ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

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ABSTRACT

BACKGROUND

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism. Additional data are needed regarding the effectiveness and safety of roxadustat as compared with standard therapy (epoetin alfa) for the treatment of anemia in patients undergoing dialysis.

METHODS

In a trial conducted in China, we randomly assigned (in a 2:1 ratio) patients who had been undergoing dialysis and erythropoiesis-stimulating agent therapy with epoetin alfa for at least 6 weeks to receive roxadustat or epoetin alfa three times per week for 26 weeks. Parenteral iron was withheld except as rescue therapy. The primary end point was the mean change in hemoglobin level from baseline to the average level during weeks 23 through 27. Noninferiority of roxadustat would be established if the lower boundary of the two-sided 95% confidence interval for the difference between the values in the roxadustat group and epoetin alfa group was greater than or equal to –1.0 g per deciliter. Patients in each group had doses adjusted to reach a hemoglobin level of 10.0 to 12.0 g per deciliter. Safety was assessed by analysis of adverse events and clinical laboratory values.

RESULTS

A total of 305 patients underwent randomization (204 in the roxadustat group and 101 in the epoetin alfa group), and 256 patients (162 and 94, respectively) completed the 26-week treatment period. The mean baseline hemoglobin level was 10.4 g per deciliter. Roxadustat led to a numerically greater mean (±SD) change in hemoglobin level from baseline to weeks 23 through 27 (0.7±1.1 g per deciliter) than epoetin alfa (0.5±1.0 g per deciliter) and was statistically noninferior (difference, 0.2±1.2 g per deciliter; 95% confidence interval [CI], –0.02 to 0.5). As compared with epoetin alfa, roxadustat increased the transferrin level (difference, 0.43 g per liter; 95% CI, 0.32 to 0.53), maintained the serum iron level (difference, 25 μg per deciliter; 95% CI, 17 to 33), and attenuated decreases in the transferrin saturation (difference, 4.2 percentage points; 95% CI, 1.5 to 6.9). At week 27, the decrease in total cholesterol was greater with roxadustat than with epoetin alfa (difference, –22 mg per deciliter; 95% CI, –29 to –16), as was the decrease in low-density lipoprotein cholesterol (difference, –18 mg per deciliter; 95% CI, –23 to –13). Roxadustat was associated with a mean reduction in hepcidin of 30.2 ng per milliliter (95% CI, –64.8 to –13.6), as compared with 2.3 ng per milliliter (95% CI, –51.6 to 6.2) in the epoetin alfa group. Hyperkalemia and upper respiratory infection occurred at a higher frequency in the roxadustat group, and hypertension occurred at a higher frequency in the epoetin alfa group.

CONCLUSIONS

Oral roxadustat was noninferior to parenteral epoetin alfa as therapy for anemia in Chinese patients undergoing dialysis. (Funded by FibroGen and FibroGen [China] Medical Technology Development; ClinicalTrials.gov number, NCT02652806.)

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In China, 120 million persons have chronic kidney disease, a prevalence that is projected to increase.[1,2] Anemia is present in more than 90% of the 500,000 patients who undergo dialysis[3] and is a complication that contributes to increased morbidity and mortality.[4] Treatment for anemia is recommended by clinical practice guidelines.[5-8] However, studies link the use of high-dose erythropoiesis-stimulating agents to increased risks of cardiovascular events and death.[9-11] Only half the patients undergoing dialysis in China reach a hemoglobin level of 10.0 g per deciliter or greater using recombinant erythropoietin therapy. This apparent undertreatment may result from the cost of the medication, hyporesponsiveness due to inflammation, or iron depletion.[12]

The kidneys of patients with kidney disease retain the ability to produce erythropoietin.[13,14] Levels of hypoxia-inducible factor (HIF) change according to changes in oxygen tension through oxygen-sensing prolyl hydroxylase enzymes.[15] When oxygen levels decrease, prolyl hydroxylase enzyme activity decreases, resulting in the accumulation of HIF-α subunits and an increase in HIF transcriptional activity, which induces the expression of erythropoietin, erythropoietin receptors, and proteins that promote intestinal absorption of iron and recycling of iron from the macrophage iron storage system.[16]

Roxadustat (FG-4592) is a potent, reversible, HIF prolyl hydroxylase inhibitor that mimics the natural response to hypoxia. The intermittent dosing strategy with roxadustat for the treatment of anemia[17] in patients with chronic kidney disease was developed to permit durable maintenance of effect.[18-20] With a half-life of approximately 10 hours,[21] roxadustat, administered three times per week, enables HIF transcriptional activity to return to baseline between doses, which results in the intermittent induction of hypoxia-inducible target genes involved in erythropoiesis.[16,22,23]

Previous phase 2 trials tested the efficacy of roxadustat in patients in China who had chronic kidney disease–related anemia.[24] We now report the results of a 6-month, phase 3 trial involving patients undergoing dialysis in China.

Methods

Trial Design and Oversight

This trial (FGCL-4592-806) was a randomized, open-label, active-controlled, phase 3 trial evaluating the efficacy and safety of roxadustat for the treatment of anemia in patients undergoing dialysis in China. The protocol, available with the full text of this article at NEJM.org, was approved by regulatory authorities and ethics committees, and the trial was conducted in accordance with local regulatory and ethics requirements.

