The efficacy and safety of roxadustat in anemia treatment in hemodialysis patients with erythropoietin-hyporesponsiveness

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Research Article

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Abstract

Background

Erythropoietin is an important drug for the treatment of anemia in hemodialysis patients. However, many patients show erythropoietin-hyporesponsiveness. Roxadustat has been shown to be effective in treating patients with anemia due to chronic kidney disease. However, its efficacy and safety in hemodialysis patients with erythropoietin-hyporesponsive anemia remain unclear.

Methods

Erythropoietin-hyporesponsiveness was defined as erythropoietin dose of more than 450U/kg intravenously or 300U/kg subcutaneously for 16 weeks, with hemoglobin rising rate below 1 g/dL/month or 11.0 g/dL. A cohort of hemodialysis patients with anemia and a low response to erythropoietin from January 2020 to December 2020 were treated with roxadustat for 12 weeks to observe changes in hemoglobin, iron metabolism, blood lipid, and inflammatory indicators and to evaluate the safety and efficacy of roxadustat.

Results

There were 56 patients with erythropoietin-hyporesponsiveness, and a total of 44 patients (78.6%) completed the 12-week follow-up, including 16 males (36.4%); patient ages were 54.6±14.2 years. The mean initial treatment dose of roxadustat was 104.4±12.4 mg thrice a week. At week 12, 30 subjects (68.2%) met the protocol-defined primary efficacy endpoint. After 12 weeks of treatment, hemoglobin was significantly increased from 7.81±1.36 g/dL to 9.80±1.94 g/dL (P<0.001), serum ferritin, serum total cholesterol and triglyceride were significantly decreased. While white blood cells and neutrophils significantly increased than baseline.

Conclusion

This study indicated that roxadustat significantly increases hemoglobin levels, improving iron absorption and utilization, reducing cholesterol and triglyceride levels, with good short-term safety profile in hemodialysis patients with erythropoietin-hyporesponsive anemia.

Introduction

Anemia is a common complication in patients with chronic kidney disease (CKD), resulting from a decreased synthesis of erythropoietin by the impaired kidneys as well as altered iron metabolism[1–3]. Although iron therapy and erythropoietin are mainstays of the current CKD-associated anemia treatment paradigm, studies have highlighted shortcomings related to convenience (e.g., mode of administration) and safety (e.g., increased risk of cardiovascular complications, mainly thromboembolic). What's more, there are about 5%-15% of patients with poor efficacy and erythropoietin hyporesponsiveness[4]. Hyporesponsiveness to erythropoietin is a common condition in maintenance hemodialysis patients with

chronic kidney disease, and is associated with increased hospitalizations and mortality. Therefore, it is necessary to explore the pathogenesis of renal anemia and develop effective therapeutic targets to improve the prognosis of patients.

Hypoxia-inducible factor (HIF) is an oxygen-sensitive transcription factor that increases hemoglobin levels by activating the body's natural response to hypoxia independent of cellular oxygen levels[5–8]. Roxadustat is the world's first innovative drug targeting the oxygen sensing pathway of HIF. Previous studies have confirmed that this drug has significant effects in most renal anemia cases[9–16], but there is still a lack of prospective studies assessing the efficacy of erythropoietin in renal anemia. This study aimed to analyze the short-term efficacy and adverse reactions of oral roxadustat in patients with erythropoietin-hyporesponsive anemia, and to evaluate the efficacy and safety of roxadustat in the treatment of erythropoietin-hyporesponsive anemia in hemodialysis patients.

