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RESEARCH ARTICLE

Roxadustat Efficacy in Hemodialysis Patients with Epoetin-Hyporesponsive Anemia

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ABSTRACT

Objective: A reduced treatment response to epoetin (EPO) therapy is a clinical challenge among hemodialysis (HD) patients. Outcomes of roxadustat in HD patients who had hyporesponse to EPO therapy were investigated.

Materials and Methods: This retrospective study analyzed adult patients undergoing long-term HD. Hyporesponsiveness to EPO was defined as a hemoglobin (Hb) level consistently below 10 g/dL despite receiving maximum EPO and having adequate iron stores for at least three months. The target Hb threshold for following roxadustat was defined as ≥11 g/dL.

Results: A total of 227 HD patients were screened, and 25 patients were enrolled. The mean age was 55.1±17.5 years. Median HD duration was 47 (19–118) months. Average Hb during the EPO treatment was 8.7±0.7 g/dL, compared to 9.8±1.3 g/dL during the roxadustat treatment. Increased Hb following roxadustat was observed in 17 patients (68.0%). Target Hb was achieved in 14 (56%) patients following roxadustat. Erythropoietin resistance index was 17.6±1.4 IU/kg/gHb in patients who responded to roxadustat, whereas it was 19.4±3.3 IU/kg/gHb in non-responders (p=0.087). The average Hb level was significantly increased during the roxadustat period (p=0.011). Lower uric acid (p=0.003) and higher Kt/V (p=0.044) were observed in patients who achieved target Hb. Pre-treatment transferrin saturation was correlated with the amount of Hb change following roxadustat (p=0.034).

Conclusion: The current study should be considered a pioneering effort, and findings support significant treatment success with roxadustat.

Keywords: Anemia, epoetin, hemodialysis, roxadustat

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INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD) and is associated with poor outcomes. The underlying mechanisms of anemia associated with CKD are diverse and complex. Diminished endogenous erythropoietin production, reduced erythrocyte survival duration, functional iron deficiency, and inflammation with increased hepcidin levels are some of the causes.[1]

The frequency and severity of anemia gradually increase in the advanced stages of kidney disease, and an association between lower estimated glomerular filtration rate (eGFR) and the prevalence of anemia is observed. Furthermore, lower hemoglobin (Hb) levels are associated with an increased risk of CKD progression, cardiovascular disease, stroke, and death when adjusting for age, race, and eGFR.[2]

The severity of anemia significantly increases in patients undergoing hemodialysis. Blood transfusion requirements also increase in this population. In addition, both iron deficiency and anemia are worsened with HD procedures and frequent blood sampling.[3]

Erythropoiesis-stimulating agents are the cornerstone of renal anemia management in iron-replete HD patients. Before the availability of recombinant human erythropoietin (rHuEPO), dialysis patients frequently required blood transfusions that exposed them to the risks of iron overload, transmission of viral infections, and enhanced immune sensitization.[4]

More recently, hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), such as roxadustat and daprodustat, have been introduced as therapeutic options for anemia in patients with CKD.[5] HIF-PHIs increase endogenous erythropoietin

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levels by stimulating transcription of the erythropoietin gene in the kidneys and liver. Additionally, HIF-PHIs increase the amount of iron available for erythropoiesis by increasing intestinal iron absorption and decreasing iron sequestration.[6]

In the current study, we examined the efficacy of roxadustat in a specific subgroup of CKD. We reported the clinical outcomes of roxadustat use among HD patients who had an insufficient response to epoetin (EPO) treatment.

MATERIALS and METHODS

Ethical Approval

This study protocol was approved by the Agri Ibrahim Cecen University Ethics Committee (date: 28.11.2024, number: 410). This clinical investigation was carried out in accordance with the 1964 Helsinki Declaration. The data for this study, obtained from the patients' medical records, were anonymized so that the patients could not be identified. Human rights are well protected.

Study Design

This retrospective study was conducted on adult hemodialysis (HD) patients with renal anemia at the Nephrology Clinic of Ağrı Training and Research Hospital. The patient screening period spanned from January 1, 2023, to January 1, 2025, encompassing a two-year duration. The key inclusion criterion was a history of oral roxadustat treatment for at least three months due to a hyporesponse to previous EPO therapy. Roxadustat treatment response was analyzed with demographic characteristics, clinical features, and laboratory findings. Patients who had not received EPO treatment prior to roxadustat initiation, or who were administered EPO and roxadustat concurrently, were excluded from the study. Additionally, patients diagnosed with hematologic disorders or malignancies were also excluded.