The trial was designed by the first two authors and the sponsor (FibroGen). The sponsor provided financial support and was responsible for data collection and analysis. All the authors had full access to the trial data and analyses and contributed to data analysis and interpretation and to the conduct of the trial. An author who is an employee of the sponsor wrote the first draft of the manuscript. All the authors reviewed the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Eligible patients were 18 to 75 years of age, had end-stage kidney disease, had received dialysis for at least 16 weeks, had been receiving stable doses of epoetin alfa for at least 6 weeks, and had a mean hemoglobin value (from the last two screening assessments) of 9.0 to 12.0 g per deciliter. A list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

Trial Treatment

Eligible patients underwent randomization in a 2:1 ratio to receive either oral roxadustat or parenteral epoetin alfa (ESPO, Kyowa Hakko Kirin) three times per week for 26 weeks. (Kyowa Hakko Kirin had no role in the trial.) Randomization was performed centrally in sequence, stratified according to the dose of epoetin alfa at baseline (<8000 IU or ≥8000 IU per week) and dialysis method (hemodialysis or peritoneal dialysis).

The starting dose of roxadustat was either 100 mg (in patients weighing 45 to <60 kg) or 120 mg (in patients weighing ≥60 kg). Patients who had been randomly assigned to receive epoetin alfa continued their prerandomization doses. Both epoetin alfa and roxadustat were supplied by the sponsor. Doses were adjusted so that the patient would have a hemoglobin level of 10.0 to 12.0 g per deciliter (Table S2 in the Supplementary Appendix). The use of oral iron therapy was allowed; intravenous iron therapy was prohibited except as rescue therapy. Rescue therapy included intravenous iron, blood transfusion, or erythro-

poiesis-stimulating agents (or a combination of these treatments) in patients who had a hemoglobin level of less than 8.0 g per deciliter or in patients who had a hemoglobin level of less than 9.0 g per deciliter as well as a confirmed decrease from baseline of more than 1.0 g per deciliter.

END POINTS

The primary efficacy end point was the mean change in the hemoglobin level from baseline to the average level during weeks 23 through 27. The prespecified noninferiority analyses were conducted in the full analysis set–intention to treat population and the per-protocol population, according to Chinese regulatory guidance.[25] The full analysis set–intention to treat population (hereafter, the intention-to-treat population) included all the patients who had undergone randomization and had baseline and postbaseline hemoglobin values assessed during treatment. The intention-to-treat analyses were performed according to the randomly assigned treatment group. The per-protocol population included all the patients who had undergone randomization, received at least 2 weeks of treatment, had baseline and postbaseline hemoglobin values assessed without the use of rescue therapy in the preceding 6 weeks, and had no major protocol violations.

Secondary efficacy end points were examined in both the intention-to-treat population and the per-protocol population; results from the intention-to-treat population are presented unless otherwise specified. The secondary efficacy end points were the following: the proportion of patients with a hemoglobin response (defined as a mean hemoglobin level, averaged over weeks 23 through 27, that was no lower than 1.0 g per deciliter below baseline); the proportion of patients with a mean hemoglobin level, averaged over weeks 23 through 27, of at least 10.0 g per deciliter; the mean change from baseline in the total cholesterol level, averaged over weeks 25 through 27; the mean change from baseline in iron biomarker levels at week 27; the first exacerbation of hypertension in a time-to-event analysis; and the mean change from baseline in the mean arterial blood pressure measured before the start of a dialysis session, averaged over weeks 23 through 27. Exploratory analyses of the hemoglobin treatment effect on the basis of inflammatory status, as assessed by the C-reactive protein level, were conducted, as specified in the protocol.

STATISTICAL ANALYSIS

For the primary efficacy analysis, we calculated that the inclusion of 300 patients would provide the trial with 90% power to test the noninferiority[26] of roxadustat to epoetin alfa (margin for hemoglobin level, 1.0 g per deciliter, as established in a previous phase 3 trial of erythropoiesis-stimulating agents[27]). The mean change in the hemoglobin level from baseline to the average level during weeks 23 through 27 was compared with the use of the mixed-model, repeated-measure model. The model included treatment, visit (class effect), treatment by visit, baseline dose of epoetin alfa (<8000 IU or ≥8000 IU per week), and dialysis method as fixed effects and the baseline hemoglobin level as a covariate, with an unstructured covariance matrix within each treatment group for a repeated-measures covariance structure. The baseline hemoglobin level was defined as the mean of the last three hemoglobin levels before the first dose of a trial drug. The 95% confidence interval for the treatment difference was constructed with the use of least-squares means. In order for the trial to show the noninferiority of roxadustat to epoetin alfa, the lower boundary of the 95% confidence interval for the treatment difference in the change in hemoglobin level had to be greater than or equal to –1.0 g per deciliter.

Sensitivity analyses with analysis of covariance (ANCOVA) were performed in which missing hemoglobin values were imputed with the use of the Markov chain Monte Carlo method,[28,29] which assumes multivariate normal distribution of hemoglobin values, to create a data set of observed plus imputed data. We used the ANCOVA model to analyze the change from baseline averaged over weeks 23 through 27 from each imputation with the same covariates as the mixed-model repeated-measures analysis. This process was repeated 1000 times to generate many data sets with imputed data, and the results of the analysis were summarized with adjustment for the variances from the imputations with the use of a multiple-imputation technique.

