AJKD
Original Investigation

Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study

Robert Provenzano, MD,[1] Anatole Besarab, MD,[2] Steven Wright, MD,[3] Sohan Dua, MD,[4] Steven Zeig, MD,[5] Peter Nguyen, MD,[6] Lona Poole, MD,[2] Khalil G. Saikali, PhD, Exec MBA,[2] Gopal Saha, MBBS,[2] Stefan Hemmerich, PhD, RAC,[2] Lynda Szczech, MD, MSCE,[2] K.H. Peony Yu, MD,[2,] and Thomas B. Neff, MD (hc)[2,*]*

Background: Roxadustat (FG-4592) is an oral hypoxia-inducible factor prolyl-hydroxylase inhibitor that promotes erythropoiesis through increasing endogenous erythropoietin, improving iron regulation, and reducing hepcidin.

Study Design: Phase 2, randomized (3:1), open-label, active-comparator, safety and efficacy study.

Setting & Participants: Patients with stable end-stage renal disease treated with hemodialysis who previously had hemoglobin (Hb) levels maintained with epoetin alfa.

Intervention: Part 1: 6-week dose-ranging study in 54 individuals of thrice-weekly oral roxadustat doses versus continuation of intravenous epoetin alfa. Part 2: 19-week treatment in 90 individuals in 6 cohorts with various starting doses and adjustment rules (1.0-2.0 mg/kg or tiered weight based) in individuals with a range of epoetin alfa responsiveness. Intravenous iron was prohibited.

Outcomes: Primary end point was Hb level response, defined as end-of-treatment Hb level change (ΔHb) of −0.5 g/dL or greater from baseline (part 1) and as mean Hb level ≥ 11.0 g/dL during the last 4 treatment weeks (part 2).

Measurements: Hepcidin, iron parameters, cholesterol, and plasma erythropoietin (the latter in a subset).

Results: Baseline epoetin alfa doses were 138.3 ± 51.3 (SD) and 136.3 ± 47.7 U/kg/wk in part 1 and 152.8 ± 80.6 and 173.4 ± 83.7 U/kg/wk in part 2, in individuals randomly assigned to roxadustat and epoetin alfa, respectively. Hb level responder rates in part 1 were 79% in pooled roxadustat 1.5 to 2.0 mg/kg compared to 33% in the epoetin alfa control arm ($P = 0.03$). Hepcidin level reduction was greater at roxadustat 2.0 mg/kg versus epoetin alfa ($P < 0.05$). In part 2, the average roxadustat dose requirement for Hb level maintenance was ~1.7 mg/kg. The least-squares-mean ΔHb in roxadustat-treated individuals was comparable to that in epoetin alfa–treated individuals (about −0.5 g/dL) and the least-squares-mean difference in ΔHb between both treatment arms was −0.03 (95% CI, −0.39 to 0.33) g/dL (mixed effect model-repeated measure). Roxadustat significantly reduced mean total cholesterol levels, not observed with epoetin alfa. No safety concerns were raised.

Limitations: Short treatment duration and small sample size.

Conclusions: In this phase 2 study of anemia therapy in patients with end-stage renal disease on maintenance hemodialysis therapy, roxadustat was well tolerated and effectively maintained Hb levels.

Am J Kidney Dis. 67(6):912-924.

INDEX WORDS: Hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI); roxadustat; anemia; dialysis; chronic kidney disease (CKD); erythropoiesis; iron transport; hemoglobin (Hb); Hb correction; Hb response; hepcidin; erythropoietin; end-stage renal disease (ESRD); Hb maintenance; randomized trial.

Prior to the availability of recombinant erythropoiesis-stimulating agents (ESAs), anemia in end-stage renal disease (ESRD) was treated with repeated blood transfusions. Because allosensitization by blood transfusions can interfere with patients' ability to receive kidney transplants,[1] minimization of transfusions is a distinct benefit of ESAs. However, cardiovascular safety findings from the Normal Hematocrit Cardiac Trial

From [1]St. John Hospital & Medical Center, Detroit, MI; [2]FibroGen, Inc, San Francisco, CA; [3]US Renal Care, Pine Bluff, AR; [4]Valley Renal Medical Group, Northridge, CA; [5]Pines Clinical Research, Pembroke Pines, FL; and [6]US Renal Care, Ft Worth, TX.

[*]K.H.P.Y. and T.B.N. contributed equally to this work.

Received June 10, 2015. Accepted in revised form December 18, 2015. Originally published online February 1, 2016. Corrected online February 10, 2016. See Item S3 for an explanation of the corrections. The errors have been corrected in the print, PDF, and HTML versions of this article.

Trial registration: www.ClinicalTrials.gov; study number: NCT01147666.