Methods

This was a 12-week, single-arm, multicenter, observational trial to evaluate the efficacy and safety of roxadustat in Chinese patients with chronic kidney disease (CKD)-associated anemia undergoing hemodialysis (HD) and showing a low response to erythropoietin. The study has been registered in the Chinese Clinical Trials Registry (ROAD, roxadustat in treating Anemia in Dialysis patients, registration number ChiCTR1900025765 at http://www.chictr.org.cn; September 7, 2019). The research drug was roxadustat capsule (FibroGen USA, Approval number EHJ-GAS001832; specifications, 50 mg/tablet and 20 mg/tablet. This is an observational study approved by the Ethics Committee of Sichuan Provincial People's Hospital (approval number: No. 196 of 2019). All study procedures complied with the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

The protocol of the original study was present elsewehere[17]. In brief, this is a multicenter, prospective, longitudinal observational cohort study assessing if Roxadustat improves prognosis in dialysis patients. Two hundred and ninety patients were recruited in Sichuan Province from November 2019 to April 2021. The current corhort is a subgroup of the ROAD who met the criteria of erythropoietin-hyporesponsiveness.

Inclusion Criteria were: 1. age ≥ 18 years; 2. dry weight ranging from 45 to 160 kg; 3. stable hemodialysis performed 3 times per week for at least 12 weeks; 4. dialysis sufficiency defined by Kt/V ≥ 1.2: 5. hemoglobin ranging from 7.5 to 11.0 g/dL; 6. erythropoietin-hyporesponsiveness (intravenous erythropoietin injection ≥ 450U/kg or subcutaneous erythropoietin injection ≥ 300U/kg for 16 weeks, including the treatment time before enrollment, but hemoglobin rising rate below 1 g/dL/month or 11.0 g/dL)[18]. Patients were excluded from the study with any other anemia caused by a disease other than CKD, such as thalassemia, sickle cell anemia, pure red blood cell regeneration disorder, or myelodysplastic syndrome; malignant tumors, obvious infection, and blood transfusion within 3 months. A maximum of 2 hemoglobin screening assessments were performed to confirm inclusion criteria.

Treatment period: All patients received oral roxadustat 3 times per week (TIW) for 12 weeks according to the approved dose in the roxadustat Chinese drug label. The recommended starting dose of roxadustat

was based on the patient's dry body weight: 100 mg (45–60 kg) or 120 mg (≥ 60 kg). Patients could take roxadustat at any time before and after dialysis treatment. Throughout the treatment period, the dose of roxadustat was adjusted according to hemoglobin levels to achieve and maintain hemoglobin levels between 11 and 12 g/dL to minimize the need for blood transfusion. During the trial, patients could continue to take antihypertensive drugs, phosphorus binders, calcium preparations, and calcium-sensitive receptor agonists, but discontinue iron medications and drugs known to affect hemoglobin concentration, including erythropoietin, androgens and immunosuppressants. Patients receiving erythropoietin must have an appropriate withdrawal period (e.g., three erythropoietin sessions for three days, and erythropoietin treatment once a week and withdrawal for 7 days).

Post-treatment follow-up: At the end of the treatment cycle, patients were followed up for life status and hospitalization, unless consent to participate was withdrawn.

The primary endpoint was the proportion of subjects demonstrating an increase in hemoglobin of 1 g/dL (for those with baseline hemoglobin < 9.5 g/dL) or 0.5 g/dL (for cases with baseline hemoglobin between 9.5 and 10.0 g/dL) at week 12. Secondary endpoints included hemoglobin levels over time and change from baseline at week 12, changes from baseline in markers of iron metabolism such as hepcidin, ferritin, transferrin, and TSAT, as well as hs-CRP and lipid metabolism.

Safety was evaluated throughout the study period. A complete baseline for each patient was determined from demographics, medical history, clinical laboratory findings, vital signs, and physical evaluation. Cumulative AEs were monitored throughout the study period. Serious adverse events and adverse events were monitored until symptoms subside or stabilize, or study completion.

The SPSS 25.0 software was used for statistical analysis. Measurement data with normal distribution were expressed as mean ± standard deviation (SD) and compared by paired sample t-test. Median and (P25, P75) were used for measurement data of non-normal distribution, which were compared by the rank-sum test. Count data were described by frequency and rate. $p < 0.05$ was considered statistically significant.