The binary response end points for hemoglobin values were assessed for noninferiority with the approach of Miettinen and Nurminen,[30] with adjustment for randomization stratification factors on multiple-imputation data. The number of patients, proportion of patients with a response, and treatment differences were averaged from the multiple imputations. The 1000 multiple-

imputed data analysis results were summarized for the treatment comparison with the use of the multiple-imputation technique. Noninferiority testing (with a noninferiority margin of 15 percentage points) was prespecified for the two hemoglobin secondary end-point measures (the proportion of patients with hemoglobin response and proportion with a mean hemoglobin level of ≥10 g per deciliter). Superiority testing was planned for the other secondary end-point measures.

We used the same mixed-model repeated-measures method to analyze the mean changes from baseline in the iron biomarker levels at week 27 and in the total cholesterol level averaged over weeks 25 through 27. We calculated the 95% confidence interval for the treatment difference that was based on the least-squares means from the mixed-model repeated-measures analysis. Since the analyses of secondary end points were not adjusted for multiple comparisons, we report point estimates and 95% confidence intervals without P values. The 95% confidence intervals have not been adjusted for multiple comparisons, and inference drawn from them may not be reproducible.

Safety was monitored by assessment of adverse events and serious adverse events during treatment for 28 days after the discontinuation of trial drug, by review of clinical laboratory values, and by physical examinations. The safety information is reported up to and including 2 days after the discontinuation of the trial drug (approximately four half-lives of roxadustat). The number and proportion of patients who received rescue therapy during trial treatment and the time to rescue therapy from the first dose during treatment were also reported.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

From December 2015 through June 2016, a total of 305 patients underwent randomization (204 patients to the roxadustat group and 101 to the epoetin alfa group) (Fig. S1 in the Supplementary Appendix). One patient in the epoetin alfa group did not receive treatment, so 304 patients were included in the full analysis set (intention-to-treat population). The per-protocol population comprised 196 patients in the roxadustat group and 98 patients in the epoetin alfa group. A total of 48 patients (42 in the roxadustat group and 6 in the epoetin alfa group) discontinued the assigned medication. A total of 256 patients (162 in the roxadustat group and 94 in the epoetin alfa group) completed treatment, for a total of 88.3 patient-years in the roxadustat group and 48.1 patient-years in the epoetin alfa group.

The baseline characteristics of the patients were similar in the two groups (Table 1). Overall, the mean hemoglobin level of the patients was 10.4 g per deciliter, and the mean dose of epoetin alfa was approximately 7500 units per week. Approximately 80% of the patients (247 patients) had a transferrin saturation (the percentage of transferrin, an iron-carrier protein, occupied by iron) of at least 20%, and 65% of the patients (198) had a ferritin level of at least 200 μg per liter. Approximately 20% of the patients (66) had a C-reactive protein level above the upper limit of the normal range.

HEMOGLOBIN LEVELS

Roxadustat treatment resulted in a numerically greater mean (±SD) increase in the hemoglobin level of 0.7±1.1 g per deciliter than did epoetin alfa treatment (0.5±1.0 g per deciliter) and was noninferior to epoetin alfa in both the intention-to-treat population and the per-protocol population (treatment difference in the intention-to-treat population, 0.2±1.2 g per deciliter; 95% confidence interval [CI], −0.02 to 0.5) (Fig. 1A). The percentage of patients with a hemoglobin response (hemoglobin level not <1.0 g per deciliter below the baseline value) was 92.5% in the roxadustat group (189 patients) and 92.5% in the epoetin alfa group (92 patients) in weeks 23 through 27, resulting in a treatment difference of 0.2 percentage points (95% CI, −7.1 to 7.6). The percentage of patients with a mean hemoglobin level of at least 10.0 g per deciliter was 87.0% in the roxadustat group (178 patients) and 88.5% in the epoetin alfa group (88 patients) in weeks 23 through 27 (treatment difference, −0.1 percentage point; 95% CI, −8.6 to 8.5). The treatment difference in the change in hemoglobin level was similar according to the ANCOVA multiple imputations (increase in hemoglobin level, 0.7±1.1 g per deciliter in the roxadustat group and 0.5±1.0 g per deciliter in the epoetin alfa group).

HEPCIDIN, IRON, AND BLOOD-PRESSURE LEVELS

At baseline, the mean hepcidin level was 180.7±136.8 ng per milliliter in the roxadustat

