Efficacy and Safety of Roxadustat for Renal Anemia in Hemodialysis Patients: A Systematic Review and Meta-Analysis (Postprint)

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Abstract

Background: Anemia is the most common clinical manifestation in patients with chronic kidney disease and a major complication of renal disease that affects patients' quality of life, accelerates disease progression, and increases mortality risk; therefore, correcting anemia and monitoring the efficacy and safety of drugs for improving renal anemia is of great significance.

Objective: To compare the efficacy and safety of roxadustat and erythropoiesis-stimulating agents in the treatment of renal anemia in maintenance hemodialysis patients.

Methods: A total of 535 relevant articles were retrieved from PubMed, FMRS, and Wanfang databases. Literature was screened according to inclusion and exclusion criteria, then evaluated using the CONSORT 2010 checklist, and statistical analysis was performed using Review Manager 5.3 software.

Results: A total of 5 articles comprising 6 randomized controlled studies with 901 patients were ultimately included. Among them, the roxadustat group had 549 cases, and the erythropoiesis-stimulating agent group had 352 cases. Meta-analysis showed that compared with the erythropoiesis-stimulating agent group, the roxadustat group was superior in improving serum iron, transferrin, and total iron-binding capacity in hemodialysis patients. There was no statistically significant difference in the incidence of adverse events between the two groups.

Conclusion: Roxadustat can effectively correct renal anemia in maintenance hemodialysis patients and demonstrates superior efficacy to erythropoiesis-stimulating agents in elevating serum iron, transferrin, and total iron-binding capacity. Short-term use of roxadustat did not increase the risk of adverse events.

Full Text

Preamble

Effectiveness and Safety of Roxadustat for Renal Anemia in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Anemia is the most common clinical manifestation in patients with chronic kidney disease (CKD) and a major complication of kidney disease that affects patients' quality of life while accelerating disease progression and mortality risk. Correcting anemia and monitoring the efficacy and safety of drugs for improving renal anemia is therefore of great significance.

Objective: To compare the efficacy and safety of roxadustat versus erythropoiesis-stimulating agents (ESAs) in treating renal anemia in maintenance hemodialysis patients.

Methods: We searched PubMed, FMRS, and WanFang databases and retrieved 535 relevant articles. Literature was screened according to inclusion and exclusion criteria, assessed using the CONSORT 2010 checklist, and analyzed using Review Manager 5.3 software.

Results: Five articles comprising six randomized controlled trials (RCTs) with 901 patients were included (roxadustat group: 549 patients; ESAs group: 352 patients). Meta-analysis showed that compared with the ESAs group, the roxadustat group demonstrated superior effects in increasing serum iron, transferrin, and total iron binding capacity in hemodialysis patients. No statistically significant difference was found in the incidence of adverse events between the two groups.

Conclusion: Roxadustat can effectively correct renal anemia in maintenance hemodialysis patients and shows better efficacy than ESAs in elevating serum iron, transferrin, and total iron binding capacity. Short-term use of roxadustat did not increase the risk of adverse events.

Keywords: Roxadustat; Erythropoiesis-stimulating agents; Renal anemia; Meta-analysis

Abbreviations: - DD-CKD: Dialysis-dependent chronic kidney disease - CKD: Chronic kidney disease - ESAs: Erythropoiesis-stimulating agents - HIF-PHI: Hypoxia-inducible factor prolyl hydroxylase inhibitor - SAEs: Serious adverse events - ESRD: End-stage renal disease - MHD: Maintenance hemodialysis - FMRS: Foreign Medical Literature Retrieval Service

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Introduction

Anemia is one of the most common clinical manifestations in patients with chronic kidney disease (CKD) and represents a major complication of kidney disease. The primary pathogenesis involves absolute or relative deficiency of erythropoietin (EPO) production due to impaired renal function [1]. Anemia affects the quality of life of CKD patients and accelerates the risk of progression to end-stage renal disease (ESRD) and mortality [2-4]. According to Chinese clinical trial data, the prevalence of anemia in CKD patients, particularly those on maintenance dialysis, can be as high as 91.6-98.2%, significantly higher than in the general population [5].

