AJKD
Original Investigation

A Randomized, Placebo-Controlled Trial of Pentoxifylline on Erythropoiesis-Stimulating Agent Hyporesponsiveness in Anemic Patients With CKD: The Handling Erythropoietin Resistance With Oxpentifylline (HERO) Trial

David W. Johnson, MBBS, DMed (Res), PhD,[1,2,3] Elaine M. Pascoe, BSc, MBiostat,[1] Sunil V. Badve, MBBS, MD,[1,2] Kim Dalziel, BHealthSc, MHealthEcon, PhD,[4] Alan Cass, MBBS, PhD,[1,5] Philip Clarke, BEc, MEc, PhD,[4] Paolo Ferrari, MD,[1,6] Stephen P. McDonald, MBBS, PhD,[1,7] Alicia T. Morrish, BSc, MPH,[1] Eugenie Pedagogos, MBBS, PhD,[1,8] Vlado Perkovic, MBBS, PhD,[1,9] Donna Reidlinger, BA, BAppSc, MPH,[1] Anish Scaria, BSc, MSc,[1] Rowan Walker, MD, MPH,[1,10] Liza A. Vergara, MSc, PhD,[1] and Carmel M. Hawley, MBBS, MMedSci,[1,2] on behalf of the HERO Study Collaborative Group*

Background: Erythropoiesis-stimulating agent (ESA)-hyporesponsive anemia is common in chronic kidney disease (CKD). Pentoxifylline shows promise as a treatment for ESA-hyporesponsive anemia, but has not been rigorously evaluated.

Study Design: Multicenter, double-blind, randomized, controlled trial.

Setting & Participants: 53 adult patients with CKD stage 4 or 5 (including dialysis) and ESA-hyporesponsive anemia (hemoglobin ≤ 120 g/L and ESA resistance index [calculated as weight-adjusted weekly ESA dose in IU/kg/wk divided by hemoglobin concentration in g/L] ≥ 1.0 IU/kg/wk/g/L for erythropoietin-treated patients and ≥0.005 μg/kg/wk/g/L for darbepoetin-treated patients).

Interventions: Pentoxifylline (400 mg/d; n = 26) or matching placebo (control; n = 27) for 4 months.

Outcomes: Primary outcome: ESA resistance index at 4 months; secondary outcomes: hemoglobin concentration, ESA dose, blood transfusion requirement, serum ferritin level and transferrin saturation, C-reactive protein level, adverse events, quality of life, and health economics.

Results: There was no statistically significant difference in ESA resistance index between the pentoxifylline and control groups (adjusted mean difference, −0.39 [95% CI, −0.89 to 0.10] IU/kg/wk/g/L; $P = 0.1$). Pentoxifylline significantly increased hemoglobin concentration relative to the control group (adjusted mean difference, 7.6 [95% CI, 1.7-13.5] g/L; $P = 0.01$). There was no difference in ESA dose between groups (−20.8 [95% CI, −67.2 to 25.7] IU/kg/wk; $P = 0.4$). No differences in blood transfusion requirements, adverse events, or quality of life were observed between groups. Pentoxifylline cost A$88.05 (US $82.94) per person over the trial and produced mean savings in ESA cost of A$1,332 (US $1,255). The overall economic impact over the trial period was a saving of A$1,244 (US $1,172) per person for the pentoxifylline group compared with controls.

Limitations: Sample size smaller than planned due to slow recruitment.

Conclusions: Pentoxifylline did not significantly modify ESA hyporesponsiveness, but increased hemoglobin concentration. Further studies are warranted to determine whether pentoxifylline therapy represents a safe strategy for increasing hemoglobin levels in patients with CKD with ESA-hyporesponsive anemia.

Am J Kidney Dis. 65(1):49-57.

INDEX WORDS: Anemia; chronic kidney disease (CKD); darbepoetin; drug sensitivity; epoetin; erythropoiesis-stimulating agent (ESA); ESA hyporesponsiveness; ESA resistance index (ERI); erythropoietin; pentoxifylline; hemoglobin; dialysis; randomized controlled trial.

From the [1]Australasian Kidney Trials Network, University of Queensland; [2]Department of Nephrology, Princess Alexandra Hospital; [3]Translational Research Institute, Brisbane; [4]Center for Health Policy, Programs & Economics, University of Melbourne, Melbourne; [5]Menzies School of Health Research, Darwin; [6]Department of Renal Medicine, Fremantle Hospital, Fremantle; [7]Department of Nephrology and Transplantation Services, University of Adelaide at Central Northern Adelaide Renal and Transplantation Services, Adelaide; [8]Department of Nephrology, Royal Melbourne Hospital, Melbourne; [9]George Institute, Sydney; and [10]Department of Renal Medicine, The Alfred Hospital, Melbourne, Australia.

[*]A list of the collaborators in the HERO Study Collaborative Group appears in the Acknowledgements.

Received February 17, 2014. Accepted in revised form June 9, 2014. Originally published online August 9, 2014. Supplementary Table S1 corrected online September 23, 2014. See Table S1 in "Supplementary Material" online for an explanation of the corrections.

Trial registration: www.anzctr.org.au; study number: 12608000199314.