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Roxadustat (N=204)	Epoetin Alfa (N=100)
Age — yr	47.6±11.7	51.0±11.8
Male sex — no. (%)	126 (61.8)	58 (58.0)
Type 2 diabetes — no. (%)	30 (14.7)	17 (17.0)
Weight — kg	62.8±11.8	61.5±9.9
Hemoglobin		
Mean value — g/dl	10.4±0.7	10.5±0.7
Distribution — no. (%)		
<10.0 g/dl	56 (27.5)	29 (29.0)
≥10.0 g/dl	148 (72.5)	71 (71.0)
Baseline epoetin alfa dose		
Mean value — IU/wk	7582±2931	7597±2931
Distribution — no. (%)		
<8000 IU/wk	99 (48.5)	50 (50.0)
≥8000 IU/wk	105 (51.5)	50 (50.0)
Dialysis method — no. (%)		
Hemodialysis	182 (89.2)	89 (89.0)
Peritoneal dialysis	22 (10.8)	11 (11.0)
Duration of dialysis — yr	4.5±3.5	4.4±2.9
Transferrin saturation		
Mean value — %	33.8±16.6	30.0±13.8
Distribution — no./total no. (%)		
<20%	32/202 (15.8)	22/99 (22.2)
≥20%	170/202 (84.2)	77/99 (77.8)
Ferritin		
Mean value — μg/liter	498.5±487.4	420.1±406.8
Distribution — no./total no. (%)		
≥200 μg/liter	136/203 (67.0)	62/100 (62.0)
100 to <200 μg/liter	24/203 (11.8)	19/100 (19.0)
<100 μg/liter	43/203 (21.2)	19/100 (19.0)
Transferrin — g/liter	1.89±0.46	1.91±0.39
Total iron-binding capacity — μmol/liter	47.4±11.4	48.3±9.0
C-reactive protein — no. (%)†		
≤ULN	158 (77.5)	80 (80.0)
>ULN	46 (22.5)	20 (20.0)
Blood pressure		
Systolic — mm Hg	148.1±16.1	148.4±16.5
Diastolic — mm Hg	85.3±9.8	84.2±10.7
Cholesterol		
Total — mg/dl	168.2±42.9	165.1±41.4
LDL — mg/dl	95.1±34.8	90.1±29.4
HDL — mg/dl	43.3±12.0	44.5±15.1
LDL:HDL	2.33±1.00	2.17±0.85

* Plus–minus values are means ±SD. The intention-to-treat population (full analysis set) included all the patients who had undergone randomization and had baseline and postbaseline hemoglobin values assessed during treatment. There were no significant between-group differences in the baseline characteristics. To convert the values for total iron-binding capacity to micrograms per deciliter, divide by 0.1791. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† The upper limit of the normal range (ULN) for the C-reactive protein level was 4.9 mg per liter.

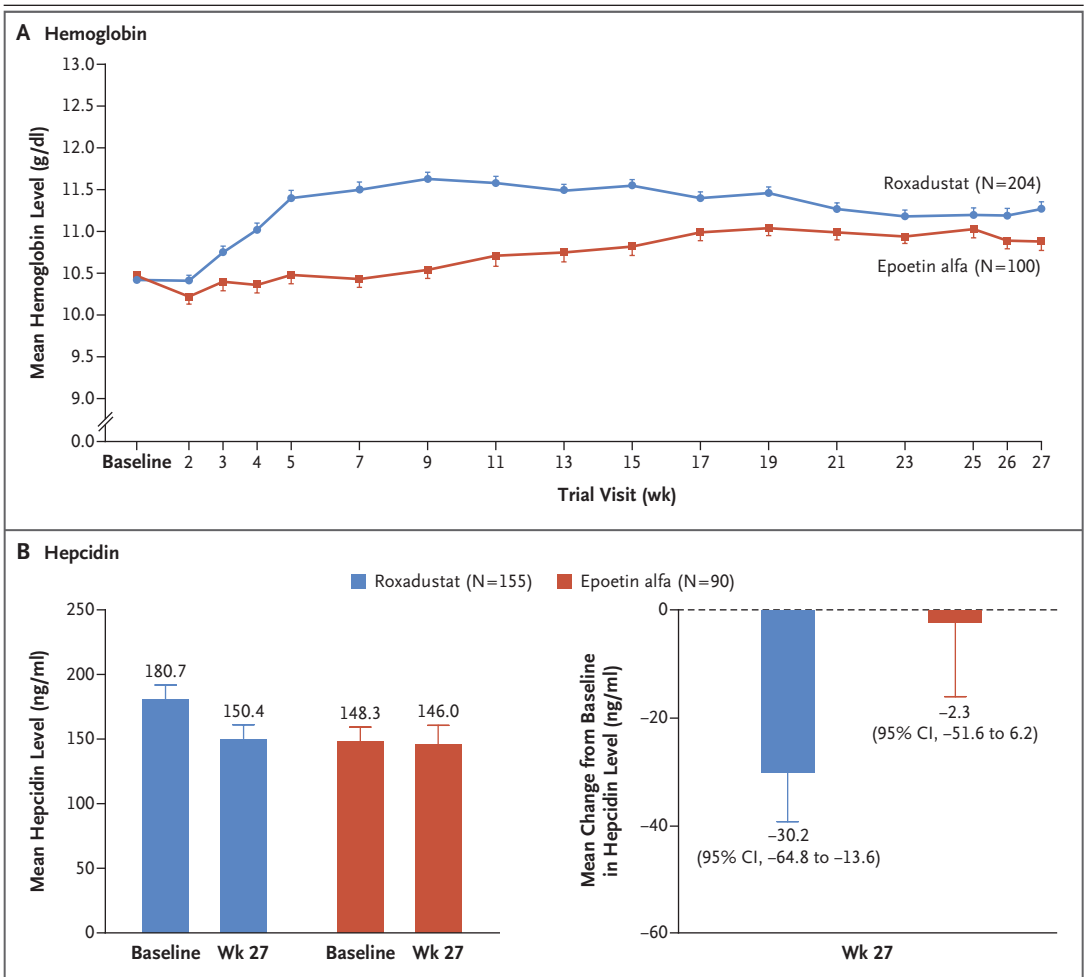

Figure 1. Mean Hemoglobin Levels over Time and Hepcidin Levels and Mean Change from Baseline at Week 27 (Intention-to-Treat Population).

