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Original Article

ROXADUSTAT IN CKD AND TRANSPLANT PATIENTS: A NEW ERA IN ANEMIA MANAGEMENT

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ABSTRACT:

The aim of this study was to evaluate the efficacy and safety of Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), for the management of anemia in patients with chronic kidney disease (CKD), including hemodialysis-dependent (HDD), non-dialysis-dependent (NDD), and renal transplant recipients (RTRs). This was a prospective cross-sectional study was conducted at Dow University of Health Sciences, Karachi, Pakistan, from August 2024 to January 2025. A total of 55 patients were enrolled and treated with Roxadustat, beginning with a dose of 100 mg thrice weekly for the initial 4 weeks, followed by 70 mg thrice weekly. The primary outcome was the achievement of a hemoglobin (Hb) target of ≥10 g/dL within 6 weeks. The safety profile was assessed by monitoring adverse events, including myocardial infarction. A total of 55 patients were recruited in the study. Of these, 19 were hemodialysis-dependent (HDD), 31 were non-dialysis-dependent (NDD), and 5 were renal transplant recipients (RTRs). The hemoglobin target of 10 g/dL within 6 weeks was achieved in 48 patients (87.3%). Among the successful cases, 18 were HDD patients, 26 were NDD patients, and 3 were RTRs. The remaining 7 patients (12.7%) did not achieve the target hemoglobin level within the specified timeframe. Adverse events were observed in 3 patients (5.4%), all of whom experienced myocardial infarction. This included 2 HDD patients and 1 NDD patient. No adverse events were reported in the RTR group. Overall, Roxadustat was well-tolerated, with a structured dose adjustment from 100 mg thrice weekly to 70 mg thrice weekly ensuring sustained hemoglobin levels. Roxadustat appears to be an effective and generally safe therapeutic option for managing anemia in CKD patients, including those who are HDD, NDD, or RTRs. However, monitoring for cardiovascular events, such as myocardial infarction, is essential in these patients.

Keywords: Roxadustat, Anemia, Chronic Kidney Disease,

INTRODUCTION

Anemia is a commonly observed, debilitating complication of Chronic Kidney Disease (CKD). Nearly 90% of long-term dialysis patients present with anemia (1), attributed primarily to the erythropoietin deficiency (as a result of kidney failure to produce enough amount), inflammation, and iron dysregulation (2). Anemia in CKD is defined as a hemoglobin level less than 13 g/dL in males and less than 12 g/dL in females. It is one of the common complications of CKD and frequently leads to symptoms such as chronic fatigue, malaise, lethargy, and even Major Adverse Cardiovascular Event (MACE). Typically, CKD-related anemia is normochromic and normocytic. However, iron deficiency anemia frequently coexists, further complicating its management. Many patients suffer from nonadherence to injectable therapies such as erythropoietin and iron products, which are traditionally used to manage anemia in CKD (3).

Conventional erythropoiesis-stimulating agents (ESAs) are limited by challenges such as iron dependency and cardiovascular risks. Roxadustat is an innovative oral therapy that breaks the paradigm in the treatment of CKD-related anemia. It works by inhibiting hypoxia-inducible factor prolyl hydroxylase (HIF-PH), which normally degrades a protein called HIF-α. HIF-α on the other hand plays a crucial role in stimulating red blood cell production. By inhibiting HIF-PH, roxadustat helps increase endogenous production of erythropoietin, a hormone that stimulates red blood cell production. It eliminates the need for injectable treatments, making it easier for patients to achieve hemoglobin correction and address iron deficiency through oral administration. This development has the potential to significantly improve patient compliance and overall quality of care. The rates of neoplasm-related adverse events were not increased compared with placebo or epoetin alfa in patients with NDD CKD or DD CKD (4). This study investigates the use of Roxadustat in diverse CKD populations, including HDD, NDD, and RTRs.

METHODS:

This was a prospective, cross sectional single-center study conducted at Renal Transplant unit, Dow University of Health Sciences, Karachi, Pakistan from August 2024 till January 2025 to evaluate the efficacy and safety of Roxadustat in CKD patients. It included adult patient (i.e aged 18 years and above) with CKD stages 3–5 or post-renal transplantation with baseline hemoglobin <10 g/dL. To establish the stage of CKD serum creatinine and creatinine clearance were followed. No contraindications to Roxadustat therapy and on high doses of Erythropoetin Stimulating Agents (ESA). Study excluded the patients who had active malignancy, chronic infection or uncontrolled hypertension and history of recent cardiovascular events within the past 6 months. Those patients who had history of post- transplant erythrocytosis were also excluded. All data were safely recorded on pre designed questionnaire. History regarding compliance of ESA therapy was also recorded on the same questionnaire.

