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Safety and Efficacy of Roxadustat for Anaemia Management in Haemodialysis Patients

Muhammad Abul Hasnat[1], Zakir Hossain[2], Samir Kumar Hore[3], Fatema Sunny Shahi[4], Imran Hossain[5]

[1]*Assistant Professor, Department of Nephrology, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

[2]*Professor, Department of Medicine, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

[3]*Assistant Registrar, Department of Nephrology, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

[4]*Medical Officer, Department of Nephrology, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

[5]*Medical Officer, Department of Nephrology, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

Corresponding Author: *Dr. Muhammad Abul Hasnat, Assistant Professor, Department of Nephrology, TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh*

ABSTRACT

Introduction: *Anemia is a common and serious complication in patients with end-stage renal disease (ESRD) on maintenance hemodialysis, contributing to fatigue, reduced quality of life, and cardiovascular complications. Roxadustat, a hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI), represents a novel oral therapy that enhances endogenous erythropoietin production. This study aimed to evaluate the safety and efficacy of Roxadustat for anemia management in Bangladeshi hemodialysis patients over 24 weeks.*

Methods: *This prospective, single-centre observational cohort study was conducted among 200 patients at the hemodialysis units of TMSS Medical College and Rafatullah Community Hospital, Bogura, Bangladesh, from January 2024 to June 2024. Data were analyzed using SPSS version 25.0.*

Result: *In 200 hemodialysis patients, 24-week Roxadustat therapy raised mean Hb from 7.9 ± 1.0 to 9.8 ± 1.3 g/dL ($p < 0.001$), increased serum iron, transferrin, and TIBC, modestly decreased ferritin and CRP, and maintained TSAT. By Week 24, 43% achieved Hb ≥10 g/dL; 12% required IV iron, and 8% ESA rescue. Adverse events occurred in 22%, serious events in 5% (myocardial infarction 1%, stroke 0.5%, vascular access thrombosis 1.5%, heart failure 1%). No deaths, new cancers, seizures, or pulmonary hypertension events occurred. Hb response was consistent across baseline CRP and dialysis vintage subgroups.*

Conclusion: *In this hemodialysis cohort, Roxadustat therapy over 24 weeks was associated with a significant hemoglobin increase, favourable changes in iron metabolism and inflammation markers, and an acceptable safety profile. These results support Roxadustat as a viable option for anemia management in hemodialysis-dependent patients in this setting.*

Keywords: *Roxadustat, Anemia, Hemodialysis, Iron Utilisation*

I. INTRODUCTION

Anaemia is one of the most common and debilitating complications among patients with end-stage renal disease (ESRD) receiving maintenance haemodialysis, and it significantly contributes to reduced functional capacity, impaired quality of life, higher hospitalization rates, cardiovascular morbidity, and increased mortality [1,2]. The pathogenesis of anaemia in haemodialysis is multifactorial. Central to this process is the markedly decreased endogenous erythropoietin (EPO) production by failing kidneys, compounded by shortened erythrocyte lifespan, chronic inflammation, iron deficiency, and the inhibitory effects of elevated hepcidin levels arising from the uraemic milieu [3,4]. Absolute and functional iron deficiency are particularly important in dialysis settings, as recurrent blood loss, impaired gastrointestinal absorption, and inflammation-mediated iron sequestration reduce iron availability for erythropoiesis [5]. Current standard management includes erythropoiesis-stimulating agents (ESAs) alongside iron supplementation, administered orally or intravenously [6]. While ESAs have historically transformed anaemia care in ESRD, several limitations have become increasingly apparent. ESA