Definitions

Hyporesponsiveness to EPO was defined as a Hb level consistently below 10 g/dL despite receiving the maximum EPO dosage and having adequate iron stores (ferritin >500 ng/mL) for at least three months. The maximum EPO dosage was defined as 150 IU/kg/week for EPO (alfa, beta, or zeta) and 0.75 mcg/kg/week for darbepoetin. A standard roxadustat regimen was defined for all patients according to: 70 mg orally, three times per week, following dialysis sessions.

Two timeframes were designated for evaluating anemia treatment. The "EPO period" referred to the last three months before initiating roxadustat, while the "roxadustat period" referred to the first three months after its initiation.

The target Hb threshold for renal anemia management in patients was defined as >11 g/dL. Based on their response to roxadustat, patients were categorized into two groups: (1) the responder group, in which patients achieved an Hb level of ≥11 g/dL at least once, and (2) the non-responder group, whose Hb levels remained below 11 g/dL throughout the treatment period.

The erythropoietin resistance index (ERI) is a widely used parameter for evaluating hyporesponsiveness to erythropoietin in clinical studies. ERI, expressed in IU/kg/gHb, is calculated by ERI = total EPO dose per week (IU) / body weight (kg) / hemoglobin (g/dL). An ERI value of ≥10.0 IU/kg/gHb is used as the threshold to define resistance to EPO.[7,8]

Laboratory values used in the analysis were obtained from the month in which the roxadustat therapy was initiated. Pre-dialysis samples were collected before the HD session to measure urea, creatinine, uric acid, electrolytes, bicarbonate, glucose, total protein, albumin, parathyroid hormone (PTH), complete blood count, ferritin, transferrin saturation (TSAT), iron levels, and nutritional values (folic acid and vitamin B12). Post-dialysis samples were obtained after reducing the blood pump rate to 100 mL/min for 15 seconds and subsequently stopping it. Post-dialysis urea and creatinine levels were recorded. Dialysis adequacy was assessed using both the urea reduction ratio (URR) and Kt/V, calculated using the second-generation single-pool Daugirdas formula.[9] URR was calculated as URR = (Predialysis Urea – Postdialysis Urea) / Predialysis Urea.

Statistical Analysis

Statistical analyses of the study were performed using SPSS 22.0 (SPSS Inc., Chicago, USA). The Shapiro-Wilk test was employed to assess whether numerical data followed a normal distribution. Numerical data showing a normal distribution were presented as mean±standard deviation, while non-normally distributed numerical data were presented as median (1st–3rd quartiles). Non-numerical (categorical) data were expressed as percentages. To compare the differences between groups, either a two-sided independent samples t-test or Mann-Whitney U test was used for continuous variables, and Pearson χ^2 analysis or Fisher's exact test was used for categorical variables. The Spearman correlation coefficient was used to explore the relationship between numerical variables. The paired t-test was used to analyze normally distributed parameters. The chi-square test was employed to assess non-numerical data. Results were evaluated at a 95% confidence interval, with significance set at $p<0.05$.

RESULTS

A total of 227 HD patients were identified, of whom 25 met the inclusion criteria and were enrolled in the study. The patients comprised 13 males (52.0%) and 12 females (48.0%). The mean age of the patients was 55.1±17.5 years, and the average body mass index (BMI) was 22.4±4.3 kg/m². The median duration of hemodialysis was 47 months (19–118). The mean URR was 75±5.6, and the median Kt/V value was 1.73±0.29. No cases of dialysis inadequacy were observed.

With respect to vascular access, 19 patients (76.0%) had an arteriovenous fistula, 5 patients (20.0%) had a tunneled dialysis catheter, and 1 patient (4.0%) had an arteriovenous graft. Baseline patient characteristics are summarized in Table 1.

Regarding EPO use, 15 patients received epoetin alfa, and 10 patients received epoetin zeta. None of the patients were treated with epoetin beta or darbepoetin. The average ERI was 18.4±2.5 IU/kg/gHb. A history of blood transfusion prior to roxadustat treatment was identified in 8 patients (32.0%). Maintenance intravenous iron supplementation was documented in 14 patients (56.0%) prior to roxadustat initiation.