Address correspondence to David W. Johnson, MBBS, DMed (Res), PhD, Department of Nephrology, Level 2, ARTS Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane Qld 4102, Australia. E-mail: david.johnson2@health.qld.gov.au

0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2014.06.020

Anemia, defined as hemoglobin (Hb) concentration < 120 g/L, is a common complication of chronic kidney disease (CKD) and has been reported to occur in more than half of all patients with stage 4 disease (estimated glomerular filtration rate [eGFR], 15-29 mL/min/1.73 m^2) and three-quarters of those with stage 5 disease (eGFR < 15 mL/min/1.73 m^2).[1] Although the cause is multifactorial, deficient renal production of erythropoietin is a major factor that can be treated effectively by administration of erythropoiesis-stimulating agents (ESAs), including recombinant human erythropoietin and darbepoetin alfa. Unfortunately, some patients with CKD exhibit ESA hyporesponsiveness necessitating a high ESA dose, often with a persistently suboptimal hematologic response.[2] Such patients have been shown to be at increased risk of hospitalization, cardiovascular events, and mortality.[3-6] Strategies for reducing ESA hyporesponsiveness include using iron supplementation and excluding treatable causes of anemia, such as infection, malignancy, severe hyperparathyroidism, aluminum overload, vitamin B_{12} deficiency, folate deficiency, inadequate dialysis, myelosuppressive agents, myelodysplasia, and antibody-mediated pure red cell aplasia.[2] However, despite implementation of these strategies, a proportion of patients with CKD remain hyporesponsive to ESAs, possibly related to inhibition of erythropoiesis by elevated levels of inflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ).[7]

A recent systematic review of interventions for ESA-hyporesponsive anemia in patients with CKD was not able to identify a consistently effective therapy and recommended further randomized controlled trials of novel therapeutic treatments in this area.[8] One such promising agent is pentoxifylline, a medication commonly used for treatment of peripheral vascular disease that has shown important anti-inflammatory properties, including antiapoptotic, antioxidant, anti–IL-6, anti–TNF-α, and anti–IFN-γ actions.[9] Seemingly mediated by inhibition of phosphodiesterase, these actions may in turn decrease hepcidin production, leading to increased iron release from bone marrow macrophages and improved availability of iron for erythropoiesis.[10-15] Four small prospective nonrandomized studies have shown that pentoxifylline might significantly improve hemoglobin concentrations in patients with CKD who have ESA-hyporesponsive anemia.[16-19] However, adequate controls were lacking, and the associated potential for selection, observer, and co-intervention biases further limited these studies.

The primary objective of this multicenter randomized controlled trial was to determine whether, compared with placebo, pentoxifylline resulted in a reduction in ESA resistance index in patients with advanced CKD and ESA-hyporesponsive anemia.

METHODS

Study Oversight

The protocol of the Handling Erythropoietin Resistance With Oxpentifylline (HERO) trial has been published previously.[20] The study was approved by ethics committees at all participating centers. All patients provided written informed consent prior to trial participation, and the trial was conducted in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice Guidelines.

The study was designed and supervised by the authors (who made up the Trial Management Committee) and coordinated by the Australasian Kidney Trials Network at the University of Queensland, Brisbane, Australia. Serious adverse events, measures of study conduct, and implementation by treatment group were monitored regularly by an independent Data and Safety Monitoring Board. Only Data and Safety Monitoring Board members and statisticians compiling closed-session reports for board meetings had access to unblinded interim data and results. Due to the short observation period and relatively small number of participants, no interim efficacy analyses were planned or conducted.

Study Population

The trial included adult patients with CKD stages 4 or 5 (receiving dialysis treatment or having eGFR < 30 mL/min/1.73 m^2) and ESA-hyporesponsive anemia on a stable dose of either erythropoietin or darbepoetin for at least 8 weeks. In the original study protocol, ESA-hyporesponsive anemia was defined as Hb concentration ≤ 110 g/L for at least 3 months despite erythropoietin dose ≥ 200 IU/kg/wk or darbepoetin dose ≥ 1 μg/kg/wk for at least 1 month.[20] In March 2010, due to slow recruitment and a large number of screen failures, the definition of ESA-hyporesponsive anemia was revised to Hb concentration ≤ 120 g/L and ESA resistance index (calculated as the weight-adjusted weekly ESA dose divided by hemoglobin concentration) ≥ 2 IU/kg/wk/g/L for erythropoietin-treated patients and ≥0.01 μg/kg/wk/g/L for darbepoetin-treated patients. Due to slow recruitment, the definition of ESA-hyporesponsive anemia was amended further in February 2011 to Hb concentration criterion ≤ 120 g/L and ESA resistance index ≥ 1 IU/kg/wk/g/L for erythropoietin-treated patients and ≥0.005 μg/kg/wk/g/L for darbepoetin-treated patients.

The exclusion criteria have been reported previously and are presented in Item S1 (provided as online supplementary material).[20] Briefly, individuals were excluded from the trial if they had a condition that interfered with their ability to understand or comply with the requirements of the study, a contraindication to pentoxifylline, an identifiable treatable cause of ESA hyporesponsiveness, or recent treatment for anemia (other than ESA and iron supplementation).

Randomization and Study Intervention

Participants were randomly assigned in a 1:1 ratio by an adaptive allocation algorithm designed to minimize imbalance in treatment groups across 3 variables: study site, CKD stage (4 or 5), and ESA class (epoetin alfa/beta or darbepoetin) using a password-protected web-based system. ESA class was added to the adaptive algorithm after a protocol amendment; 16 participants were randomly assigned prior to this amendment. Participants, treating physicians, and outcome assessors were blinded to ensure adequate concealment of allocation.

Participants in the experimental arm received pentoxifylline (Trental; Sanofi-Aventis), 400 mg, daily orally, whereas those in the control arm received identical matching placebo. Iron supplementation was performed according to local unit protocols. Vitamin B, folic acid, and vitamin C supplementation were permitted, provided daily doses were kept constant throughout the study period. Melatonin and androgen therapy were prohibited.

