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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

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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.

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.

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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.