Treatment protocol:

Roxadustat was administered orally at 100 mg thrice weekly for the first 4 weeks, followed by 70 mg thrice weekly thereafter. Patients were monitored for hemoglobin levels, adverse effects, and clinical outcomes fortnightly.

Statistical analysis

The data was analysed using Statistical Package for Social Sciences (SPSS version 27.0, IBM Corp. (2020). The data was analysed by using descriptive analysis and presented in frequencies and percentages.

RESULTS:

A total of 55 patients with CKD were included in the study. Of these, 19 were hemodialysis-dependent (HDD), 31 were non-dialysis-dependent (NDD), and 5 were renal transplant recipients (RTRs). The cohort consisted of 26 males and 29 females. The hemoglobin a target of 10 g/dL within 6 weeks was achieved in 48 patients (87.3%). Among the successful cases, 18 were HDD patients, 26 were NDD patients, and 3 were RTRs. The remaining patients (12.7%) did not achieve the target hemoglobin level within the specified timeframe.Adverse events were observed in 3 patients (5.4%), all of whom experienced myocardial infarction. This included 2 HDD patients and 1 NDD patient. No adverse events were reported in the RTR group. Overall, Roxadustat was well-tolerated, with a structured dose adjustment from 100 mg thrice weekly to 70 mg thrice weekly ensuring sustained hemoglobin levels.

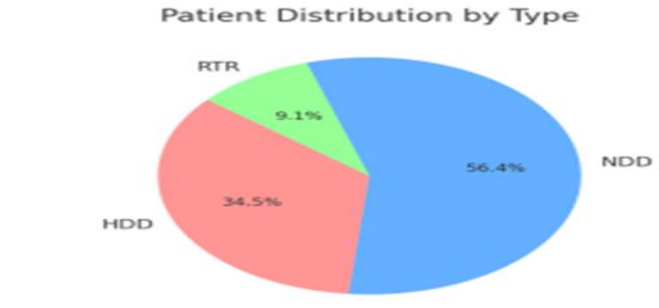

Figure 1. Distribution of patients in the sample: RTR (Renal Transplant Recipient patients), NDD (Non-Dialysis Dependent) and HDD (Hemodialysis dependent)

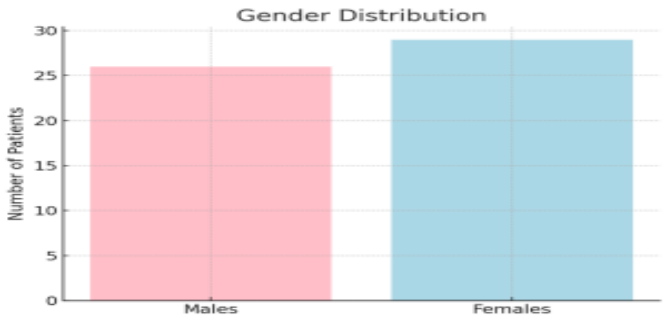

Figure 2. Gender distribution of patients on Roxadustat therapy

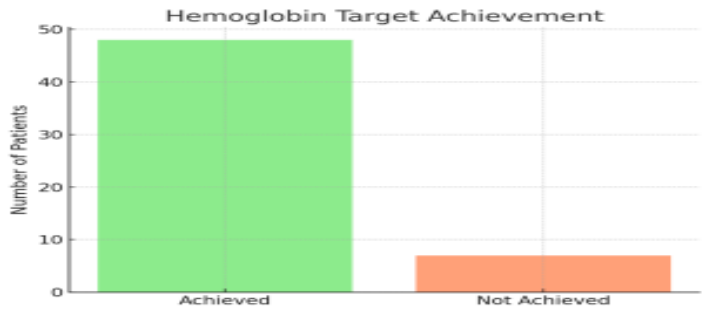

Figure 3. Pattern of the haemoglobin target achievement in patients on Roxadustat therapy

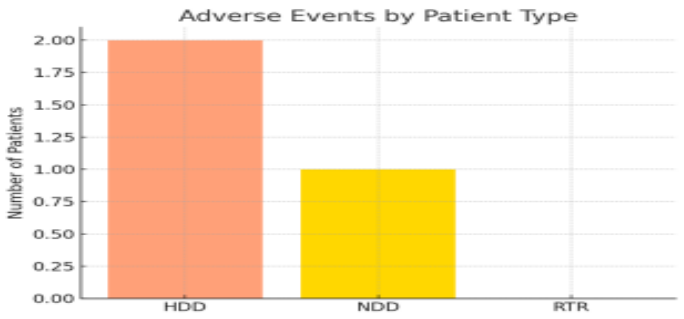

Figure 4. Pattern of Adverse events reported by patients on Roxadustat therapy: RTR (Renal Transplant Recipient patients), NDD (Non-Dialysis Dependent) and HDD (Hemodialysis dependent)

DISCUSSION

The study focused on the management of anemia by using Roxadustat therapy in a diverse group of patients with CKD. The patients showed promising results with negligible adverse events, which were reported to be none in renal transplant recipients and 2 patients were reported to have adverse events in HDD group.