The intention-to-treat population (full analysis set) included all the patients who underwent randomization and had baseline and postbaseline hemoglobin values assessed during treatment. I bars (Panel A) and T bars (Panel B) indicate the standard error.

group and 148.3±104.2 ng per milliliter in the epoetin alfa group. At week 27, the change from baseline was −30.2±113.3 ng per milliliter (95% CI, −64.8 to −13.6) in the roxadustat group and −2.3±130.7 ng per milliliter (95% CI, −51.6 to 6.2) in the epoetin alfa group (Fig. 1B).

In the roxadustat group, the mean serum iron level was clinically stable, with an increase in the transferrin level and total iron-binding capacity (Table 2). As compared with epoetin alfa, roxadustat increased the transferrin level (treatment difference, 0.43±0.05 g per liter; 95% CI, 0.32 to 0.53), maintained the serum iron level (difference, 25±4 μg per deciliter; 95% CI, 17 to 33 [4.4±0.7 μmol per liter; 95% CI, 3.0 to 5.9]), and attenuated decreases in the transferrin saturation (difference, 4.2±1.4 percentage points; 95% CI, 1.5 to 6.9) (Table 2). In patients in the epoetin alfa group, the mean serum iron level declined without a change in the transferrin level and total iron-binding capacity. This resulted in a greater decline in transferrin saturation in the epoetin alfa group than in the roxadustat group. The mean change in the mean arterial pressure from baseline to the average value during weeks 23 through 27 was −2.1 mm Hg in the roxadustat group and −0.7 mm Hg in the epoetin alfa group (difference, −1.4 mm Hg; 95% CI, −3.7 to 1.0).

Table 2. Mean Change from Baseline in Iron Biomarker Levels at Week 27 (Intention-to-Treat Population).*

Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Iron					
No. of patients	160	160	94	94	
Mean (μmol/liter)	15.2±8.1	0.1±8.3	10.6±4.0	−3.7±7.2	
Least-squares mean (μmol/liter)		0.6±0.7		−3.9±0.5	4.4±0.7 (3.0 to 5.9)
Transferrin					
No. of patients	160	160	94	94	
Mean (g/liter)	2.29±0.66	0.40±0.48	1.86±0.45	−0.04±0.36	
Least-squares mean (g/liter)		0.38±0.05		−0.05±0.04	0.43±0.05 (0.32 to 0.53)
Total iron-binding capacity					
No. of patients	160	159	94	93	
Mean (μmol/liter)	57.4±16.5	10.0±11.9	46.6±11.3	−1.1±9.0	
Least-squares mean (μmol/liter)		9.5±1.2		−1.2±1.1	10.7±1.3 (8.1 to 13.3)
Transferrin saturation					
No. of patients	160	159	94	93	
Mean (%)	28.0±15.8	−5.7±15.4	23.0±8.5	−7.6±13.8	
Least-squares mean (%)		−4.5±1.2		−8.7±1.0	4.2±1.4 (1.5 to 6.9)
Ferritin					
No. of patients	160	160	94	94	
Mean (μg/liter)	373±470	−119±208	294±294	−136±220	
Least-squares mean (μg/liter)		−99±19		−133±21	35±24 (−12 to 82)

* Plus–minus values are means ±SD or least-squares means ±SE. Baseline values are provided for patients who had paired values at week 27 for comparison. To convert the values for iron to micrograms per deciliter, divide by 0.1791.

Four patients (three in the roxadustat group and one in the epoetin alfa group) received rescue therapy (red-cell transfusion, intravenous iron therapy, or treatment with erythropoiesis-stimulating agent), and there was no significant between-group difference (hazard ratio, 1.68; 95% CI, 0.18 to 16.19). During treatment, 67 patients (32.8%) in the roxadustat group received oral iron therapy, as compared with 43 (43.0%) in the epoetin alfa group.

CHOLESTEROL LEVELS

At baseline, the mean total cholesterol level was 168.2±42.9 mg per deciliter (4.35±1.10 mmol per liter) in the roxadustat group and 165.1±41.4 mg per deciliter (4.25±1.05 mmol per liter) in the epoetin alfa group, and the mean low-density lipoprotein (LDL) cholesterol level was 95.1±34.8 mg per deciliter (2.45±0.90 mmol per liter) in the roxadustat group and 90.1±29.4 mg per deciliter (2.30±0.75 mmol per liter) in the epoetin alfa group (Fig. S2 in the Supplementary Appendix). At week 27, the mean decreases in lipid levels in the roxadustat group were as follows: 26.7±30.6 mg per deciliter (0.69±0.79 mmol per liter) in the total cholesterol level (treatment difference vs. epoetin alfa, −22 mg per deciliter; 95% CI, −29 to 16 [−0.58 mmol per liter; 95% CI, −0.74 to −0.41]), 24.0±24.7 mg per deciliter (0.62±0.64 mmol per liter) in the LDL cholesterol level (treatment difference, −18 mg per deciliter; 95% CI, −23 to −13 [−0.47 mmol per liter; 95% CI, −0.60 to −0.34]),