Results

Study population

Of the 56 subjects who received roxadustat, 44 (78.6%) completed the 12-week treatment period and 12 (21.4%) were withdrawn. The reasons for withdrawal were death (n = 1), kidney transplantation (n = 1), blood transfusion (n = 1), drug discontinuation caused by adverse events (n = 2), and loss to follow-up (n = 7) (Fig. 1). Participant average age was 54.6 years, and slightly less males (36.4%) than females were enrolled (Table 1). About 29.4% of subjects were diabetic. Mean baseline hemoglobin content was 7.81 g/dL, and all subjects had baseline hemoglobin levels < 10 g/dL. The median prior ESA dose per HD session was 20,000 IU per week, and ESA doses per session were between 20,000 IU and 30,000 IU. All 44

subjects received a roxadustat starting dose of 50 to 120 mg Tiw. The average dose was 104.4 ± 12.4 mg Tiw.

Table 1
Demographic and baseline characteristics

characteristics	Mean
Age, yr	54.6 ± 14.2
Male, n (%)	16 (36.4%)
Diabetic, n (%)	10 (29.4%)
Hgb, g/dl	7.81 ± 1.37
Hs-CRP, ng/l	13.35 ± 25.13
Ferritin, pg/ml	586.2 ± 445.5
TSAT, %	37.6 ± 21.5
Hct, %	25.2 ± 4.5
iPTH, pg/ml	501.1 ± 345.6
WBC, *10^9/L	5.25 ± 2.07
N, *10^9/L	3.79 ± 0.40
L, *10^9/L	0.99 ± 0.40
PLT, *10^9/L	137.8 ± 88.0
ALT, U/L	10.4 ± 8.1
AST, U/L	14.8 ± 7.7
TBIL, U/L	7.8 ± 3.1
TG, mmol/L	2.6 ± 2.3
TC, mmol/L	3.39 ± 1.04
LDL-C, mmol/L	1.78 ± 0.63
ESA dose, U/W	22590.9 ± 4238.9
Roxa dose, mg tiw	104.4 ± 12.4

Efficacy Results

At week 12, 30 subjects (68.2%) met the criteria for protocol-defined primary efficacy endpoint (Table 2). Of these subjects, 25 had baseline hemoglobin levels < 9.5 g/dL and > 1 g/dL increases in hemoglobin

levels from baseline at week 12. At week 12, 5 subjects had hemoglobin increases of 0.5 g/dL, with 9.5 g/dL ≤ baseline hemoglobin levels < 10.0 g/dL (Table 2).

Table 2
Summary of subjects meeting the efficacy endpoints

week	12
Number of patients	44
Overall subjects met primary endpoint	30(68.2%)
Hgb increase 1g/dl with baseline Hgb < 9.5 g/dl	25(69.4%)
Hgb increase 0.5 g/dl with 9.5 g/dl ≤ baseline Hgb < 10.0 g/dl	5(62.5%)

After 12 weeks of roxadustat treatment, mean hemoglobin levels in 37 patients increased from 7.81 ± 1.36 g/dL to 9.80 ± 1.94 g/dL (Fig. 2). Mean hemoglobin levels throughout the roxadustat treatment period were between 8.61 g/dL and 9.87 g/dL. Mean increases in hemoglobin levels from baseline were observed at all visits during the treatment period (Fig. 2).

Changes In Iron Metabolism

After 12 weeks of roxadustat treatment, serum ferritin decreased from 626.91 ± 469.68 ng/ml to 426.07 ± 358.73 ng/ml (Fig. 3), and the difference was statistically significant. TSAT decreased from 44.74–37.58%, and the difference was not statistically significant (Fig. 3), suggesting that roxadustat could improve iron metabolism and keep TSAT stable.