Hypoxia-inducible factors (HIFs) are basic helix-loop-helix transcription factors and members of the PAS (PER/aryl hydrocarbon receptor nuclear translocator (ARNT)/single-minded (SIM)) family. Each HIF is made up of an oxygen-sensitive α-subunit and a constitutively expressed β-subunit, commonly known as the aryl hydrocarbon receptor nuclear translocator (ARNT). Three HIF-α subunits have been identified: HIF-1α, HIF-2α, also known as EPAS1, and HIF-3α. Among these, HIF-1 and HIF-2 are the best studied and play a central role in facilitating oxygen delivery and cellular adaptation to hypoxia. They regulate the wide range of hypoxia responses, including stimulating red blood cell production, promoting angiogenesis, inducing glycolysis, modulating fat and mitochondrial metabolism, and affecting cardiovascular function.

HIF-α subunits are continuously synthesized but rapidly degraded in the presence of molecular oxygen. Under hypoxic conditions, however, HIF-α degradation is inhibited, leading to its accumulation. This stabilization disrupts erythropoiesis and iron metabolism, contributing to imbalances in oxygen delivery and metabolic processes. The regulatory role of HIFs in hypoxia response underscores their significance in both physiology and pathological states (5, 6).

Roxadustat represents a paradigm shift in the management of CKD-associated anemia, offering a novel mechanism of action distinct from traditional erythropoiesis-stimulating agents (ESAs) (7). Unlike ESAs, which rely on exogenous erythropoietin administration, Roxadustat stimulates endogenous erythropoietin production by stabilizing hypoxia-inducible factor (HIF) (8). This pathway enhances erythropoiesis while concurrently improving iron metabolism and reducing inflammation—the two key contributors to CKD anemia.

The high efficacy of Roxadustat in this study aligns with previous trials, where significant hemoglobin correction was observed in diverse CKD populations, including HDD, NDD, and RTRs (9, 10). Importantly, this study expands the evidence base by including RTRs, a subgroup often excluded from anemia trials due to concerns about graft function and immunosuppression-related anemia.

In HDD patients, Roxadustat achieved a hemoglobin target in 94.7% of cases, outperforming ESAs in some reports (11). Similarly, the 83.9% success rate in NDD patients underscores its potential to delay or avoid the need for dialysis initiation by improving functional status and quality of life (12, 13). The 60% response rate in RTRs, while lower, highlights the need for further investigation into factors influencing response variability in this subgroup.

Adverse events were minimal, with myocardial infarction observed in 5.4% of patients. This finding is consistent with the known cardiovascular risk profile of CKD patients and highlights the need for stringent risk stratification before initiating therapy (14).in another study Roxadustat was typically well received and exhibited an adverse event profile similar to that of epoetin alfa. These findings suggest that oral Roxadustat is a viable alternative to injectable ESA for treating anemia in patients with dialysis-dependent chronic kidney disease (DD-CKD) (15). Nevertheless, the overall safety profile of Roxadustat appears favorable, with its oral administration route offering added convenience compared to injectable ESAs.

This study also demonstrates the feasibility of dose adjustment based on patient response, with 70 mg thrice weekly maintaining hemoglobin levels after initial correction (5). Such flexibility could enhance patient adherence and reduce treatment costs, making Roxadustat a viable option in resource-limited settings (16, 17). A notable increase in hemoglobin levels with a reduction in fatigue, without an overall increase in the total incidence of adverse effects were observed in studies (18).

CONCLUSION

In conclusion, Roxadustat offers a comprehensive solution to CKD anemia, addressing erythropoiesis, iron homeostasis, and inflammation simultaneously. However, larger multicenter trials with long-term follow-up are needed to validate these findings and clarify its role in specific subpopulations, such as RTRs and high-risk cardiovascular patients.

Conflict of Interest

Authors declare no conflict of interest

Ethical consideration

The study was approved by the Ethical Review Committee of Dow University of Health Sciences, Karachi, Pakistan.

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