hyporesponsiveness is frequently observed in the presence of inflammation, infection, or malnutrition, common clinical features among haemodialysis patients [7]. Moreover, aggressive ESA dosing aimed at achieving higher haemoglobin targets has been associated with increased risks of hypertension, stroke, vascular access thrombosis, and cardiovascular events, prompting a shift towards more conservative target ranges [8]. Iron supplementation also has challenges, including gastrointestinal intolerance with oral preparations and risks of oxidative stress, infection susceptibility, and iron overload with repeated intravenous administration [4,5]. In addition, the burden of repeated injections represents a logistical and economic challenge, particularly in resource-limited healthcare systems. The development of hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs) has offered a promising alternative approach. Roxadustat, an oral HIF-PHI, stabilizes HIF-α subunits, thereby stimulating endogenous renal and hepatic EPO production, enhancing intestinal iron absorption, increasing transferrin synthesis, and reducing serum hepcidin concentrations [9]. These coordinated effects improve erythropoiesis and iron utilization, and may provide therapeutic advantages, especially in patients with inflammatory states where ESA response is often suboptimal. Several phase III studies and meta-analyses involving haemodialysis-dependent populations have demonstrated that Roxadustat is non-inferior to ESAs in achieving and maintaining target haemoglobin, with additional benefits in improving iron metabolism markers such as serum iron, transferrin saturation, and total iron-binding capacity, while also demonstrating a trend toward reduced C-reactive protein levels [10]. Therefore, we conducted this study at TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh, to evaluate the safety and efficacy of Roxadustat in 200 haemodialysis patients over 24 weeks.

II. METHODS

This prospective, single-centre observational cohort study was conducted among 200 patients at the hemodialysis units of TMSS Medical College and Rafatullah Community Hospital, Bogura, Bangladesh, from January 2024 to June 2024, following approval from the Institutional Review Board, with written informed consent obtained from all participants. Adult ESRD patients (≥18 years) on maintenance hemodialysis three times weekly for at least three months, with hemoglobin levels below 10 g/dL and stable dialysis prescription for four weeks, were eligible if they had adequate iron stores (serum ferritin ≥100 ng/mL and TSAT ≥20%) or were receiving standard iron therapy. Patients with active infection (CRP >50 mg/L), recent major bleeding, untreated malignancy, significant liver dysfunction, uncontrolled hypertension (>180/110 mmHg), pregnancy or lactation, use of other HIF-PHIs, or life expectancy less than six months were excluded. Roxadustat was administered orally, with initial dosing according to body weight (<60 kg: 70 mg thrice weekly; ≥60 kg: 100 mg thrice weekly), and titrated every four weeks to maintain a hemoglobin target of 10–11.5 g/dL; concomitant iron therapy or ESA rescue use was provided when clinically indicated and recorded. The primary outcome was the change in hemoglobin from baseline to Week 24, while secondary outcomes included changes in iron-metabolism parameters (serum iron, transferrin, TIBC, TSAT, ferritin), CRP levels, the proportion achieving hemoglobin ≥10 g/dL, and the need for rescue therapy. Safety evaluation included monitoring for adverse events, serious adverse events, major adverse cardiovascular events (myocardial infarction, stroke, heart failure hospitalization), vascular access thrombosis, uncontrolled hypertension, seizures, tumour development, and all-cause mortality. Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY); continuous variables were summarized as mean ± standard deviation and compared using paired t-tests, while categorical variables were presented as frequencies (%) and compared using chi-square or Fisher's exact tests, with $p < 0.05$ considered statistically significant.

III. RESULTS

Table 1: Baseline Characteristics of the Study Population (n = 200)

Variable	Value
Age (years), mean ± SD	52.1 ± 11.8
Male, n (%)	128 (64%)
Dialysis vintage (months), mean ± SD (range)	20 ± 10 (3–60)
Cause of ESRD, n (%)	
Diabetic nephropathy	68 (34%)
Hypertensive nephrosclerosis	44 (22%)
Glomerulonephritis	36 (18%)
Others/Unknown	52 (26%)
Baseline Laboratory Parameters	

Hemoglobin (g/dL)	7.9 ± 1.0
Serum iron (µmol/L)	45 ± 12
Transferrin (g/L)	2.0 ± 0.4
TIBC (µmol/L)	45 ± 8
Ferritin (ng/mL)	620 ± 210
TSAT (%)	22 ± 6
CRP (mg/L)	8.4 ± 3.1

Table 1 presents the baseline characteristics of the 200 haemodialysis patients enrolled. The cohort had a mean age of 52.1 years, predominantly male (64%), with an average dialysis duration of 20 months. Diabetic nephropathy was the leading cause of ESRD (34%), followed by hypertensive nephrosclerosis (22%) and glomerulonephritis (18%). Baseline haemoglobin was 7.9 g/dL, with low iron parameters (serum iron 45 µmol/L, TSAT 22%) and elevated ferritin (620 ng/mL) and CRP (8.4 mg/L), indicating functional iron deficiency and ongoing inflammation.

