factor. *N Engl J Med* 2002;347:1968–70.
12. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients

- treated with recombinant human erythropoietin. *Am Heart J* 1992; 124:424-7.
13. London GM, Zins B, Pannier B, Naret C, Berthelot JM, Jacquot C, et al. Vascular changes in hemodialysis patients in response to recombinant human erythropoietin. *Kidney Int* 1989;36:878-82.
 14. Levin A. Anemia and left ventricular hypertrophy in chronic kidney disease populations: a review of the current state of knowledge. *Kidney Int* 2002;61(Suppl 80):35-8.
 15. Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in pre-dialysis patients. *Am J Kidney Dis* 1997;29:541-8.
 16. Hayashi T, Suzuki A, Shoji T, Togawa M, Okada N, Tsubakihara Y, et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 2000;35:250-6.
 17. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-90.
 18. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000;58:1325-35.
 19. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 2003;18:353-61.
 20. Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. *Nephrol Dial Transplant* 2003;18:141-6.
 21. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737-44.
 22. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001; 37:1775-80.
 23. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. The effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;107:294-9.
 24. Macdougall IC, Cooper AC. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 2002;17(Suppl 11):39-43.
 25. Trivedi HS, Brooks BJ. Erythropoietin therapy in pre-dialysis patients with chronic renal failure: lack of need for parenteral iron. *Am J Nephrol* 2003;23:78-85.
 26. Beguin Y. Prediction of response and other improvements on the limitations of recombinant human erythropoietin therapy in anemic cancer patients. *Haematologica* 2002;87:1209-21.
 27. Macdougall IC. Darbepoetin alfa: a new therapeutic agent for renal anemia. *Kidney Int Suppl* 2002:55-61.
 28. Macdougall IC, Matcham J, Gray SJ. Correction of anaemia with darbepoetin alfa in patients with chronic kidney disease receiving dialysis. *Nephrol Dial Transplant* 2003;18:576-81.
 29. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). *Nephrol Dial Transplant* 2003;18:362-9.