The mean Hb level during the EPO treatment period was 8.7±0.7 g/dL, compared to 9.8±1.3 g/dL during the roxadustat treatment period. An increase in Hb level following roxadustat therapy was observed in 17 patients (68.0%). These results are illustrated in Figure 1.

Prior to roxadustat treatment, the median serum ferritin level was 655 ng/mL (570–914), serum iron was 49 µg/dL (41–73), TSAT percentage was 28 (26–43), folic acid was 6.3 µg/L (5.3–8.1), and vitamin B12 was 457 pg/mL (326–687). The mean MCV was 89.1±5.9 fL, the mean leukocyte count was 6.8 ±2.2 ×10³/µL, and the median platelet count was 173×10³/µL (143–205).

Target Hb level was achieved in 14 (56%) patients after roxadustat treatment. In a comparison of the two anemia treatment periods, the average Hb level was statistically significantly increased during the roxadustat period (p=0.011). The course of Hb levels according to treatment periods was demonstrated in Figure 2.

The ERI was 17.6±1.4 IU/kg/gHb in patients who responded to roxadustat and 19.4±3.3 IU/kg/gHb in non-responders. Although the average ERI was lower in patients who achieved the target Hb following roxadustat treatment, the difference was not statistically significant (p=0.082).

Patients were compared based on their response to roxadustat treatment. In the demographic analysis, there were no significant differences between the responder and non-responder groups in terms of age, duration of HD, or BMI. The proportion of female patients who achieved the target Hb level following roxadustat therapy was significantly higher than that of male patients (83.3% vs. 30.7%, p=0.008).

In the laboratory comparison, significant differences were observed between the two groups in pre-dialysis levels of urea, potassium, uric acid, and vitamin B12. Additionally, the mean Kt/V value was higher in patients who responded to

Table 1. Baseline characteristics of the patients

Parameters	**Results**	
	n	**%**
Gender		
Male	13	52
Female	12	48
Age (years)	55.1±17.5	
BMI (kg/m²)	22.4±4.3	
Hemodialysis duration (months)	47 (19–118)	
Kt/V	1.73±0.29	
URR (%)	75±5.6	
Vascular access		
AV fistula	19	76
Tunneled catheters	5	20
AV graft	1	4
CKD etiology		
Diabetes mellitus	9	36
Hypertension	7	28
Glomerulonephritis	5	20
Urological problems	2	8
Others	2	8
Blood transfusion history	8	32
Kidney transplantation history	3	12
RAS blockage use		
ARBs	6	24
ACEIs	5	20
Treatments		
Iron repletion	14	56
Vitamin D analogs	17	68
Calcimimetics	9	36
Vitamin supplements	25	100

Values are expressed as n (%), mean±standard deviation, median (1st-3rd quartiles). BMI: Body mass index; BSA: Body surface area; CKD: Chronic kidney disease; URR: Urea reduction rate; AV: Arteriovenous; ACEIs; Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; RAS: Renin-angiotensin system