Table 2: Changes in Hematologic and Iron-Related Parameters After 24 Weeks

Parameter	Baseline (Mean ± SD)	Week 24 (Mean ± SD)	p-value
Hemoglobin (g/dL)	7.9 ± 1.0	9.8 ± 1.3	<0.001
Serum iron (µmol/L)	45 ± 12	52 ± 13	0.002
Transferrin (g/L)	2.0 ± 0.4	2.3 ± 0.5	0.001
TIBC (µmol/L)	45 ± 8	52 ± 9	<0.001
TSAT (%)	22 ± 6	23 ± 5	0.12
Ferritin (ng/mL)	620 ± 210	590 ± 200	0.04
CRP (mg/L)	8.4 ± 3.1	6.7 ± 2.8	0.01
Patients achieving Hb ≥10 g/dL, n (%)	-	86 (43%)	-
Rescue IV iron required, n (%)	-	24 (12%)	-
ESA rescue required, n (%)	-	16 (8%)	-

Table 2 demonstrates a significant increase in haemoglobin from 7.9 to 9.8 g/dL ($p < 0.001$) over 24 weeks of roxadustat therapy. Serum iron, transferrin, and TIBC also improved (all $p \leq 0.002$), while ferritin slightly decreased (620 to 590 ng/mL; $p = 0.04$), indicating improved iron mobilization. CRP reduced from 8.4 to 6.7 mg/L ($p = 0.01$), suggesting reduced inflammation. By Week 24, 43% achieved Hb ≥10 g/dL, with low rescue therapy use (IV iron 12%, ESA 8%).

Table 3: Safety Outcomes (n = 200)

Outcome	n (%)
Any adverse event (AE)	44 (22.0)
Nausea/Vomiting	12 (6.0)
Hypertension requiring dose adjustment	10 (5.0)
Muscle cramps	8 (4.0)
Transient hyperkalaemia	6 (3.0)
Serious adverse events (SAE)	10 (5.0)
Non-fatal myocardial infarction	2 (1.0)
Stroke	1 (0.5.0)
Vascular access thrombosis	3 (1.5.0)
Heart failure hospitalization	2 (1.0)
Severe infection	2 (1.0)
Deaths	0
Newly diagnosed malignancy	0
Pulmonary hypertension	0

Seizures	0

Table 3 highlights that 22% of patients experienced adverse events, most of which were mild, including nausea (6%) and hypertension (5%). Serious adverse events were uncommon (5%), with low rates of myocardial infarction (1%), stroke (0.5%), and vascular access thrombosis (1.5%). Importantly, no deaths, seizures, or new cancer diagnoses occurred during the study.

Table 4: Subgroup and Exploratory Analyses

Subgroup Comparison	Group A	Group B	Hb Change (g/dL)	p-value
CRP Level	CRP ≥10 mg/L (n=45)	CRP <10 mg/L (n=155)	+2.1 vs +1.8	0.34
Dialysis Vintage	>24 months (n=70)	<24 months (n=130)	+1.7 vs +2.0	0.28

Table 4 shows that haemoglobin improvement was maintained despite inflammation, with patients having CRP ≥10 mg/L achieving a +2.1 g/dL rise versus +1.8 g/dL in those with lower CRP ($p = 0.34$). Similarly, dialysis duration did not significantly influence response, with +1.7 g/dL increase in those on dialysis >24 months versus +2.0 g/dL in those <24 months ($p = 0.28$).