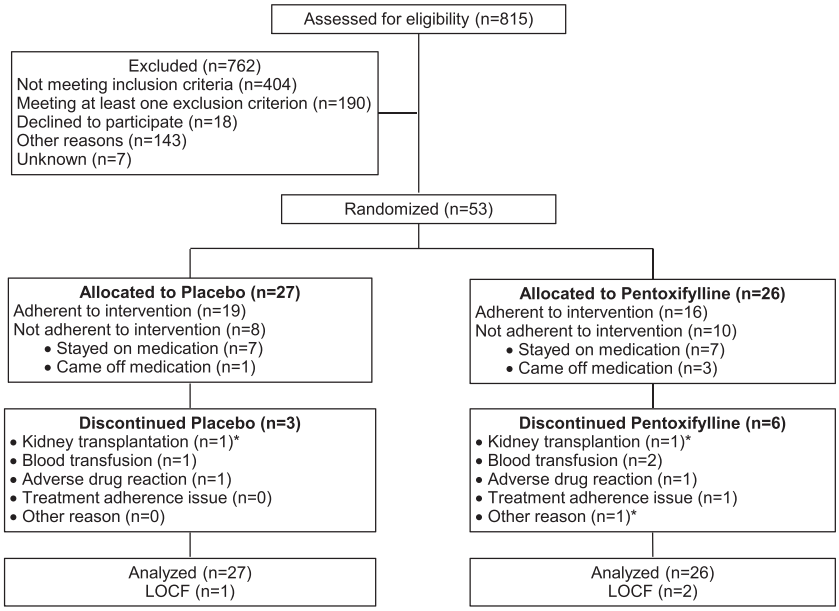

Figure 1. Flow chart of patient progression through the trial. Abbreviation: LOCF, last observation carried forward. *Discontinued follow-up.

Erythropoietin and darbepoetin doses were not increased during the study and were decreased only if Hb concentration was >120 g/L or the rate of Hb level increase was >10 g/L per month. Blood transfusion was allowed at the treating physician's discretion. Study medication adherence was assessed at each study visit by counting the number of pills returned.

Follow-up and Study End Points

The follow-up period was 4 months unless a participant experienced Hb concentration < 65 g/L or required a blood transfusion.

The primary efficacy outcome originally was specified as the difference in Hb concentrations between the 2 groups at the end of the 4-month study period, adjusted for baseline values.[20] In March 2010, the primary outcome was changed from Hb concentration to ESA resistance index due to the significantly increased risks of stroke and thromboembolic events observed in darbepoetin-treated patients assigned to a higher Hb target in TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) and the increasing evidence against the validity of Hb level as a surrogate end point.[21,22] ESA resistance index for darbepoetin-treated patients was converted to an erythropoietin-equivalent value using a dose conversion factor of 200:1.[23]

Secondary outcome variables were: (1) Hb concentration, (2) ESA dose (either erythropoietin or darbepoetin), (3) blood transfusion rate, (4) adverse event rate, (5) costs, and (6) quality of life. Hb, serum ferritin, and serum transferrin saturation were measured at baseline and monthly thereafter over 4 months. Health-related quality of life was measured by the 36-Item Short Form Health Survey, administered at baseline and 4 months.[24]

Costs of ESA treatment during the study were based on the Australian Pharmaceutical Benefits Scheme schedules for Eprex (epoetin alfa; Janssen; A$1,057.34 for 5,000 IU × 6 syringes), NeoRecormon (epoetin beta; Roche; A$1,057.36 for 5,000 IU × 6 syringes), and Aranasep (darbepoetin alfa; Amgen; A$1,376.78 for 50 μg × 4 syringes).[25] The cost of pentoxifylline (Trental; Sanofi-Aventis; 400 mg) used in the trial was based on a cost of A$39.39 for a pack of 50 tablets.[26]

Statistical Analysis

Results are expressed as frequency (percentage) for categorical variables, mean ± standard deviation for continuous normally distributed variables, and median and interquartile range for continuous non-normally distributed variables. The primary and secondary efficacy end points were analyzed in accordance with the intention-to-treat principle. Treatment groups were compared on ESA resistance index at 4 months, adjusted for baseline ESA resistance index, using analysis of covariance. Similar analyses were performed for the secondary outcomes of Hb concentration, ESA dose, serum ferritin level, and transferrin saturation. The primary outcome (ESA resistance index) and main secondary outcomes (Hb concentration and ESA dose) were compared between treatment groups according to whether baseline serum C-reactive protein (CRP) concentrations were elevated (>5 vs ≤5 mg/L). Treatment by CRP subgroup interactions tests were performed on each outcome using linear regression. Blood transfusion requirements, adverse drug reactions, and serious adverse events by treatment group were analyzed using Poisson regression models. Treatment groups were compared on quality of life (change from baseline), weekly ESA dose, and total cost of ESA using independent-samples *t* tests. Treatment groups were compared on adverse events using generalized linear models from the binomial family with an identity link.

The study was designed to have 90% statistical power to detect a difference in ESA resistance index of 0.6 IU/kg/wk/g/L after 4 months of treatment, assuming a population standard deviation of 0.7 IU/kg/wk/g/L and $\alpha = 0.05$. The difference of 0.6 represented 20% of an assumed ESA resistance index of 3.1 IU/kg/wk/g/L for the control group, based on an audit of hemodialysis and peritoneal dialysis patients at Princess Alexandra Hospital, Central Northern Adelaide, and Renal Transplant Service and the published literature.[16,19] Estimated sample size was 30 per group. After adjustment for 20% treatment nonadherence and 5% dropout, the final sample size was estimated to be 55 per group (rounded up by 5 per group, 110 in total). Commencing June 12, 2009, it initially was anticipated that trial recruitment would be completed by December 31, 2011, with final follow-up completed by April 30, 2012. As of August 12, 2012, a total of 53 patients had been recruited into the study, accounting for 48% of the target. A decision was made by the Trial Management Committee to halt further recruitment on the basis of poor feasibility (ie, insufficient recruitment rate to reach projected target within a reasonable time frame considering trial logistics and funding).