Changes In Serum Lipid Metabolism

Serum total cholesterol amounts in enrolled patients decreased from 3.61 ± 0.93 mmol/L to 2.70 ± 0.63 mmol/L, low-density lipoprotein cholesterol decreased from 1.88 ± 0.60 mmol/L to 1.31 ± 0.40 mmol/L, and serum triglyceride decreased from 2.09 ± 1.02 mmol/L to 1.47 ± 0.73 mmol/L, and the differences were statistically significant (Fig. 3), suggesting that oral administration of roxadustat 3 times a week could lower serum lipid amounts in patients with maintenance hemodialysis.

After 12 weeks of roxadustat treatment, there were no significant changes in hS-CRP levels (Fig. 3), but WBC levels in the enrolled patients increased from 5.25 ± 2.07*10^9/L to 5.86 ± 2.58 10^9/L, while neutrophils increased from 3.79 ± 1.65*0^9/L to 4.30 ± 2.29*0^9/L, and the differences were statistically significant (Fig. 3).

We also divided these patients into the ineffective (patients not reaching the endpoint events) and effective (patients who reached the endpoint events) groups, and found no significant differences in these parameters at baseline between the two groups (Table 3).

Table 3
subgroup analysis by divided patients into ineffective (patients who didn't reach the endpoint events) and effective (patients who reached the endpoint events) groups.

characteristics	Ineffective N = 14	Effective N = 30	P-value
Age, yr	50.3 ± 15.1	56.7 ± 13.5	0.166
Male, n (%)	6(42.9%)	10(33.3%)	0.738
Hgb, g/dl	7.77 ± 1.38	7.82 ± 1.38	0.908
hsCRP, ng/l	5.87 ± 5.28	14.96 ± 27.52	0.586
Ferritin, pg/ml	546.77 ± 451.34	612.46 ± 452.65	0.700
TSAT, %	32.50 ± 13.30	40.86 ± 25.22	0.281
Hct, %	24.09 ± 4.41	25.73 ± 4.49	0.262
iPTH, ng/l	525.38 ± 259.14	490.32 ± 381.84	0.784
WBC, *10^9/L	5.46 ± 2.15	5.14 ± 2.07	0.676
N, *10^9/L	3.85 ± 1.78	3.76 ± 1.62	0.879
L, *10^9/L	1.16 ± 0.42	0.90 ± 0.37	0.076
PLT, *10^9/L	149.83 ± 101.42	131.23 ± 81.55	0.564
ALT, U/L	10.84 ± 6.14	10.24 ± 9.12	0.829
AST, U/L	13.89 ± 8.16	15.27 ± 7.50	0.597
TBIL, U/L	8.45 ± 2.52	7.37 ± 3.32	0.302
TG, mmol/L	3.47 ± 3.51	2.12 ± 0.97	0.262
TC, mmol/L	3.78 ± 0.78	3.15 ± 1.13	0.137
LDL-C, mmol/L	2.04 ± 0.55	1.63 ± 0.66	0.159

Discussion

Maintenance hemodialysis is the main treatment for end-stage renal disease, which can prolong the survival time of patients, but easily leads to renal anemia. Erythropoietin is an important drug for the treatment of anemia in hemodialysis patients. However, there are many patients with erythropoietin-hyporesponsive anemia. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that has been shown to be effective in treating patients with anemia due to chronic kidney disease. This study indicated for that roxadustat significantly increased hemoglobin levels, improved iron absorption and

utilization and reduced cholesterol, with good short-term safety in hemodialysis patients with erythropoietin-hyporesponsive anemia.

Hypoxia-inducible factor (HIF) is a transcriptional factor that regulates gene expression in RBC production, angiogenesis, and anaerobic metabolism under hypoxia[7, 8, 19]. Roxadustat, the only new drug marketed by HIF-PHI, has been shown to be effective in the treatment of renal anemia in both dialysis and non-dialysis patients with CKD anemia in phase I-III clinical studies[9–11, 15, 20]. The results of this study showed that in hemodialysis patients with erythropoietin-hyporesponsive anemia, the levels of hemoglobin and HCT in 44 patients after 12 weeks of roxadustat treatment were significantly higher than baseline values. Moreover, hemoglobin began to increase significantly after taking roxadustat, especially at week 12, indicating that roxadustat can quickly and effectively improve anemia index level in renal anemia patients with maintenance hemodialysis.