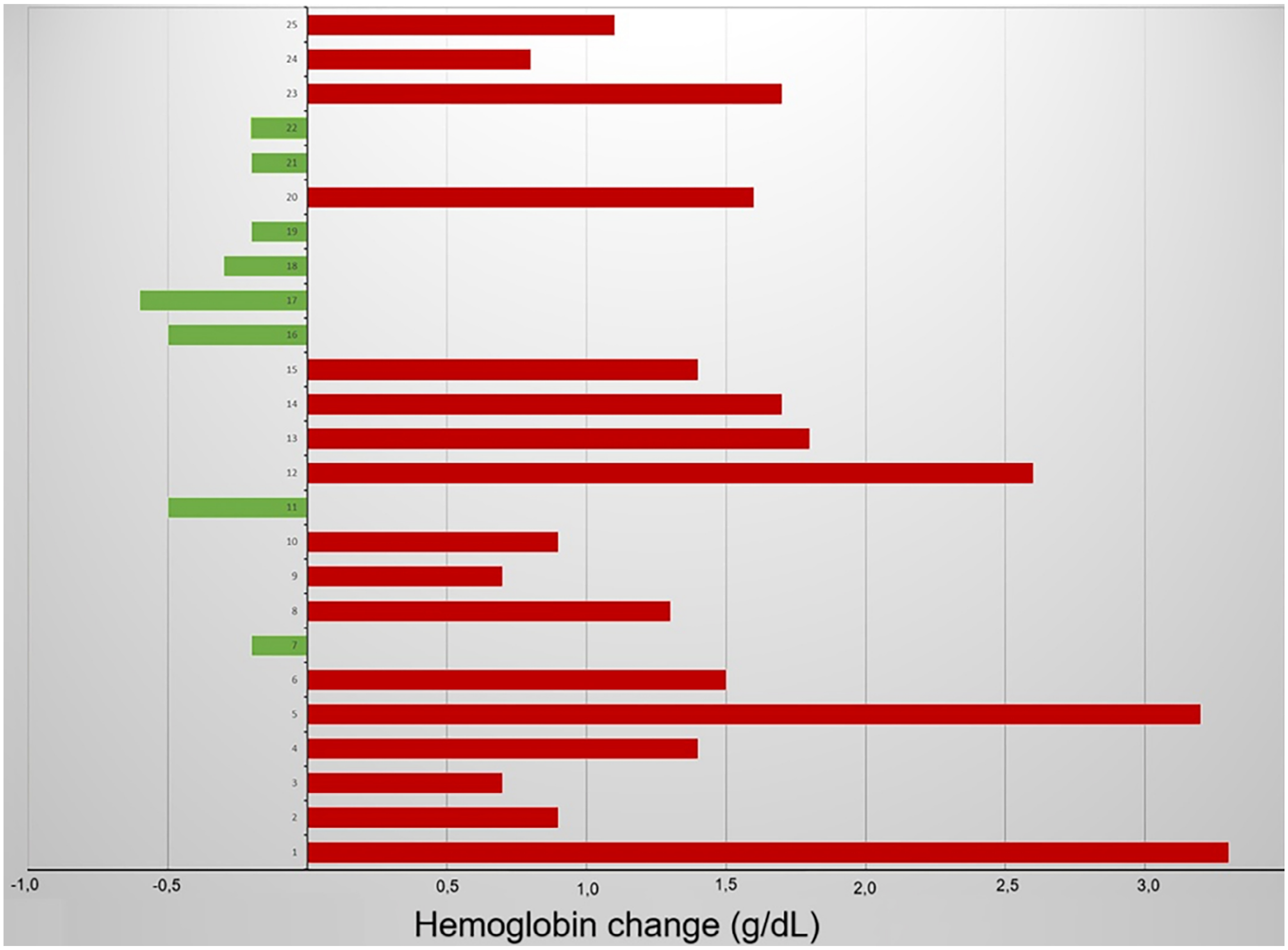

Figure 1. Quantitative hemoglobin change after roxadustat treatment for each patient

roxadustat treatment (1.83±0.3) compared to those who did not respond (1.60±0.2), with a statistically significant difference (p=0.044). In contrast, URR did not differ significantly between the groups (p=0.087). A summary of these findings is presented in Table 2.

The change in Hb levels was significantly correlated with TSAT percentage (p=0.034), as illustrated in Figure 3. However, no significant correlation was observed between Hb changes and either ferritin levels (p=0.893) or serum iron levels (p=0.306). Also, there was no correlation between ERI and change in Hb level (p=0.333). Additionally, an inverse correlation was found between Hb change and patient age (p=0.018), and this is shown in Figure 4. The increase in hemoglobin following roxadustat treatment was inversely associated with PTH levels (p=0.039), whereas no significant correlation was observed between the ERI value and PTH levels (p=0.080). Roxadustat treatment response was not associated with RAS blockage use (p=0.495).

DISCUSSION

In this study, we demonstrated the results of roxadustat treatment in HD patients who could not reach an adequate Hb level with conventional EPO treatment. We observed that 56% of the patients achieved the target Hb level (≥11 g/dL) following roxadustat treatment over a 12-week period. This rate is not negligible for an arduous patient subgroup, because all patients had persistently low Hb levels (<10 g/dL) for at least 3 months under 150 IU/kg per week EPO treatment. Also, the average ERI was 18.4±2.5 IU/kg/gHb in our cohort.