Table 1. Baseline Characteristics by Treatment Group

	Control (n = 27)	Pentoxifylline (n = 26)
Age (y)	65.1 ± 16.3	59.2 ± 14.7
Male sex	10 (37%)	14 (54%)
Ethnicity		
White	20 (74%)	23 (88%)
Aboriginal or Torres Strait Islander	1 (4%)	0 (0%)
Maori or Pacific Islander	1 (4%)	0 (0%)
Asian	2 (7%)	3 (12%)
Other	3 (11%)	0 (0%)
Cause of kidney disease[a]		
Diabetes	9 (34.6%)	12 (46.2%)
Glomerulonephritis	4 (15.4%)	3 (11.5%)
Analgesic nephropathy	1 (3.8%)	0 (0%)
Polycystic kidney disease	3 (11.5%)	0 (0%)
Reflux nephropathy	1 (3.8%)	2 (7.7%)
Renovascular disease	2 (7.7%)	0 (0%)
Other	6 (23.1%)	9 (34.6%)
CKD stage[a]		
Stage 4	1 (4%)	0 (0%)
Stage 5	25 (96%)	26 (100%)
Dialysis modality[a]		
Hemodialysis	25 (96%)	25 (96%)
Peritoneal dialysis	0 (0%)	1 (4%)
Body mass index (kg/m^2)	29.3 ± 6.7	29.5 ± 6.6
Obese: BMI ≥ 30 kg/m^2	10 (37%)	10 (38%)
Systolic blood pressure (mm Hg)[a]	146 ± 22	141 ± 24
Diastolic blood pressure (mm Hg)[a]	69 ± 15	72 ± 16
Smoking status[a]		
Never	11 (42%)	12 (46%)
Former	13 (50%)	11 (42%)
Current	2 (8%)	3 (12%)
Diabetes mellitus[b]	11 (58%)	14 (70%)
Ischemic heart disease[b]	9 (47%)	9 (45%)
Congestive heart failure[b]	5 (26%)	3 (15%)
Cerebrovascular disease[b]	2 (11%)	2 (10%)
Peripheral vascular disease[b]	5 (26%)	5 (25%)
Hemoglobin (g/L)	106 ± 12	106 ± 10
Mean cellular volume (fL)	94.3 ± 8.0	95.1 ± 5.2
Reticulocyte count (10^9/L)	68 ± 35	63 ± 27
Serum albumin (g/L)[a]	35 ± 4	35 ± 5
Serum ferritin (μg/L)	481 [298-734]	492 [333-594]
CRP (mg/L)	10 [3-32]	13 [3-23]
ESA type		
Darbepoetin	9 (33%)	9 (35%)
Erythropoietin α or β	18 (67%)	17 (65%)
ESA dose (IU/kg/wk)[c]	225 [188-300]	247 [136-305]
ERI (IU/kg/wk/g/L)	2.38 ± 0.94	2.36 ± 1.09

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; ERI, erythropoiesis-stimulating agent resistance index; ESA, erythropoiesis-stimulating agent.

[a]One missing value in the control group.

[b]Eight missing values in the control group and 6 missing values in the pentoxifylline group.

[c]Patients on darbepoetin therapy were converted to an erythropoietin-equivalent dose using a conversion factor of 200:1.

RESULTS

Patients

Fifty-three patients were randomly assigned to receive either pentoxifylline (n = 26) or placebo (control; n = 27; Fig 1). Baseline characteristics are listed in Table 1. Only one (1.9%) randomly assigned patient was not on dialysis therapy.

Primary Outcome

Mean ESA resistance index values at the end of the 4-month study period were 15% lower in the pentoxifylline group compared with controls (adjusted mean difference, −0.39 [95% confidence interval [CI], −0.89 to 0.10] IU/kg/wk/g/L; $P = 0.1$), although the difference was not statistically significant (Table 2).

Secondary Outcomes

Mean Hb concentration at the end of the 4-month study period was significantly higher in the pentoxifylline group compared with controls, after adjustment for baseline values (adjusted mean difference, 7.6 [95% CI, 1.7-13.5] g/L; $P = 0.01$; Table 2).

Mean ESA dose at the end of the 4-month study period was 8% lower in the pentoxifylline group compared with controls (adjusted mean difference, −20.8 [95% CI, −67.2 to 25.7] IU/kg/wk; $P = 0.4$), although the difference was not statistically significant (Table 2).

No significant differences were observed between the 2 groups with respect to serum ferritin level (Table 2) or serum transferrin saturation (Table 2).

Blood transfusions were administered to 2 patients in the pentoxifylline group and one control patient (incidence rate ratio, 2.12; 95% CI, 0.20-22.01; $P = 0.5$; Table S1).

Treatment adherence was assessed by pill count at each study visit. Twenty-two of 26 (85%) pentoxifylline participants and 18 of 27 (67%) control participants were fully adherent throughout the study ($P = 0.1$).

Quality of Life

Quality-of-life results were available for 26 study participants (pentoxifylline, n = 11; control, n = 15).