22.8±29.4 mg per deciliter (0.59±0.76 mmol per liter) in the non–high-density lipoprotein (HDL) cholesterol level (treatment difference, –21 mg per deciliter; 95% CI, –27 to –15 [–0.54 mmol per liter; 95% CI, –0.70 to –0.38]), 4.3±7.7 mg per deciliter (0.11±0.20 mmol per liter) in the HDL cholesterol level (treatment difference, –2 mg per deciliter; 95% CI, –4 to –0.1 [–0.05 mmol per liter; 95% CI, –0.10 to –0.002]), and 6.2±88.6 mg per deciliter (0.07±1.00 mmol per liter) in the triglyceride level (treatment difference, –12.4 mg per deciliter; 95% CI, –31.9 to 6.2 [–0.14 mmol per liter; 95% CI, –0.36 to 0.07]); these decreases translated to reductions of 17%, 24%, 19%, 9%, and 8%, respectively. There was a 14% improvement from baseline in the LDL:HDL cholesterol ratio with roxadustat as compared with epoetin alfa (–0.32±0.89; 95% CI for treatment difference, –0.50 to –0.17). In addition, there was a mean treatment difference between the roxadustat group and the epoetin alfa group of –12.4±9.7 mg per deciliter (–0.14±0.11 mmol per liter) in the decrease in triglyceride level.

MARKERS OF INFLAMMATION

The proportion of patients with a C-reactive protein level above the upper limit of the normal range was similar at baseline in the roxadustat group (46 of 204 patients) and the epoetin alfa group (20 of 100 patients) (Table 1). There was an interaction between C-reactive protein level and treatment group (P=0.01 for interaction). In a comparison of subgroups according to C-reactive protein level, the mean hemoglobin levels over weeks 23 through 27 in roxadustat-treated patients were similar among patients with an elevated C-reactive protein level (11.3±1.0 g per deciliter) and among those with a normal C-reactive protein level (11.2±0.9 g per deciliter), both of whom used similar doses (Fig. 2). Among patients receiving epoetin alfa, patients with an elevated C-reactive protein level had a lower mean hemoglobin level than those with a normal C-reactive protein level (10.7±0.9 g per deciliter vs. 11.0±0.8 g per deciliter), even though the patients with higher C-reactive protein levels received higher doses of epoetin alfa. In a comparison of the subgroups of patients with an elevated C-reactive protein level, roxadustat resulted in a greater change from baseline in the hemoglobin level than epoetin alfa (0.9±1.0 g per deciliter vs. 0.3±1.1 g per deciliter).

ADVERSE EVENTS AND SAFETY

A total of 159 of 204 patients (77.9%) treated with roxadustat and 63 of 100 patients (63.0%) treated with epoetin alfa reported having at least one adverse event during treatment. The most frequently reported event was upper respiratory infection, which occurred in 37 patients (18.1%) in the roxadustat group and in 11 (11.0%) in the epoetin alfa group. A total of 29 patients (14.2%) treated with roxadustat and 10 (10.0%) treated with epoetin alfa reported having at least one serious adverse event during treatment. The most frequently reported serious adverse event was vascular-access complication, which occurred in similar proportions of the treatment groups (6 patients [2.9%] in the roxadustat group and 3 patients [3.0%] in the epoetin alfa group) (Table S3 in the Supplementary Appendix). (Vascular-access complications included the terms arteriovenous fistula occlusion, arteriovenous fistula site complication, and arteriovenous fistula thrombosis.) No deaths occurred during the reporting period.

Adverse events that occurred in at least 5% of the patients in either group are listed in Table 3. Hyperkalemia was reported more frequently in the roxadustat group than in the epoetin alfa group in this open-label trial. On the basis of central laboratory assessments of blood samples obtained at baseline (week 1) and every 4 weeks, the mean changes in potassium level were as follows: at week 5, a change of 0.12 mmol per liter in the roxadustat group and 0.01 mmol per liter in the epoetin alfa group; at week 13, a change of –0.04 mmol per liter and –0.01 mmol per liter, respectively; and at week 21, a change of –0.07 mmol per liter and –0.02 mmol per liter, respectively. The proportion of patients with potassium values within categories from 5.5 mmol per liter or less, more than 5.5 to 6.0 mmol per liter, more than 6.0 to 6.5 mmol per liter, and more than 6.5 mmol per liter at baseline and at weeks 13 and 27 were generally similar in the treatment groups (Table S4 in the Supplementary Appendix).

DISCUSSION

This 26-week, phase 3 trial showed the noninferiority of the oral HIF prolyl hydroxylase enzyme inhibitor roxadustat as compared with parenteral epoetin alfa for the treatment of anemia in