Data from both clinical and experimental studies reveal that the etiology of anemia in CKD is multifactorial; however, relative erythropoietin deficiency remains the most prominent factor. Furthermore, the positive outcomes observed in patients treated with rHuEPO strongly support the notion that erythropoietin deficiency is the primary driver of anemia in this population.[10] Several factors—including advanced age,

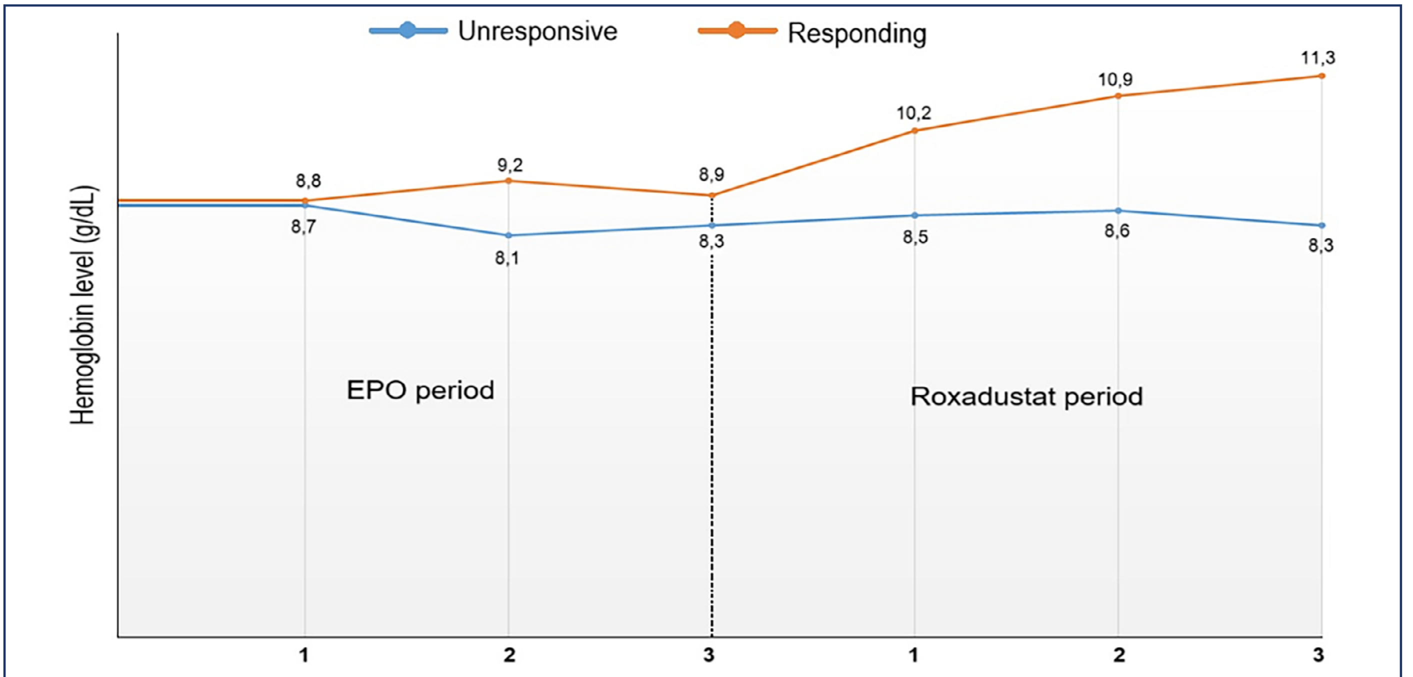

Figure 2. Comparison of the outcomes between two anemia treatment periods

higher BMI, use of renin-angiotensin system (RAS) blockers, diabetes mellitus, and severe secondary hyperparathyroidism—are associated with higher EPO dosage requirements.[11]

A reduced responsiveness to EPO therapy is a common clinical challenge among dialysis patients and is linked to increased mortality and a greater need for erythrocyte transfusions.[12] The underlying mechanisms of hyporesponsiveness to EPO are not yet fully understood. The common causes are iron deficiency, inadequate dialysis, and chronic inflammation.