This study also showed that in hemodialysis patients with erythropoietin-hyporesponsive anemia, roxadustat significantly reduced serum ferritin and maintained TSAT stability. This corroborates studies evaluating the safety and efficacy of roxadustat in the treatment of non-dialysis and dialysis-dependent patients with chronic kidney disease[9–11, 14, 15]. However, no significant difference in TSAT was observed in this study, which may be related to the small sample size of this study. Hemodialysis patients have an imbalance of iron homeostasis due to a variety of reasons, including decreased appetite in CKD patients, commonly used drugs (such as phosphorus binding agents and antacids) affecting the uptake of iron by small intestinal epithelial cells, concurrent inflammatory state and so on. In particular, the relative iron supply is insufficient due to the increased iron demand during the use of erythropoietin[16, 21, 22]. Roxadustat improves anemia by reducing serum ferritin amounts, increasing total iron-binding and increasing iron utilization[6, 23, 24]. It has a potential clinical application value in erythropoietin hyporesponsive anemia patients with iron metabolism disorder.

In addition to the erythropoietic effects of roxadustat, it was associated with lower plasma lipid levels in this study. This was consistent with previous studies of roxadustat in patients with non-dialysis-dependent and dialysis-dependent CKD[16, 25–27]. This is the first time that roxadustat was found to have the same cholesterol and triglyceride lowering effects in hemodialysis patients with erythropoietin-hyporesponsive anemia. None of the enrolled patients took lipid-lowering drugs during the whole study period. The underlying mechanisms of roxadustat involved in lowering lipid levels may be related to HIF1α directly regulating the expression of a number of genes possibly affecting lipid metabolism[16, 25, 28, 29].

In addition, no statistically significant difference was observed in hsCRP levels after 12 weeks of roxadustat treatment in this study, while WBC and neutrophil amounts were significantly increased. These findings are inconsistent with previous studies assessing the effect of roxadustat in patients with inflammation[11, 26]. This may indicate that inflammation does not affect the therapeutic effect of roxadustat in hemodialysis patients with erythropoietin-hyporesponsive anemia.

Of the 56 subjects administered roxadustat, 44 (78.6%) completed the 12-week treatment period and 12 (21.4%) were withdrawn. The reasons for withdrawal were death (n = 1), kidney transplantation (n = 1), blood transfusion (n = 1), drug discontinuation caused by adverse events (n = 2), and loss to follow-up (n = 7). There were no significant differences in liver function, iPTH, and hsCRP among the 44 patients treated with roxadustat at 12 weeks from baseline. The short-term safety of roxadustat is good. Studies have shown that the main adverse reactions of roxadustat include mild diarrhea, nausea, and headache[30, 31]. Such adverse reactions were not recorded in this study, which may be related to the short observation time. Closer attention should be paid to the safety of roxadustat, especially regarding its potential effects on tumor formation and the cardiovascular system. In addition, long-term clinical trials are warranted to examine the long-term safety of roxadustat.

This study had some limitations, including the small sample size and insufficient observation time. As a new drug, the long-term efficacy and safety of HIF-PHI in patients with erythropoietin-hyporesponsive anemia need to be further clarified; specifically, in terms of long-term treatment, more evidence-based findings are needed.

This study indicate that roxadustat can significantly increase hemoglobin levels, improve iron absorption and utilization and reduce lipid levels, with a good short-term safety profile in hemodialysis patients with erythropoietin-hyporesponsive anemia. Moreover, the drug is an oral preparation and easy to use, has good compliance, and can be popularized in patients with erythropoietin hyporesponsiveness.