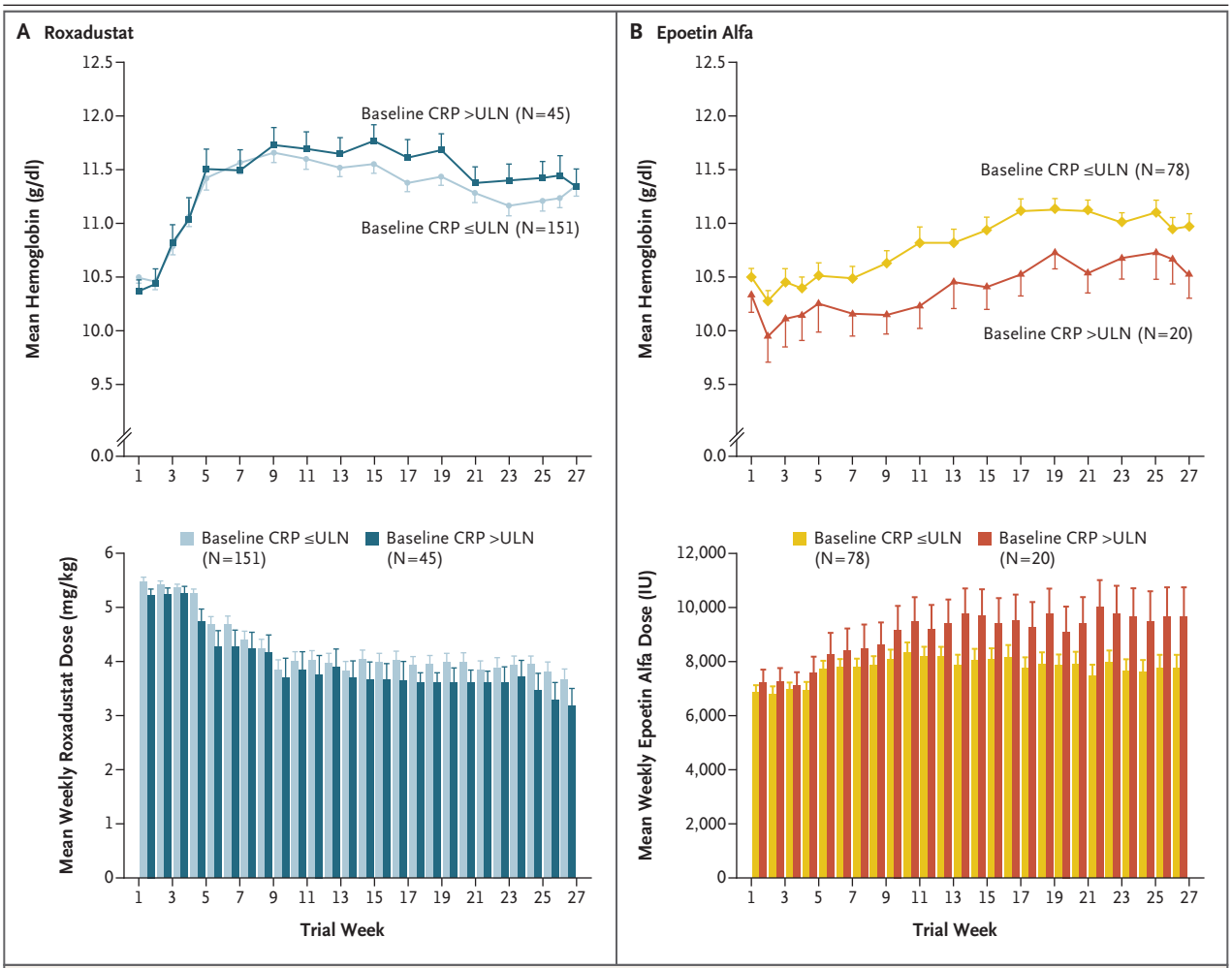

Figure 2. Mean Doses of Roxadustat and Epoetin Alfa and Hemoglobin Levels over Time, According to C-Reactive Protein Subgroup (Per-Protocol Population).

The upper limit of the normal range (ULN) for C-reactive protein (CRP) was 4.9 mg per liter. I bars (top graphs) and T bars (bottom graphs) indicate the standard error of the mean.

patients undergoing hemodialysis or peritoneal dialysis in China. The percentage of patients who received rescue therapy or who did not reach the lower end of the hemoglobin target range (10 g per deciliter) did not differ substantially between groups.

Patients in the epoetin alfa group who had elevated C-reactive protein levels had lower hemoglobin responses than those with normal C-reactive protein levels, despite receiving higher doses of epoetin alfa — a finding that is consistent with results in published studies showing that inflammation suppresses response to erythropoiesis-stimulating agents.[31,32] In contrast, and in a finding consistent with results in phase 2 studies of roxadustat, it was suggested that apparent inflammation, as assessed on the basis of C-reactive protein levels, did not appear to affect the hemoglobin response with roxadustat.[33] In the present trial, among patients with elevated C-reactive protein levels, patients in the roxadustat group had a greater increase in the hemoglobin level than those in the epoetin alfa group. Inflammation is known to increase the hepcidin level, resulting in functional iron deficiency. We speculate that the hepcidin level–lowering effect that has been associated with roxadustat and the mobilization of internal iron stores may have contributed to these findings.