Table 2. Comparison of laboratory findings according to roxadustat treatment response

Parameters	Target hemoglobin response		p	Parameters	Target hemoglobin response		p
	Present (n=14)	Absent (n=11)			Present (n=14)	Absent (n=11)	
Kt/V	1.83±0.3	1.60±0.2	**0.044**	Protein (g/dL)	6.8±0.6	6.7±0.6	0.718
URR	76.9±5.8	73.1±4.8	0.087	Albumin (g/dL)	3.7±0.3	3.4±0.4	0.099
Urea (mg/dL)	110±33	148±50	**0.030**	Glucose (mg/dL)	113 (97–138)	139 (106–190)	0.250
Creatinine (mg/dL)	6.9±1.8	8.3±2.1	0.100	MCV (fL)	87.7±5.8	89.3±5.8	0.473
Uric acid (mg/dL)	5.2±0.9	6.7±1.2	**0.003**	Iron (µg/dL)	53 (43–75)	45 (37–72)	0.460
Sodium (mmol/L)	136±2.9	136±3.1	0.853	TSAT (%)	29 (27–48)	26 (22–42)	0.170
Potassium (mmol/L)	4.6±0.6	5.3±0.8	**0.039**	Ferritin (ng/mL)	647 (537–993)	780 (602–887)	0.381
Calcium (mg/dL)	9.2±0.8	8.8±0.6	0.213	Vitamin B12	352 (297–532)	680 (483–1062)	**0.021**
Phosphate (mg/dL)	5.2±1.2	5.4±1.2	0.661	Folic acid	5.6 (4.9–6.4)	5.3 (4.5–14.3)	0.874
CaXP (mg^2/dL^2)	47.±10.9	47.3±10.9	0.970	Leukocyte ($10^3/µL$)	6.3 (5.7–8.1)	5.6 (5.0–8.0)	0.477
PTH (pg/mL)	519 (420–893)	368 (285–721)	0.171	Platelet ($10^3/µL$)	189 (171–252)	155 (132–176)	0.071

Values are expressed as mean±standard deviation, median (1st-3rd quartiles). URR: Ure reduction rate; BMI: Body mass index; PTH: Parathyroid hormone; TSAT: Transferin saturation; MCV: Mean corpuscular volume

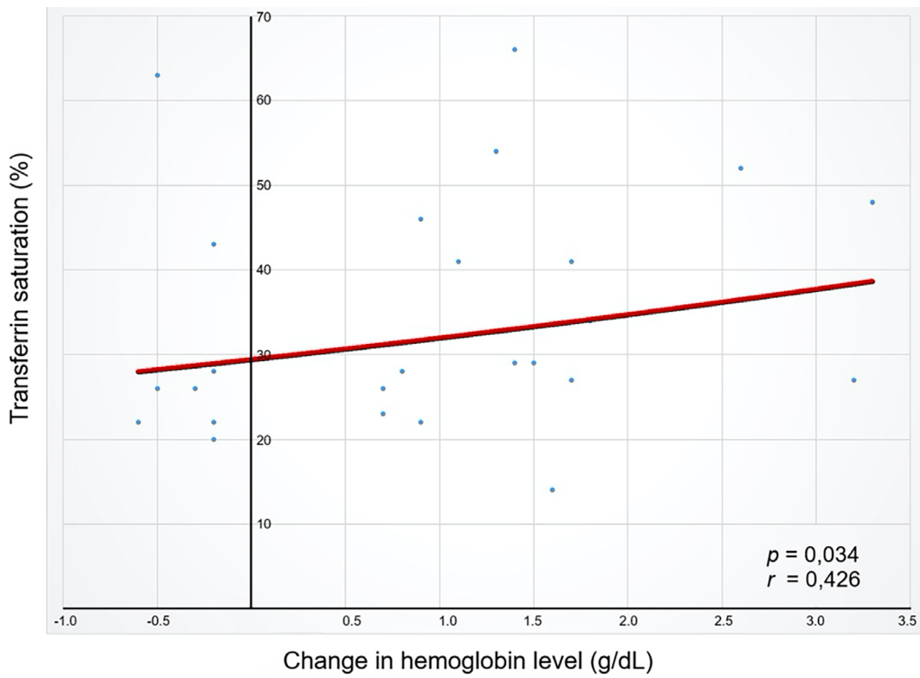

Figure 3. Spearman correlation analysis test revealed the relationship between transferrin saturation and changes in hemoglobin