Table 2. Primary and Secondary Outcomes at 4 Months by Treatment Group

Outcome	Control (n = 27)	Pentoxifylline (n = 26)	Difference[a] (95% CI)	P
ERI (IU/kg/wk/g/L)[b]	2.60	2.21	−0.39 (−0.89 to 0.10)	0.1
Hemoglobin (g/L)	103.2	110.9	7.6 (1.7 to 13.5)	0.01
ESA dose (IU/kg/wk)[b]	261.2	240.4	−20.8 (−67.2 to 25.7)	0.4
Serum ferritin (μg/L)	543	471	−72 (−215 to 72)	0.3
Serum transferrin saturation (%)	24.5	25.7	1.2 (−3.9 to 6.2)	0.7

Note: Outcomes adjusted for baseline values.

Abbreviations: CI, confidence interval; ERI, erythropoiesis-stimulating agent resistance index; ESA, erythropoiesis-stimulating agent.

[a]Difference = pentoxifylline − control.

[b]Patients on darbepoetin therapy were converted to an erythropoietin-equivalent dose using a conversion factor of 200:1.

Mean change in health-related quality of life from baseline to the end of the 4-month study period was 0.04 ± 0.11 in the pentoxifylline group and 0.05 ± 0.09 in the control group (between-group difference, −0.01; [95% CI, −0.09 to 0.07]; $P = 0.8$).

Costs

Mean length of treatment was 111.8 ± 26.4 days for the pentoxifylline group and 116.3 ± 21.5 days for the control group. There were 6 patients in the pentoxifylline group who stopped treatment early compared with 3 patients in the control group. If all patients were to have received the full dose for the full 4 months, the cost would have been a mean of A$95.92 (US $90.36) per patient.

The weekly ESA dose was nonsignificantly higher in the control group than in the pentoxifylline group during the 4 months of the trial ($P = 0.3$; Table 3). The cost of ESAs also was not statistically significantly higher in the control group at a mean total of A$12,437 (US $11,716) over 4 months compared to a mean total of A$11,105 (US $10,461) in the pentoxifylline group, a difference of A$1,332 ($P = 0.4$; Table 3).

Table 3. Doses and Costs of ESA by Treatment Group

	Control (n = 27)	Pentoxifylline (n = 26)
Dose of ESA (IU/kg/wk)	266 ± 103	237 ± 116
Cost of ESA for 4 mo		
A$	12,437 ± 5,798	11,105 ± 5,059
US $[a]	11,716 ± 5,462	10,461 ± 4,766

Note: Values are given as mean ± standard deviation. Darbepoetin dose is converted to erythropoietin equivalent by multiplying by 200. Cost per unit of dose was calculated and applied to trial doses. Costs were taken from the Pharmaceutical Benefits Scheme schedule for Eprex 5000 (A$1,057.34 for 5,000 IU × 6 syringes), NeoRecormon 5000 (A$1,057.36 for 5,000 IU × 6 syringes) and Aranesp 50 (A$1,376.78 for 50 μg × 4 syringes).[25]

Abbreviation: ESA, erythropoiesis-stimulating agent.

[a]Currency conversion from A$ to US $ was based on a rate on November 19, 2013, of 0.942 (www.xe.com/currencytables/?from=AUD&date=2013-11-19).

Considering the costs of treatment (pentoxifylline) and costs of the resulting ESA dose, the intervention group had cost savings of A$1,244 (US $1,172) per person over the 4 months of the trial. This was driven largely by the reduction in cost of ESAs for the pentoxifylline group.

Exploratory Analyses

No significant differences in ESA resistance index, Hb concentration, ESA dose, serum ferritin level, or serum transferrin saturation were observed at the end of the 4-month study period between the 2 treatment groups according to whether baseline serum CRP level was elevated (Table 4). No significant interactions were observed for treatment group by CRP subgroup on any of the outcomes (Table 4).

Adverse Events

There were 31 serious adverse events in total, with no significant differences between the pentoxifylline and control groups in total serious adverse events (Table 5; Table S1), type of serious adverse event (Table 5), or serious adverse event body system (Table 5). One serious adverse event in the pentoxifylline group was thought by the investigator to be possibly related to study medication (patient hospitalized with anemia, lower respiratory tract infection, and pulmonary venous congestion). Two adverse drug reactions were reported during the 4-month study period in each of the pentoxifylline and control groups (incidence rate ratio, 1.06; 95% CI, 0.16-6.99; $P = 0.9$). Two of the 4 adverse drug reactions were classified as severe and the patient ceased study medication use, one in the pentoxifylline group (decreased appetite, nausea, vomiting, indigestion, and dizziness) and one in the control group (severe abdominal pain and headaches).

DISCUSSION

This study demonstrated that when compared to matched placebo, oral administration of pentoxifylline in a dose of 400 mg daily did not result in a significant change in the primary outcome of ESA resistance

Table 4. Effect of Treatment on ERI, ESA Dose, Hemoglobin Concentration, Serum Ferritin Level, and Serum Transferrin Saturation for CRP Subgroups