The use of intravenous iron therapy was re-

Table 3. Adverse Events Occurring in at Least 5% of Patients in Either Treatment Group and All Serious Adverse Events (Intention-to-Treat Population).*

Event	Roxadustat (N=204)	Epoetin Alfa (N=100)	Total (N=304)
	number of patients (percent)		
Adverse events			
Any adverse event during treatment	96 (47.1)	38 (38.0)	134 (44.1)
Upper respiratory tract infection	37 (18.1)	11 (11.0)	48 (15.8)
Hypertension	25 (12.3)	16 (16.0)	41 (13.5)
Hyperkalemia†	15 (7.4)	1 (1.0)	16 (5.3)
Chest discomfort‡	13 (6.4)	0	13 (4.3)
Vomiting	12 (5.9)	2 (2.0)	14 (4.6)
Asthenia	12 (5.9)	2 (2.0)	14 (4.6)
Alanine aminotransferase increased	11 (5.4)	4 (4.0)	15 (4.9)
Dizziness	10 (4.9)	6 (6.0)	16 (5.3)
Hypotension	10 (4.9)	6 (6.0)	16 (5.3)
Muscle spasms	5 (2.5)	5 (5.0)	10 (3.3)
Serious adverse events, according to system organ class§			
Any serious adverse event during treatment	29 (14.2)	10 (10.0)	39 (12.8)
Blood or lymphatic system disorder	1 (0.5)	0	1 (0.3)
Cardiac disorder	5 (2.5)	1 (1.0)	6 (2.0)
Endocrine disorder	1 (0.5)	0	1 (0.3)
Gastrointestinal disorder	2 (1.0)	0	2 (0.7)
Hepatobiliary disorder	2 (1.0)	0	2 (0.7)
Immune system disorder	2 (1.0)	0	2 (0.7)
Infection or infestation	5 (2.5)	3 (3.0)	8 (2.6)
Injury, poisoning, or procedural complication¶	7 (3.4)	5 (5.0)	12 (3.9)
Metabolism or nutrition disorder	1 (0.5)	0	1 (0.3)
Nervous system disorder	3 (1.5)	0	3 (1.0)
Product issue	0	1 (1.0)	1 (0.3)
Renal or urinary disorder	4 (2.0)	0	4 (1.3)
Reproductive system or breast disorder	1 (0.5)	0	1 (0.3)
Vascular disorder	2 (1.0)	0	2 (0.7)

* Adverse and serious adverse events during treatment were defined as those that occurred from randomization up to and including 2 days after trial-drug discontinuation.

† An adverse reaction is defined as an adverse event that is considered to be related or possibly related to the trial drug by the investigator. The trial sites had different criteria for the reporting of hyperkalemia as an adverse event during treatment. Trend analyses from baseline to the end of the trial did not show any mean increase in potassium levels. Considering the underlying disease (chronic kidney disease), the causal relationship between the adverse reaction of hyperkalemia and roxadustat is unclear.

‡ Patients with chest discomfort had events that were noncardiac in nature.

§ Serious adverse events are reported according to system organ class preferred terms from the *Medical Dictionary for Regulatory Activities*. The patient with a blood or lymphatic system disorder had anemia, the patient with an endocrine disorder had an event related to hyperparathyroidism, the patient with a metabolism or nutrition disorder had fluid overload, the patient with a product issue had a device malfunction, and the patient with a reproductive system or breast disorder had hydrosalpinx.

¶ Vascular-access complications, including the terms arteriovenous fistula occlusion, arteriovenous fistula site complication, and arteriovenous fistula thrombosis, are included in this system organ class.

stricted in both groups — a design that was based on the previous observation that oral iron therapy provided results equivalent to those of intravenous iron therapy with roxadustat.[34] The mechanism of action of epoetin alfa is limited to stimulation of the erythropoietin receptor; oral iron is expected to be ineffective relative to intravenous iron with epoetin alfa in the treatment of anemia in patients undergoing dialysis.[35] Overall, changes in iron biomarker levels showed improvement with roxadustat as compared with epoetin alfa. The serum iron level is strongly affected by the serum transferrin level, which is increased with roxadustat. The attenuation of the decrease in transferrin saturation with roxadustat as compared with epoetin alfa, despite the increase in transferrin level, supports an effect on enteric iron absorption with roxadustat. Improvements in iron delivery to the bone marrow could result in a reduced use of intravenous iron therapy and an increased efficacy of oral iron therapy.

The adverse events during treatment that we observed are consistent with those expected in patients undergoing dialysis. Hyperkalemia was reported more often in patients who received roxadustat than in those who received epoetin alfa. Analyses of central laboratory data did not show any clinically significant changes in the mean potassium levels over time or between groups. Although it is possible that the reporting of hyperkalemia might reflect a potential bias inherent in open-label trial design,[36] in a double-blind trial comparing roxadustat with placebo in patients with chronic kidney disease not undergoing dialysis, hyperkalemia and metabolic acidosis were reported more frequently in the roxadustat group.[37] The intermittent central laboratory monitoring may not have detected potassium elevations, and therefore continued evaluation will be important in presently ongoing trials (ClinicalTrials.gov numbers, NCT02052310 and NCT02273726) and as wider experience with roxadustat occurs. More patients receiving roxadustat discontinued treatment owing to adverse events than did patients receiving epoetin alfa. Furthermore, we speculate that the between-group difference in the percentage of patients who discontinued may have been due to the open-label trial design, given that the comparator, epoetin alfa, was the only approved treatment option for anemia in patients with chronic kidney disease in China, so there may have been concerns regarding the use of an unfamiliar therapy. No clustering of severe adverse events during treatment was observed in either group. However, the small sample size of this trial and the placebo-controlled trial[37] relative to the larger, international phase 3 trials (NCT02052310 and NCT02273726) should be considered. Long-term safety will also need to be assessed in the international trials.

In conclusion, this phase 3 trial comparing 26 weeks of roxadustat therapy with epoetin alfa therapy in patients undergoing dialysis showed the noninferiority of roxadustat in the treatment of anemia.

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APPENDIX

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