Address correspondence to K.H. Peony Yu, MD, FibroGen, Inc, 409 Illinois St, San Francisco, CA 94158. E-mail: pyu@fibrogen.com

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.12.020

(NHCT), the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, the Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE) study, and the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT),[2-5] which targeted hemoglobin (Hb) values > 11 g/dL, prompted regulatory authorities to institute warnings to use the lowest ESA dose adequate for reducing the need for red blood cell transfusion. The warning also states that no trial has identified an Hb target level, ESA dose, or dosing strategy that does not increase these risks.[6] Similar recommendations have also been made based on observational studies.[7] Post hoc analyses of the mentioned trials point to high ESA doses as the mediator of cardiovascular risk while consistently supporting an inverse relationship between achieved Hb levels and risk.[8] These restrictions on ESAs have subsequently been associated with a decline in Hb levels and an increase in transfusions in patients with ESRD in the United States.[9]

Hepcidin has been recently identified as the master regulator of iron metabolism,[10,11] and levels are elevated in patients with ESRD[12] and those with inflammation. Hepcidin reduces duodenal iron absorption and export of tissue-stored iron-impairing responsiveness to erythropoietin (EPO). Anemia in patients with ESRD is not simply an "EPO-deficiency state," but one of EPO dysregulation coupled with major abnormalities in iron metabolism leading to the need for intravenous (IV) iron.[13] Recent studies demonstrate a role for hypoxia-inducible factor (HIF) in the regulation of endogenous EPO production, the iron transport system,[14] and hepcidin. A new class of drugs, HIF−prolyl hydroxylase inhibitors (HIF-PHIs), taking advantage of natural physiology in coordinated erythropoiesis, is being evaluated for the treatment of anemia in chronic kidney disease.[15]

Roxadustat (FG-4592) is an orally bioavailable HIF-PHI with a half-life of around 12 hours; thrice-weekly administration leads to intermittent activation of genes associated with erythropoiesis, notably including well-characterized HIF targets such as EPO and proteins promoting iron absorption, iron transport, and heme synthesis.[16-18] In an earlier placebo-controlled 4-week phase 2a study, roxadustat increased Hb levels in non–dialysis-dependent patients with chronic kidney disease in a dose-dependent manner and improved iron homeostasis, limiting transient endogenous EPO levels to within or near physiologic range.[19] In ESA-naive incident hemodialysis and peritoneal dialysis patients, roxadustat treatment resulted in a maximum Hb level increase of +3.1 ± 0.2 (standard error [SE] of the mean) g/dL over 12 weeks despite a lack of iron repletion requirement at baseline, with Hb values of hemodialysis patients receiving oral iron responding as well as those on IV iron therapy.[20] We present a phase 2 study of patients with ESRD on maintenance hemodialysis therapy whose Hb levels had been previously maintained by epoetin alfa, randomly assigned to roxadustat or to continue epoetin alfa to demonstrate roxadustat's efficacy in maintaining Hb levels when converting from an ESA and to establish the optimum starting dose and dose adjustment regimen to maintain target Hb values.

METHODS

Study Design

This was a randomized, multicenter, open-label, consecutive-cohort, multidose study with active comparator IV epoetin alfa in patients with ESRD treated by maintenance hemodialysis in the United States whose Hb levels were previously maintained with IV epoetin alfa (dosage, 75-450 U/kg/wk) and IV iron in the 4 weeks preceding screening. The study, conducted between May 17, 2010, and October 15, 2012, consisted of a screening period of up to 4 weeks, a treatment period of 6 (part 1) or 19 (part 2) weeks, and an 8- (part 1) or 4-week (part 2) follow-up period.

The study was approved by Aspire Institutional Review Board, La Mesa, CA. Participants provided written informed consent.

Participants and Treatment

Eligible patients were aged 18 to 75 years and receiving maintenance hemodialysis thrice weekly for 4 or more months. Hb levels were 9.0 to 13.5 g/dL for 8 weeks, and patients had stable epoetin alfa dosages ≤ 450 U/kg/wk for 4 weeks prior to randomization. A comprehensive list of eligibility criteria is provided (Item S1).

The study design is illustrated in Fig 1. Part 1 consisted of 3.5 consecutive 6-week dose cohorts in which participants were randomly assigned up to n = 16 per cohort, 3:1 (roxadustat to epoetin alfa), with oral roxadustat doses fixed at 1.0, 1.5, 1.8, or 2.0 mg/kg thrice weekly. Results of part 1 were used to refine optimal roxadustat starting doses for part 2 (19-week treatment), consisting of 6 consecutive-dose cohorts in which participants were converted to roxadustat from epoetin alfa treatment (Table 1). Part 2 comprised 90 patients randomly assigned to 6.5 cohorts of roxadustat (n = 67, with various starting doses) or to continue on epoetin alfa therapy (n = 23).

Treatment with androgens was prohibited; IV iron use and red blood cell transfusions were guided by rescue criteria (Item S2). Oral iron supplementation was permitted but not required. During the post-treatment follow-up period, roxadustat-treated patients switched back to epoetin alfa.

Dose Modifications

Hb was measured weekly; investigators titrated the roxadustat dose after the initial fixed dosing period based on cohort-specific rules every 4 weeks (Table 2). If Hb level increased by >2.0 g/dL in any 2 weeks, the dose was reduced 1 dose step. For participants randomly assigned to epoetin alfa, dose adjustments were made based on the local standard of care.

Assessments

The primary end point in part 1 (6-week cohorts) was the proportion of participants whose Hb levels did not decrease by >0.5 g/dL from baseline (defined as the mean of the last 3 Hb values obtained prior to the first dose of study treatment). The primary end point in part 2 (19-week cohorts) was the proportion of participants whose mean Hb level was ≥11 g/dL averaged over the last 4 weeks (weeks 16 through 19). Exploratory analysis