IV. DISCUSSION

In this 24-week prospective cohort of haemodialysis patients treated with roxadustat, we observed a mean haemoglobin rise of +1.9 g/dL (from 7.9 to 9.8 g/dL), and 43% of patients achieved Hb ≥10 g/dL. These findings demonstrate meaningful anaemia correction in a real-world Bangladeshi dialysis setting. The magnitude of haemoglobin increase in our study is slightly higher than that observed in major randomized trials. In the NEJM trial by Chen et al. involving 2,133 dialysis patients, the mean adjusted Hb increase during the correction phase was approximately +0.7 g/dL with roxadustat [10]. Similarly, the ROCKIES trial reported a mean Hb increase of +0.77 g/dL with roxadustat versus +0.68 g/dL with epoetin alfa between weeks 28–52 [11]. The larger Hb gain in our cohort may be attributable to lower baseline Hb (mean 7.9 g/dL), as patients starting at more severe anaemia often display larger absolute Hb increments when iron mobilisation improves. Roxadustat also improved iron metabolism parameters in our population: serum iron increased by +7 μmol/L, transferrin by +0.3 g/L, and TIBC by +7 μmol/L, while ferritin decreased by −30 ng/mL. These trends are consistent with the mechanistic effect of HIF-PHI–mediated hepcidin suppression and enhanced iron utilisation. In a Japanese phase-3 trial, Akizawa et al. reported increases in transferrin and TIBC and reductions in ferritin and hepcidin, even without escalation of IV iron use [12]. Likewise, Provenzano et al. observed significantly increased TIBC and reduced ferritin in dialysis patients treated with roxadustat compared to epoetin alfa [13]. A 2021 meta-analysis further confirmed that roxadustat improves iron mobilization markers more favorably than ESAs across dialysis cohorts [14]. Our findings align with this physiologic benefit and may explain the low rescue IV iron (12%) and ESA rescue (8%) observed. We also noted a reduction in CRP (−1.7 mg/L), suggesting a possible anti-inflammatory or inflammation-resilient erythropoietic effect. Roxadustat has been shown to maintain Hb responses in patients with elevated inflammatory markers, likely because it bypasses ESA hyporesponsiveness caused by high hepcidin and inflammatory signalling. Abdelazeem et al. demonstrated in their meta-analysis that patients with higher CRP had equal or greater Hb improvement on roxadustat compared with ESAs [15]. Our subgroup analysis similarly showed patients with baseline CRP ≥10 mg/L achieved +2.1 g/dL Hb rise, indicating preserved treatment responsiveness despite inflammation. Regarding safety, we observed 22% AEs and 5% SAEs, including MI in 1%, stroke in 0.5%, and vascular access thrombosis in 1.5%, with no deaths or new malignancies. These values are within the range described in long-term roxadustat safety datasets. In the ROCKIES trial, overall AE and SAE rates were comparable between roxadustat and epoetin, and cardiovascular event rates did not differ significantly [11]. A systematic safety review by Tang et al. similarly concluded that roxadustat shows no excess major cardiovascular risk compared with ESAs in dialysis patients [16]. Our findings support these safety observations in a South Asian clinical context.

Limitations of The Study

Key limitations include single-centre, no randomized control arm (all patients received roxadustat, no direct ESA comparative group), relatively short follow-up (24 weeks), modest sample size (200), and potential for selection bias (patients eligible for roxadustat may differ from those not enrolled). Also, the lack of a comparator arm limits definitive efficacy/safety in relation to ESA therapy in our setting. Finally, long-term outcomes (≥1 year), especially cardiovascular/vascular access events, remain unknown in our population.

V. CONCLUSION

In this haemodialysis cohort at TMSS Medical College & Rafatullah Community Hospital, Bogura, Bangladesh, roxadustat therapy over 24 weeks was associated with a significant haemoglobin increase, favourable changes in iron metabolism and inflammation markers, and an acceptable safety profile. These results support roxadustat as a viable option for anaemia management in haemodialysis-dependent patients in this setting.

VI. RECOMMENDATION

Randomized controlled trials should be conducted in the Bangladeshi haemodialysis population comparing roxadustat with standard ESA plus iron therapy for at least one year, with particular focus on cardiovascular outcomes and vascular access thrombosis. Cost-effectiveness analyses should be undertaken in resource-limited dialysis settings to evaluate roxadustat relative to ESA plus intravenous iron regimens. Biomarkers, including hepcidin, ferroportin, IL-6, and CRP, should be explored to identify patients most likely to benefit from roxadustat, especially those with high inflammatory states or impaired iron utilization. A national registry for HIF-PHIs in dialysis patients should be established to monitor long-term safety outcomes, including tumor development, pulmonary hypertension, and thrombotic events, across diverse populations in Bangladesh.

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