Declarations

Competing interests

The authors declare that the research was conducted in the absence of anycommercial or financial relationships that could be construed as a potentialconflict of interest.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at Sichuan Provincial People's Hospital (2019 − 196). The informed consent obtained from study participants will be written.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Authors' contributions

Yang Zou, Dan Chang, Amanda Y Wang, Jingdong He, Mingzhu Li, Yanrong Cai, Jinxi Wei, Dongmei Yang, Dong He, Min Lei, Fei Deng, Qiang He, Hen Xue, Daqing Hong, and Guisen Li contributed to acquisition and interpretation of data. Dan Chang participated in writing the manuscript. Yang Zou, Dan Chang, Amanda Y Wang, Jingdong He, Mingzhu Li, Daqing Hong, and Guisen Li have read and approved the final version for submission. Jingdong He and Daqing Hong substantially revised it.

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Figures

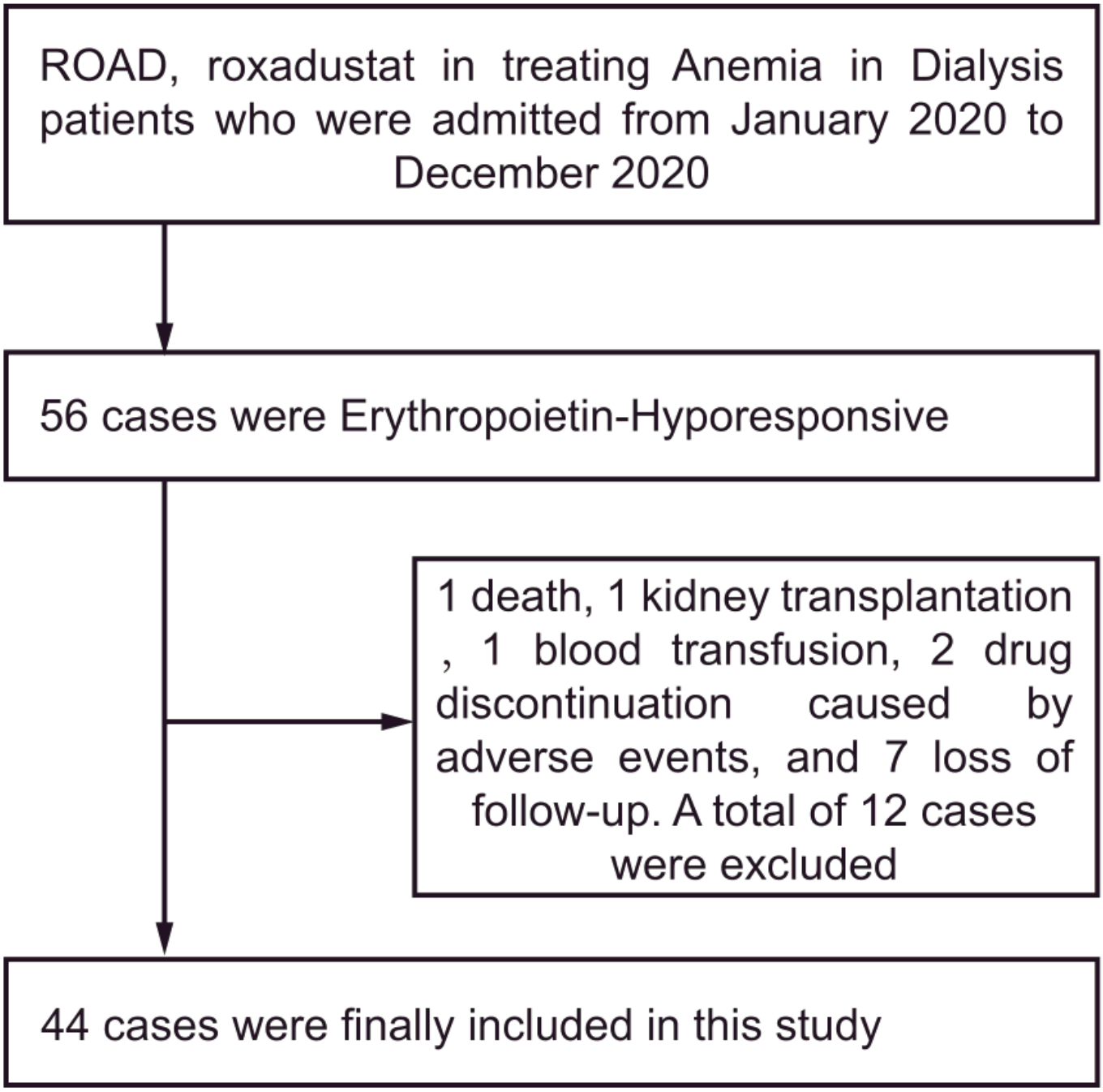

Figure 1

Patients flow

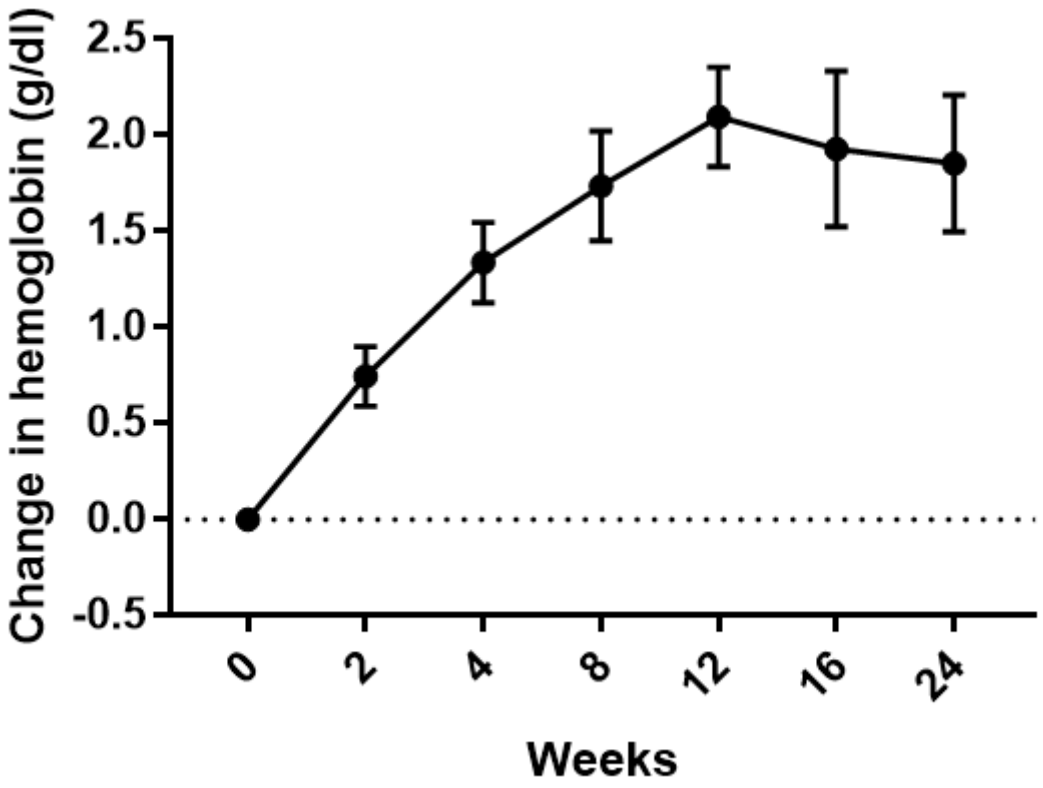

Figure 2

Hemoglobin over time and change from baseline at selected visits

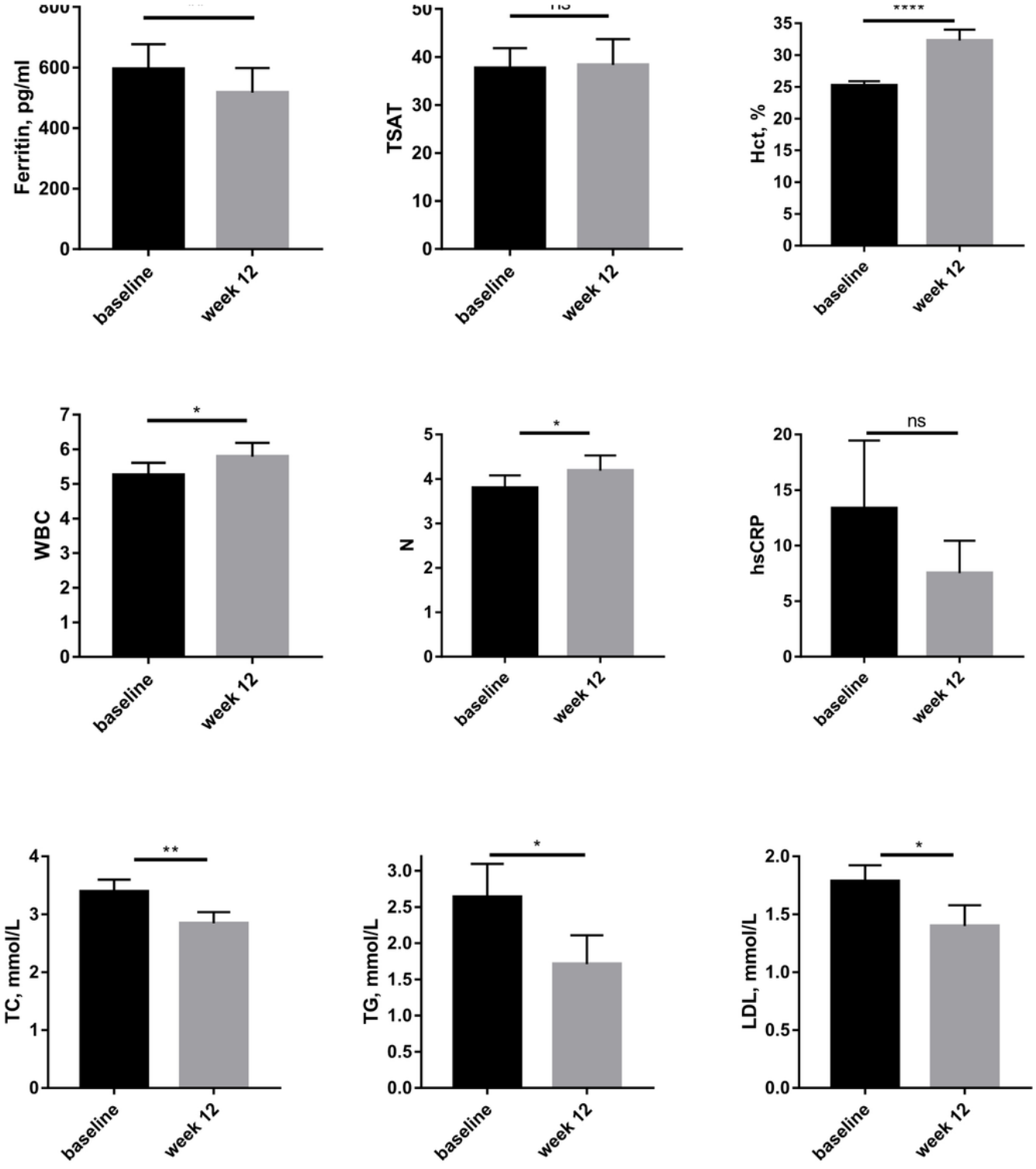

Figure 3

parameters changes from baseline to 12 weeks after roxadustat treatment.