Erythropoiesis-stimulating agents (ESAs), primarily recombinant human erythropoietin (rHuEPO), are currently effective drugs for improving renal anemia. The kidneys are richly supplied with blood and are extremely sensitive to changes in oxygenation. Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) are a newly developed class of oral medications for treating renal anemia that regulate EPO production through changes in oxygenation [6]. Roxadustat (FG-4592) is the first HIF-PHI drug approved and marketed by the China National Medical Products Administration, providing an alternative treatment option for renal anemia. However, standardized application guidelines for roxadustat are lacking, with limited research reports on initial treatment timing, prognosis, and adverse reactions. Therefore, we conducted this meta-analysis to review and evaluate the efficacy and safety of roxadustat in treating renal anemia in hemodialysis patients.

Methods

1.1 Search Strategy

We searched PubMed, FMRS, and WanFang databases from inception to January 19, 2022, using a combination of free-text terms and MeSH terms to retrieve

relevant literature. Chinese search terms included: “罗沙司他” (roxadustat), “肾替代治疗” (renal replacement therapy), “终末期肾病” (end-stage renal disease), “低氧诱导因子-脯氨酰羟化酶抑制剂” (hypoxia-inducible factor prolyl hydroxylase inhibitor), “慢性肾脏病” (chronic kidney disease), “贫血” (anemia), “肾性贫血” (renal anemia), and “血液透析” (hemodialysis). English search terms included: “roxadustat,” “HIF-PHI,” “FG-4592,” “dialysis-dependent,” “End-stage renal disease,” “chronic kidney disease,” “anemia,” “kidney disease,” and “hemodialysis.” We also examined references from selected articles and searched ClinicalTrials.gov.

1.2 Inclusion Criteria

(1) Randomized controlled trials (RCTs); (2) Intervention group receiving roxadustat and control group receiving erythropoietin; (3) Maintenance hemodialysis patients with dialysis duration $ $3 months; (4) Study outcomes including at least one of the following: hemoglobin, serum iron, transferrin, transferrin saturation, ferritin, total iron binding capacity, soluble transferrin receptor, hepcidin, or adverse events.

1.3 Exclusion Criteria

(1) Non-randomized controlled studies; (2) Animal experiments, case reports, and pharmacological studies; (3) Non-hemodialysis patients; (4) Studies not using roxadustat; (5) Duplicate records.

1.4 Data Extraction

Two independent investigators (Li Qing and Huang Jingjing) reviewed the literature, extracted data, and evaluated study quality according to the inclusion and exclusion criteria. The full-text and supplementary materials from original trial reports were assessed using the standardized CONSORT 2010 checklist. Any discrepancies were adjudicated by a third investigator (Nie Jingwen). Extracted data from each trial included baseline characteristics (author, study region, sample size, publication year, single-center or multicenter, gender ratio), patient characteristics (study duration, clinical trial details, interventions, baseline hemoglobin, roxadustat dosage), and outcomes (hemoglobin, ferritin, serum iron, transferrin saturation, transferrin, total iron binding capacity, transferrin receptor, hepcidin, and adverse reactions). Data from eligible studies were entered into relevant software for analysis.

1.5 Risk of Bias Assessment

The risk of bias for all included RCTs was assessed using the Cochrane Collaboration’ s tool [7-8]. The ClinicalTrials.gov registry was searched to obtain registration information for relevant studies.

1.6 Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan) 5.3 software. Continuous variables were expressed as standard deviations, and binary variables were assessed using relative risk ratios. A fixed-effects model was used when heterogeneity was low (P>0.1, I^2<50%), while a random-effects model was employed when heterogeneity was high (P$ 0.1, $I^{2}$$ $50%). Statistical significance was set at P<0.05.