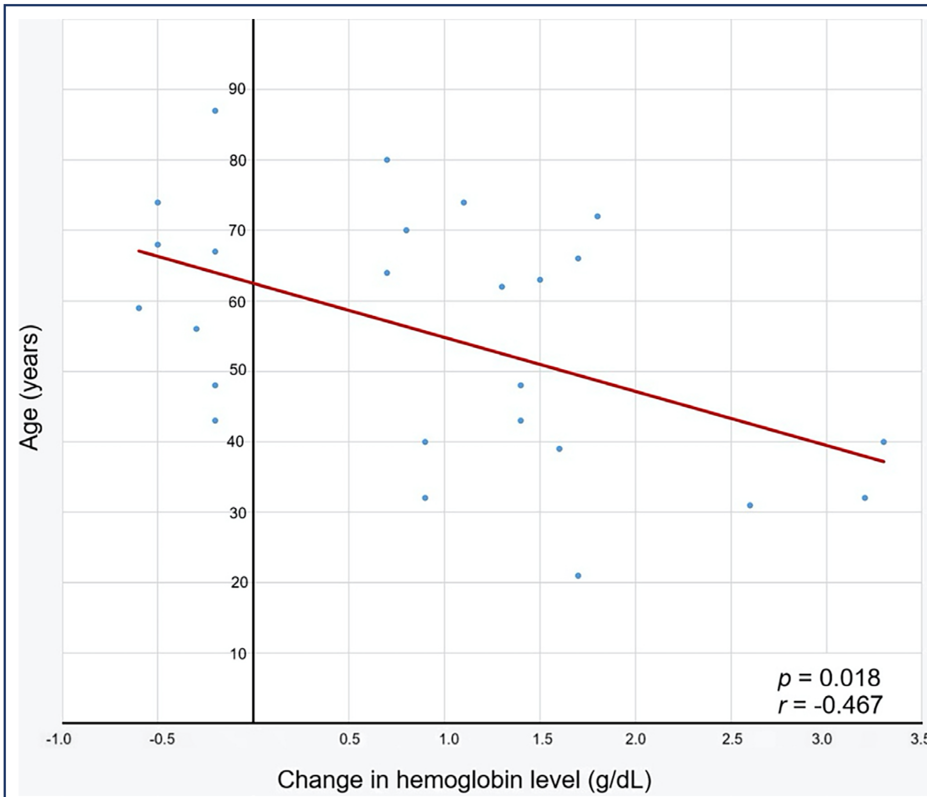

Figure 4. Spearman correlation analysis test revealed the relationship

Criteria for EPO hyporesponsiveness are not well defined. The Kidney Disease Outcomes Quality Initiative (KDOQI) suggests a criterion of inability to achieve a desired Hb concentration using a maximum dose of 450 IU/kg per week intravenous EPO or 300 IU/kg per week subcutaneous EPO.[13] According to data from the United States Renal Data System (USRDS), a study analyzing adult HD patients between 2016 and 2019 reported varying prevalence rates of EPO hyporesponsiveness depending on the definition used. When defined by a high ERI, the prevalence was 22.2%, whereas it ranged from only 2.1% to 6.0% when defined as having a Hb level below 10 g/dL for a duration of 3 to 6 months.[14] A retrospective study analyzing data from 1,934 hemodialysis patients receiving treatment for renal anemia found that the ERI was lower in patients with higher serum albumin levels and higher TSAT levels. In contrast, elevated PTH levels and the use of RAS blockers were associated with increased EPO resistance.[15] In our HD center, the prevalence of EPO hyporesponsiveness anemia was 11.0%.

We analyzed ERI regarding response to roxadustat treatment. Although the average ERI was lower in patients who achieved the target Hb, the difference was not statistically significant. Also, there was no correlation between ERI and Hb changes.

In addition, we determined several laboratory parameters which were associated with roxadustat treatment response. Lower uric acid level, lower predialysis urea level, and higher Kt/V values were observed in patients who achieved target Hb following roxadustat. Furthermore, TSAT percentage prior to treatment was correlated with the change in Hb level following roxadustat treatment.