	Control (n = 27)	Pentoxifylline (n = 26)	Difference (95% CI)	P[a]
CRP ≤ 5 mg/L	(n = 9)	(n = 9)		
ERI (IU/kg/wk/g/L)	2.16	1.65	−0.50 (−1.51 to 0.51)	0.3
Dose of ESA (IU/kg/wk)	213.09	187.57	−25.5 (−109 to 57.79)	0.5
Hemoglobin (g/L)	104.42	115.47	11.05 (−2.01 to 24.11)	0.09
Serum ferritin (μg/L)	583.38	455.87	−128 (−452 to 197.1)	0.4
Serum transferrin saturation (%)	30.12	26.76	−3.36 (−16.4 to 9.68)	0.6
CRP > 5 mg/L	(n = 18)	(n = 17)		
ERI (IU/kg/wk/g/L)	2.83	2.49	−0.35 (−0.96 to 0.26)	0.3
Dose of ESA (IU/kg/wk)	286.25	267.27	−19.0 (−78.9 to 40.98)	0.5
Hemoglobin (g/L)	102.54	108.55	6.01 (−0.57 to 12.59)	0.07
Serum ferritin (μg/L)	510.49	493.07	−17.4 (−183 to 148.1)	0.8
Serum transferrin saturation (%)	22.72	24.35	1.63 (−3.76 to 7.01)	0.5

Note: Difference = pentoxifylline − control.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ERI, erythropoiesis-stimulating agent resistance index; ESA, erythropoiesis-stimulating agent.

[a]Treatment group by CRP subgroup interaction test *P* values for each outcome were: ERI ($P = 0.8$); hemoglobin concentration ($P = 0.6$); ESA dose ($P = 0.1$); serum ferritin level ($P = 0.4$); serum transferrin saturation ($P = 0.7$).

index, but significantly increased Hb concentration by 7.6 g/L. Treatment with pentoxifylline resulted in cost savings of ∼A$3,000 (∼ US $2,800) per annum as a result of the 8% reduction in ESA dose, although results did not reach statistical significance. No significant differences were observed between the pentoxifylline and control groups with respect to the other secondary outcome measures of blood transfusions, serum ferritin level, serum transferrin saturation, quality of life, and adverse events.

These results contrast to those of a randomized controlled trial reported by Mortazavi et al[27] in which 25 anemic hemodialysis patients treated with pentoxifylline, 400 mg, daily exhibited similar Hb concentrations after 6 months compared with 25 controls receiving placebo (106 ± 14 vs 101 ± 17 g/L,

Table 5. Serious Adverse Events by Treatment Group

	Total Events	Control (n = 27)	Pentoxifylline (n = 26)	% Difference in Proportions (95% CI)	P
Any SAE	31[a]	10 (37)	8 (31)	−6.3% (−31.1% to 19.2%)	0.6
Death	0	0 (0)	0 (0)	—	—
Life-threatening events	0	0 (0)	0 (0)	—	—
Initial or prolonged hospitalization	30	10 (37)	8 (31)	−6.3% (−31.1% to 19.2%)	0.6
Disability	0	0 (0)	0 (0)	—	—
Congenital abnormality	0	0 (0)	0 (0)	—	—
Important medical event	1	0 (0)	1 (4)	4%	—
SAEs by system[b]					
Cardiovascular	3	1 (4)	1 (4)	0.1% (−12.6% to 13.2%)	0.9
Central nervous system	1	0 (0)	1 (4)	3.8% (3.8% to 3.8%)	—
Diabetes, endocrine, reproductive	0	0 (0)	0 (0)	−0.0% (−0.0% to −0.0%)	—
Gastrointestinal	2	2 (7)	0 (0)	−7.4% (−7.4% to −7.4%)	—
Hematologic	2	1 (4)	1 (4)	0.1% (−12.6% to 13.2%)	0.9
Hepatic	1	1 (4)	0 (0)	−3.7% (−3.7% to −3.7%)	—
Musculoskeletal	4	0 (0)	3 (12)	11.5% (11.5% to 11.5%)	—
Other	4	2 (7)	2 (8)	0.3% (−15.5% to 16.4%)	0.9
Renal dialysis complication	11	5 (19)	2 (8)	−10.8% (−29.9% to 7.7%)	0.2
Respiratory	3	1 (4)	2 (8)	4.0% (−9.8% to 19.2%)	0.5

Note: Unless otherwise indicated, values are given as number or number (percentage).

Abbreviations: CI, confidence interval; SAE, serious adverse event.

[a]There were 18 events in the control group and 13 in the pentoxifylline group.

[b]Ten control and 8 pentoxifylline participants had at least one event. Summing across body systems within a treatment group exceeds the number of participants with at least one event because some participants had 2 or more events that were classified under different body systems.

respectively; $P = 0.3$). Unfortunately, ESA resistance index was not examined by the investigators. Although the trial was of similar size to the present investigation, the lack of a significant increase in Hb concentration in the former study may have been because recruited patients did not have to be ESA hyporesponsive to participate. It was not clear that all participants were even receiving ESA therapy given that this was not listed as an inclusion criterion for the trial. Moreover, end-of-study Hb levels were compared by *t* test without adjustment for baseline values, as occurred in the current study. Although there were no significant differences between groups with respect to age, sex, or kidney disease cause, it is not known how well matched the groups were otherwise because additional baseline characteristics were not presented. It therefore is possible that there may have been an imbalance in patient characteristics that potentially blunted the effect of pentoxifylline, given that methods of randomization and allocation concealment were not reported in the article.