Results

2.1 Literature Search

Initially, 535 articles were retrieved from the databases (PubMed: 247 articles; FMRS: 204 articles; WanFang: 84 articles). After removing 198 duplicate articles, two independent investigators screened titles and abstracts, excluding 307 articles. The full texts of the remaining 30 RCTs were carefully reviewed. Subsequently, 19 articles not using roxadustat were excluded, followed by 4 non-dialysis studies, 1 pharmacokinetic study, and 1 iron supplement study. Finally, 5 articles comprising 6 clinical trials were included in the meta-analysis [9-13] (see Figure 1 [Figure 1: see original paper]).

2.2 Characteristics of Included Studies

This study included 5 articles comprising 6 clinical trials with 901 patients, including 549 patients in the oral roxadustat group and 352 patients in the ESAs group. The basic characteristics of the included studies are shown in Table 1 .

2.3 Risk of Bias Assessment

Among the selected studies, Akizawa (2020) was a multicenter, double-blind, randomized controlled trial [9], while Chen Nan' s studies were two open-label, randomized clinical controlled trials [11-12]. Provenzano' s study was a multicenter, randomized, open-label clinical controlled trial [13]. All six clinical trials used random sequences, and the results were complete with no reports of selection bias (Figure 2 [Figure 2: see original paper]).

2.4 Meta-Analysis Results

Six studies including 887 participants [9-13] compared the difference in hemoglobin (Hb) levels between roxadustat and ESAs in hemodialysis patients. As shown in Figure 3 [Figure 3: see original paper], significant heterogeneity existed among the trials (P<0.00001, I^2=99%). Therefore, a random-effects model was used for meta-analysis, and the results showed no statistically significant difference in Hb level elevation between the two groups [MD=0.47, 95%CI (-0.08,1.01), Z=1.68, P=0.09].

Six studies including 887 dialysis patients [9-13] compared the difference in serum iron levels between roxadustat and ESAs in treating renal anemia. As shown in Figure 4 [Figure 4: see original paper], moderate heterogeneity existed among the trials (P=0.03, I^2=60%). Meta-analysis using a random-effects model showed that the roxadustat group was superior to the ESAs group in improving serum iron levels [MD=2.49, 95%CI(0.82, 4.16), Z=2.92, P=0.004].

Six studies including 887 dialysis patients [9-13] compared the difference in serum ferritin levels between roxadustat and ESAs in hemodialysis patients with renal anemia. As shown in Figure 5 [Figure 5: see original paper], significant heterogeneity existed among the studies (P=0.04, I^2=57%). Meta-analysis using a random-effects model showed no statistically significant difference between the two groups in serum ferritin levels [MD=-6.85, 95%CI(-43.46, 29.75), Z=0.37, P=0.71].

Four studies including 743 hemodialysis patients [9-12] compared the effect of roxadustat versus ESAs on serum transferrin. As shown in Figure 6 [Figure 6: see original paper], significant heterogeneity existed among the trials (P=0.001, I^2=81%). Meta-analysis using a random-effects model showed that transferrin levels were significantly higher in the roxadustat group than in the ESAs group [MD=0.31, 95%CI(0.17, 0.44), Z=4.56, P<0.00001].

Six studies including 887 hemodialysis patients [9-13] compared the difference in transferrin saturation between roxadustat and ESAs (Figure 7 [Figure 7: see original paper]). Significant heterogeneity existed among the trials (P<0.00001, I^2=91%). Meta-analysis using a random-effects model showed no significant difference in transferrin saturation levels between the roxadustat and ESAs groups [MD=5.31, 95% CI(-1.35, 11.97), Z=1.56, P=0.12].