Peritubular interstitial fibroblast-like cells are the primary source of erythropoietin production in the kidneys. The rapid induction of erythropoietin synthesis is among the earliest and most sensitive physiological responses to hypoxia. The hypoxia-inducible factors (HIFs) regulate the molecular mechanisms linking hypoxia and erythropoiesis. The transcriptional activity of HIFs is primarily managed by their degradation rate, which is controlled by oxygen-sensing enzymes known as prolyl hydroxylase. Under hypoxic conditions, the activity of prolyl hydroxylase enzymes decreases, leading to the accumulation of HIF-α subunits and enhanced HIF transcriptional activity. This, in turn, stimulates the expression of erythropoietin, erythropoietin receptors, and proteins that facilitate intestinal iron absorption and the recycling of iron from macrophage iron stores.[6,16–19]

Recognizing the crucial roles of the HIF-prolyl hydroxylase pathway in regulating erythropoiesis has paved the way for new therapeutic strategies in the management of renal anemia. Roxadustat is a member of oral HIF-PHI. Additionally, roxadustat is now safely used worldwide in the management of anemia in kidney diseases as an alternative to EPO therapy.

Chen et al.[5] evaluated the efficacy of roxadustat in comparison to epoetin alfa in 305 long-term dialysis patients. The study found that roxadustat led to a greater increase in Hb levels from baseline compared to EPO alfa. Additionally, roxadustat was more effective in increasing transferrin and serum iron levels, while also attenuating the decrease in transferrin saturation when compared to EPO alfa. Furthermore, roxadustat was associated with a mean reduction in hepcidin of 30.2 ng/mL, compared to a reduction of only 2.3 ng/mL in the epoetin alfa group. As a result, the authors concluded that oral roxadustat was noninferior to EPO alfa in the anemia treatment.

Although peritoneal dialysis patients generally tend to have higher Hb levels and require lower EPO doses, roxadustat proved effective in the treatment of anemia in these patients, showing non-inferiority to EPO treatment.[20] Additionally, roxadustat improved Hb levels without compromising renal function in kidney transplant recipients with post-transplant anemia.[21] Furthermore, red blood cell (RBC) survival time was significantly longer in HD patients treated with roxadustat (75.5 days) compared to those treated with rHuEPO (65.0 days).[22]

Xu et al.[23] investigated the effect of roxadustat on erythropoietin-hyporesponsive anemia in patients undergoing chronic hemodialysis. The addition of low-dose roxadustat (50 to 70 mg, three times per week) to EPO treatment resulted in an increase in Hb levels after 12 weeks. The mean Hb level rose from 7.7 g/dL to 9.2 g/dL following roxadustat treatment. The Hb response rate was observed to increase by 72%. In our HD center, the roxadustat response rate was 56% in a similar population.

Daprodustat is another member of the HIF-PHI class, and its efficacy was investigated as an anemia treatment in HD patients who were hyporesponsive to rHuEPO. A total of 15 participants were enrolled, with 7 (47%) completing the 16-week treatment regimen. At the 16-week mark, 2 of the 7 subjects (29%) experienced an increase of >1 g/dL in Hb from baseline.[24] In our HD center, 12 patients (48%) experienced an increase of >1 g/dL in Hb from baseline after roxadustat.

When considered in the context of previous research, our findings are consistent with those reported in the literature. One of the key findings of this study is the absence of a statistically significant association between the response to roxadustat treatment and the ERI value. Moreover, in terms of patient numbers, although our sample size may appear small, similar numbers have been reported in studies in the literature conducted on comparable patient groups (HD patients with EPO hyporesponsiveness).

The most important reported adverse effects of roxadustat include thrombotic events (2.9%), liver damage (3.9%), thyroid dysfunction, and hyperkalemia.[25] In our HD center, all patients well tolerated oral roxadustat treatment. No treatment-related complications were observed in the patients throughout the study period.

One of the key limitations of this study is the relatively small sample size, which is attributable to the study being conducted at a single center. Additionally, multiple dosing regimens of roxadustat were not administered, as the retrospective nature of the study limited such variations in treatment. Furthermore, pre-treatment hepcidin levels were not analyzed, which could have offered valuable insights into the potential association between baseline hepcidin status and treatment response. These factors may have limited the depth of interpretation and generalizability of the findings.

CONCLUSION

In conclusion, the current study can be considered a pioneering effort. We aimed to share our experience with this novel treatment option in a challenging patient population. Our findings demonstrate significant treatment success with roxadustat. We believe that our results will provide valuable guidance to clinicians in the management of renal anemia.

Disclosures

Ethics Committee Approval: The study was approved by the Agri Ibrahim Cecen University Ethics Committee (No: 410, Date: 28/11/2024).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The author have no conflict of interest to declare.

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