In contrast, 4 previous nonrandomized studies showed improvement in Hb concentrations with pentoxifylline in patients with non–dialysis-dependent or dialysis-dependent CKD.[16-19] Furthermore, Cooper et al[16] reported significant reductions in ex vivo T-cell expression of TNF-α and IFN-γ. Both these proinflammatory cytokines have been shown to be upregulated in patients with ESA hyporesponsiveness and to inhibit erythropoiesis.[28] A significant decrease in serum TNF-α concentrations was reported by Navarro et al,[19] but not by Mohammadpour et al.[18] Another study reported a significant reduction in serum IL-6 concentrations with pentoxifylline.[17] Although these studies suggested that pentoxifylline may increase Hb levels in patients with CKD through inhibition of proinflammatory cytokines, no difference in hematologic response was observed between HERO trial participants according to whether serum CRP level was elevated. This was a prespecified exploratory analysis of the HERO trial because some studies have reported an association between levels of this inflammatory marker and ESA hyporesponsiveness,[29,30] whereas another study was unable to confirm this.[31]

The strengths of this study include its robust design, involvement of multiple centers, analysis of results according to a prespecified statistical analysis plan to mitigate reporting bias, and inclusion of quality-of-life and health economic analyses. These strengths should be balanced against the trial's limitations, the main one of which was recruitment to only 48% of the intended target. This resulted in the trial being inadequately powered to detect the prespecified clinically meaningful difference in ESA resistance index of 20%. However, it should be noted that the observed difference in ESA resistance index between the intervention and control groups was only 15%. Interestingly, if the original primary outcome of the study, Hb concentration, had been unchanged, results of the current study would have been considered in favor of pentoxifylline. Although pentoxifylline was well tolerated in this study, the small sample size limited adequate evaluation of the safety of increasing Hb levels with this agent in patients with CKD. Another limitation was the variable nature of the dose conversion factor between erythropoietin and darbepoetin, which can differ appreciably from the 200:1 ratio used in this study, particularly in the setting of ESA hyporesponsiveness.[32]

The study also highlights the challenges in timely recruitment of participants due to the stringent inclusion criteria resulting in an extremely high screen failure rate of 93%. An alternate study design involving ESA-hyporesponsive and ESA-sensitive patients with CKD would enable more timely participant recruitment in the trial and determine whether pentoxifylline can be used as an adjunct therapy to ESA by improving ESA responsiveness. The study did not include participants of black ethnicity. Therefore, results may not be generalizable to African American and other black patients with CKD, groups with greater ESA hyporesponsiveness.[33]

In conclusion, pentoxifylline did not significantly modify the primary outcome measure of ESA resistance index, but significantly increased Hb concentration. Further research in this area is warranted.

ACKNOWLEDGEMENTS

The HERO Study Collaborative Group comprises the Trial Management Committee (Emmanuel d'Almeida [Department of Nephrology, John Hunter Hospital, Newcastle, Australia], Rob Fassett [Department of Nephrology, Royal Brisbane and Women's Hospital, Brisbane, Australia], Carl Kirkpatrick [Center for Medicine Use and Safety, Monash University, Melbourne, Australia], Richard Phoon [Department of Nephrology, Westmead Hospital, Sydney, Australia], and the members of the Writing Committee); the Data and Safety Monitoring Board (Andrew Tonkin [Chair; Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia], Andrew Forbes [Statistician; Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia], Adeera Levin [Department of Medicine, University of British Columbia, Vancouver, Canada], David C. Wheeler [Center for Nephrology, Royal Free and University College Medical School, London]); the Investigators (Meg Jardine, Jenny Burman, Samantha Hand [New South Wales: Concord Repatriation General Hospital]; Emmanuel D'Almeida, Leanne Garvey [John Hunter Hospital]; Michael Suranyi, Margaret Gilbert [Liverpool Hospital]; Zoltan Endre, Katheen McNamara [Prince of Wales]; Paul Snelling, Jenny Burman, Samantha Hand [Royal Prince Alfred Hospital]; Kumar Mahadevan, Andrea Pollock [Queensland: Nambour General Hospital]; David Johnson, Diana Leary [Princess Alexandra Hospital]; Sharad Ratanjee, Julie Kirby [Royal Brisbane Women's Hospital]; Rajiv Juneja, Kathy Hill [South Australia: Flinders Medical Center]; Natasha Cook, Pascal Bisscheroux [Victoria: Austin Health]; Lawrence McMahon, Annette Kent [Eastern Health Integrated Renal Service- Box Hill Hospital]; Eugenie Pedagogos, Matija Raspudic [Royal Melbourne

Hospital]; Paolo Ferrari, Uli Steinwandel [Western Australia: Fremantle Hospital]; Sharan Dogra, Susan Pellicano [Sir Charles Gairdner Hospital]; and the Project Management Team (Alicia Morrish, Elaine Pascoe, Peta-Anne Paul-Brent, Donna Reidlinger, Anish Scaria, Liza Vergara [Australasian Kidney Trials Network, Brisbane, Queensland, Australia]).

The authors listed on the first page of this article constitute the HERO Trial Writing Committee.

Support: The HERO trial was funded by research grants from Roche Foundation for Anemia Research (RoFAR) (Grant number 3210249431), Amgen, Janssen-Cilag (Grant number S/1742620/1), and the National Health and Medical Research Council of Australia (Grant number APP1008604). The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

Financial Disclosure: Dr Johnson has previously received consultancy fees from Sanofi-Aventis and consultancy fees, speakers' honoraria, research grants, and travel sponsorships from Amgen, Roche, and Janssen-Cilag. He was the recipient of a RoFAR grant, which partly funded the HERO trial, and a Queensland Government Health Research Fellowship. Dr Hawley has previously received consultancy fees, speakers' honoraria, research grants, and/or travel sponsorships from Amgen, Roche, and Janssen-Cilag. Dr Cass has previously received consultancy fees, speakers' honoraria, and/or research grants from Amgen, Roche, Baxter, Fresenius, and Merck. Dr Walker has previously received consultancy fees, speakers' honoraria, research grants, and travel sponsorships from Amgen, Roche, and Janssen-Cilag and has served on Advisory Boards for Amgen, Roche, and Janssen-Cilag. The other authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: DJ, SB, AC, PC, PF, SM, AM, EP, VP, DR, RW, LV, CH; data acquisition: EMP, AS, AM, DR; data analysis/interpretation: DJ, EMP, SB, KD, AC, PC, PF, SM, AM, EP, VP, DR, AS, RW, LV, CH; statistical analysis: EMP, AS, KD; supervision or mentorship: DJ, CH, PC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DJ takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and registered) have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Adverse events by treatment group.