Five studies including 831 hemodialysis patients [9,11-13] compared the effect of roxadustat versus ESAs on total iron binding capacity. Significant heterogeneity existed between the two groups (P=0.0005, I^2=80%). Meta-analysis using a random-effects model showed that total iron binding capacity was significantly higher in the roxadustat group than in the ESAs group [MD=7.51, 95%CI(5.01,10.01), Z=5.89, P<0.00001] (Figure 8 [Figure 8: see original paper]).

Six studies including 887 hemodialysis patients [9-13] compared the effect of roxadustat versus ESAs on hepcidin. Significant heterogeneity existed among the trials (P=0.02, I^2=64%). Meta-analysis using a random-effects model showed no statistically significant difference in hepcidin levels between the two groups [MD=-14.18, 95%CI(-34.22, 5.86), Z=1.39, P=0.17] (Figure 9 [Figure 9: see original paper]).

2.4.8 Adverse Events Five studies compared adverse events (AEs) between roxadustat and ESAs during treatment, including total AEs, drug-related serious AEs (SAEs), gastrointestinal AEs, and infection events. As shown in Figure 10 [Figure 10: see original paper], the included studies showed low heterogeneity

(P=0.1, I^2=49%), so a fixed-effects model was used. No statistically significant difference was found in total AEs between the roxadustat and ESAs groups [RR=1.10, 95%CI (0.99, 1.22), Z=1.82, P=0.07].

For drug-related SAEs (P=0.87, I^2=0%), gastrointestinal AEs (P=0.28, I^2=21%), and infection events (P=0.97, I^2=0%), meta-analysis used a fixed-effects model. The results showed no statistically significant differences between roxadustat and ESAs in drug-related SAEs [RR=1.3, 95%CI(0.82, 2.07), Z=1.10, P=0.27] (Figure 11 [Figure 11: see original paper]), gastrointestinal AEs [RR=1.27, 95%CI (0.86,1.88), Z=1.19, P=0.24] (Figure 12 [Figure 12: see original paper]), or infection incidence [RR=1.13, 95%CI(0.89,1.44), Z=1.00, P=0.32] (Figure 13 [Figure 13: see original paper]).

Discussion

The incidence of renal anemia is high among dialysis patients, but the awareness and control rates are low [14]. According to data from China' s Blood Purification Case Information Registration System [15], less than 67% of hemodialysis patients had hemoglobin >100 g/L before treatment. Due to kidney damage leading to reduced EPO production, and because CKD patients produce less EPO than non-CKD patients under the same degree of anemia and hypoxic stimulation, anemia persists. Additionally, inflammatory status, secondary hyperparathyroidism, and uremic toxins can all lead to decreased EPO activity [16]. Many clinical guidelines recommend that CKD patients undergo regular anemia evaluation [17-18]. Currently, the main drugs for correcting renal anemia are ESAs and iron supplements, with numerous comparative studies reported. However, as a relatively new drug for correcting renal anemia, roxadustat lacks standardized application guidelines. Therefore, we conducted this meta-analysis to compare the efficacy and safety of roxadustat versus ESAs in renal anemia.

Meta-analysis showed that overall, roxadustat increased hemoglobin levels in maintenance hemodialysis patients and effectively corrected renal anemia. EPO is an acidic glycoprotein composed of peptide and carbohydrate chains, with the peptide chain consisting of 165 amino acids connected by four carbohydrate chains via disulfide bonds, forming four stable α-helical structures [19]. Approximately 90% of EPO is produced by renal interstitial cells and binds to EPO receptors on the surface of myeloid erythroid progenitor cells, promoting differentiation of erythroid-committed stem cells, hemoglobin synthesis, and red blood cell release. ESAs are artificial recombinant human erythropoietin that supplement the body' s EPO deficiency but require subcutaneous or intravenous injection, causing inconvenience for home treatment. Furthermore, infection and inflammation can easily lead to reduced responsiveness to ESAs therapy, while increased ESAs doses raise the risk of cardiovascular and cerebrovascular events, thrombosis, blood pressure elevation, and stroke [20-21]. Oral iron supplements may cause gastrointestinal discomfort, while high-dose intravenous iron may cause severe allergic reactions, oxidative stress, cardiovascular disease, and infection, with frequent intravenous injections reducing patient compliance

[22].

Hypoxia is the main factor stimulating EPO synthesis and release, a process regulated by hypoxia-inducible factor (HIF) [23]. The kidneys are richly supplied with blood and are extremely sensitive to oxygenation changes. Under hypoxic conditions, HIF acts as a transcription factor coordinating gene expression for erythropoiesis, angiogenesis, and anaerobic metabolism. HIF-PHI stabilizes HIF levels in the body by inhibiting hypoxia-inducible factor-prolyl hydroxylase, thereby regulating transcription and expression of downstream target genes in the HIF signaling pathway, activating EPO gene expression, and promoting EPO production to correct anemia. Roxadustat is a second-generation oral HIF-PHI that was first launched in China, with multiple clinical trials confirming its effectiveness in correcting renal anemia [9-13], consistent with this meta-analysis.

Meta-analysis also indicated that roxadustat was superior to ESAs in improving serum iron, transferrin, and total iron binding capacity levels, meaning it outperformed ESAs in improving iron metabolism indicators. Animal experiments have also suggested that HIF-PHI increases iron absorption and improves serum iron levels [24], consistent with current research findings. Studies have found that hepcidin levels increase with the degree of iron deficiency in CKD patients, and roxadustat can effectively downregulate hepcidin levels and increase iron utilization, thereby improving iron absorption, transport, and utilization [25], ultimately reducing iron requirements and promoting EPO formation to correct anemia. This opens new therapeutic options beyond ESAs and iron supplements for treating renal anemia [26].

Additionally, studies have found that roxadustat is less affected by inflammation compared with ESAs [27]. In this meta-analysis, Akizawa' s study [9] also noted that when high-sensitivity CRP>3 mg/L, maintaining the same hemoglobin level requires increasing the ESAs dose, whereas roxadustat is not affected by inflammatory status and does not require dose adjustment. However, since only one included RCT described this situation, the inflammatory status factor was not included in this meta-analysis. Moreover, compared with ESAs, roxadustat' s oral administration avoids the pain and fear associated with subcutaneous or intravenous injections, resulting in higher treatment compliance [28]. In this study, no statistically significant differences were found between the two groups regarding ferritin, transferrin saturation, and hepcidin levels.

In terms of adverse drug reactions, meta-analysis indicated no significant differences between the two groups in drug-related serious adverse events, gastrointestinal adverse events, and infections. However, the longest observation period for adverse events was only 26 weeks, necessitating longer research observation periods.

This study has several limitations: First, we only included Phase II and III trials of maintenance hemodialysis patients, excluding non-dialysis patients. Second, the study only included RCTs with available results, some of which were not

double-blind designs, and potential differences between studies may have been influenced by study design and participant numbers. Third, there was a lack of comparison between roxadustat and iron therapy.

Conclusion

This meta-analysis provides evidence for the efficacy and safety of roxadustat in treating renal anemia in maintenance hemodialysis patients. Roxadustat can effectively increase hemoglobin levels in maintenance hemodialysis patients, thereby correcting anemia. Compared with ESAs, roxadustat can improve serum iron, transferrin, and total iron binding capacity levels, demonstrating superior improvement in iron metabolism-related indicators. No statistically significant difference was found in adverse event incidence between the two groups, though its long-term efficacy and safety require further investigation. We look forward to future long-term, large-sample, high-quality RCTs to provide evidence for clinical drug application.

Author Contributions: Li Qing was responsible for conceptualization, design, and manuscript writing; Li Jiaqing for study implementation, feasibility analysis, and manuscript revision; Yang Qing, Yuan Dunlu, Chang Qing, and Nie Jingwen for data collection and classification; Huang Jingjing for data analysis and statistical processing; Zhou Zhu for supervision and interpretation of results.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.