Item S1: Exclusion criteria for the HERO trial.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.06.020) is available at www.ajkd.org

REFERENCES

1. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin*. 2004;20(9):1501-1510.

2. Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. *Nephrology*. 2007;12(4):321-330.

3. Badve SV, Hawley CM, Johnson DW. Is the problem with the vehicle or the destination? Does high-dose ESA or high haemoglobin contribute to poor outcomes in CKD? *Nephrology*. 2011;16(2):144-153.

4. Kausz AT, Solid C, Pereira BJ, Collins AJ, St Peter W. Intractable anemia among hemodialysis patients: a sign of suboptimal management or a marker of disease? *Am J Kidney Dis*. 2005;45(1):136-147.

5. Zhang Y, Thamer M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality in hemodialysis patients. *Am J Kidney Dis*. 2004;44(5):866-876.

6. Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med*. 2010;363(12):1146-1155.

7. Macdougall IC, Cooper AC. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. *Nephrol Dial Transplant*. 2002;17(suppl 11):39-43.

8. Badve SV, Beller EM, Cass A, et al. Interventions for erythropoietin-resistant anaemia in dialysis patients. *Cochrane Database Syst Rev*. 2013;8:CD006861.

9. Neuner P, Klosner G, Schauer E, et al. Pentoxifylline in vivo down-regulates the release of IL-1 beta, IL-6, IL-8 and tumour necrosis factor-alpha by human peripheral blood mononuclear cells. *Immunology*. 1994;83(2):262-267.

10. Lee P, Peng H, Gelbart T, Wang L, Beutler E. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. *Proc Natl Acad Sci U S A*. 2005;102(6):1906-1910.

11. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest*. 2004;113(9):1271-1276.

12. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306(5704):2090-2093.

13. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood*. 2003;101(7):2461-2463.

14. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem*. 2001;276(11):7806-7810.

15. Semmler J, Gebert U, Eisenhut T, et al. Xanthine derivatives: comparison between suppression of tumour necrosis factor-alpha production and inhibition of cAMP phosphodiesterase activity. *Immunology*. 1993;78(4):520-525.

16. Cooper A, Mikhail A, Lethbridge MW, Kemeny DM, Macdougall IC. Pentoxifylline improves hemoglobin levels in patients with erythropoietin-resistant anemia in renal failure. *J Am Soc Nephrol*. 2004;15(7):1877-1882.

17. Ferrari P, Mallon D, Trinder D, Olynyk JK. Pentoxifylline improves haemoglobin and interleukin-6 levels in chronic kidney disease. *Nephrology*. 2010;15(3):344-349.

18. Mohammadpour AH, Nazemian F, Khaiat MH, et al. Evaluation of the effect of pentoxifylline on erythropoietin-resistant anemia in hemodialysis patients. *Saudi J Kidney Dis Transplant*. 2014;25(1):73-78.

19. Navarro JF, Mora C, Garcia J, et al. Effects of pentoxifylline on the haematologic status in anaemic patients with advanced renal failure. *Scand J Urol Nephrol*. 1999;33(2):121-125.

20. Johnson DW, Hawley CM, Rosser B, et al. Oxpentifylline versus placebo in the treatment of erythropoietin-resistant anaemia: a randomized controlled trial. *BMC Nephrol*. 2008;9:8.

21. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361(21):2019-2032.

22. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med*. 2010;153(1):23-33.

23. Roger SD, Cooper B. What is the practical conversion dose when changing from epoetin alfa to darbepoetin outside of clinical trials? *Nephrology*. 2004;9(4):223-228.

24. Ware JE, Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

25. Australian Government Department of Health. Pharmaceutical benefits scheme. http://www.pbs.gov.au/pbs/home. Accessed September 17, 2013.

26. Discount Chemist Warehouse. Search results. http://www.chemistwarehouse.com.au. Accessed September 17, 2013.

27. Mortazavi M, Seyrafian S, Taheri S, et al. Role of pentoxifylline in treatment of anemic patients suffering chronic hemodialysis: a randomized clinical trial. *Med Arhiv*. 2012;66(2):84-86.

28. Macdougall IC. Could anti-inflammatory cytokine therapy improve poor treatment outcomes in dialysis patients? *Nephrol Dial Transplant*. 2004;19(suppl 5):V73-V78.

29. Locatelli F, Andrulli S, Memoli B, et al. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. *Nephrol Dial Transplant*. 2006;21(4):991-998.

30. Schneider A, Schneider MP, Scharnagl H, Jardine AG, Wanner C, Drechsler C. Predicting erythropoietin resistance in hemodialysis patients with type 2 diabetes. *BMC Nephrol*. 2013;14:67.

31. Panichi V, Rosati A, Bigazzi R, et al. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. *Nephrol Dial Transplant*. 2011;26(8):2641-2648.

32. Bock HA, Hirt-Minkowski P, Brunisholz M, et al. Darbepoetin alpha in lower-than-equimolar doses maintains haemoglobin levels in stable haemodialysis patients converting from epoetin alpha/beta. *Nephrol Dial Transplant*. 2008;23(1):301-308.

33. Kalantar-Zadeh K, Lee GH, Miller JE, et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. *Am J Kidney Dis*. 2009;53(5):823-834.