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ORIGINAL

COMPARATIVE EFFECTIVENESS AND COST-EFFECTIVENESS OF RHUEPO AND ROXADUSTAT IN TREATING RENAL ANEMIA IN ATHLETIC PATIENTS: A PHARMACOECONOMIC ANALYSIS

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ABSTRACT

Purpose: This study aims to evaluate the effectiveness and cost-effectiveness of recombinant human erythropoietin (rHuEPO) and Roxadustat in treating renal anemia, particularly in athletic patients undergoing regular hemodialysis. **Methods:** Between January 2020 and December 2021, 150 athletic patients on continuous ambulatory regular hemodialysis were enrolled. They were divided equally into rHuEPO and Roxadustat groups. We assessed hemoglobin (Hb), hematocrit (Hct), serum ferritin (SF), and transferrin (TRF) levels, along with adverse reactions, allergic responses, coagulation function, and liver and kidney function parameters (ALT, CCr) before and after treatment. The study also compared the cost-effectiveness of these treatments. **Results**: Basic demographic information (gender, duration of illness, weight, dialysis method, age) showed no significant difference between groups ($P > 0.05$). The Roxadustat group demonstrated a significantly higher total effective rate (92.00%) compared to the rHuEPO group (74.67%), with $P < 0.05$. Post-treatment, improvements in Hb, Hct, SF, TRF, and coagulation and liver and kidney function indices were observed in both groups, with Roxadustat showing superior outcomes ($P < 0.05$). Adverse reactions were lower in the Roxadustat group (9.33%) compared to the rHuEPO group (24.00%), $P < 0.05$. Roxadustat's Incremental Cost-Effectiveness Ratio (ICER) was 41,134.10 yuan, deemed tolerable against the backdrop of thrice the per capita GDP. **Conclusion:** Both Roxadustat and rHuEPO are effective in treating renal anemia in athletes. However, Roxadustat shows superior efficacy, safety, ease

of oral administration, patient acceptance, and cost-effectiveness. It becomes the preferred choice for athletic patients with a willingness to pay exceeding 41,134.10 yuan, marking it as the most economically viable option.

KEYWORDS: Roxadustat; rHuEPO; renal anaemia; effects; pharmacoeconomics; cost-effectiveness

1. INTRODUCTION

Renal anemia (RA) is the most common complication in athletic patients with advanced chronic kidney disease (CKD).(Locatelli & Del Vecchio, 2022) RA is the result of a multifactorial process that includes reduced production of erythropoietin (EPO), suppressed erythropoiesis due to uremia, shortened erythrocyte survival, and imbalance in iron In the end stages of CKD, this can lead to severe renal fibrosis (RF) (Tonelli & Thadhani, 2022). As CKD progresses, the overall prevalence of anaemia increases, with the probability of RA in athletic patients with end-stage renal disease (ESKD) ranging from 80.2% to 100.0% (Yang et al., 2021).

In addition, iron deficiency has been shown to lead to a reduced quality of life in athletic patients with CKD, and may exacerbate the progression of CKD and increase the incidence of cardiovascular events and mortality in athletic patients (Nguyen, Li, Yan, & Krzyzanski, 2021). The main therapeutic agents for renal anaemia are iron drugs for iron supplementation, the erythropoiesis-stimulating agent recombinant human erythropoietin (rHuEPO), and the hypoxia-inducible factor inhibitor Roxadustat, which promotes erythropoiesis and improves iron metabolism (Cai, Zhu, Lin, & Luo, 2021). rHuEPO changes are an important factor in renal anaemia, and currently, rHuEPO is one of the means of treatment for RA (Susantad et al., 2021). rHuEPO promotes the production of red blood cells to improve anemia due to chronic kidney disease (Benjamin, Adam, Krishna, & Assounga, 2020).

In the early second half of the 20th century, Erslev recognized that plasma from anemic rabbits contained a factor that stimulated erythropoiesis and could potentially be used as a therapeutic agent.(Kaufner et al., 2020) In 1957, researchers discovered that this erythropoietic factor was produced by the kidneys. Two decades later, it was isolated from the urine of athletic patients with aplastic anemia and named erythropoietin (Nguyen, Meaney, Rao, Panesar, & Krzyzanski, 2020). Thanks to advances in biotechnology, the EPO gene was successfully isolated and cloned. This discovery paved the way for the development of recombinant human erythropoietin. The ability to stimulate erythropoiesis with therapeutic agents became a milestone and probably the greatest breakthrough in nephrology (Nguyen et al., 2020).

Roxadustat is a novel drug developed in recent years (Mittal et al., 2019) that improves renal anemia by regulating EPO synthesis in vivo and improving

iron metabolism (Gavish et al., 2018). In addition, the occurrence of RA is closely related to red blood cell survival, and Roxadustat treats RA by increasing red blood cell survival (Wan & Zhang, 2018). In this study, the efficacy of rHuEPO and Roxadustat in the treatment of renal anemia were compared, and the cost-effectiveness of the two treatments was further analyzed by cost/effectiveness in pharmacoeconomics, in order to investigate the economic cost advantages. To provide a reference for clinical selection of an effective, safe, and cost-effective treatment option.

2. Information and methods

2.1 General information

One hundred and fifty athletic patients who were treated in The Third Hospital of Hebei Medical University with renal anaemia on continuous ambulatory regular hemodialysis from January 2020 to December 2021 were selected for inclusion in the standard western diagnostic index with reference to the Clinical Practice Guidelines for Anaemia in Chronic Kidney Disease (Wheeler & Winkelmayer, 2017) (2017 Version). They were randomly divided into the rHuEPO group and Roxadustat group. There were 75 cases in each group.

2.2 Case selection criteria

2.2.1 Diagnostic criteria

A) Endogenous creatinine clearance (Ccr) <50 ml/min. B) Serum ferritin (SF) <500ug/L. C) Renal anemia erythrocyte count (hematocrit, Hct) <30% and hemoglobin (Hb) <90g/L.

2.2.2 Inclusion criteria

(1) All athletic patients participating in the study were receiving hemodialysis for at least 3 months of treatment and had a confirmed diagnosis of renal anemia on examination. (2) None of the athletic patients had a history of blood transfusion therapy within 60 days prior to participation in this study. (3) Athletic Patients are all between the ages of 18 and 75 years. (4) The athletic patient's family volunteered to participate in this study (Fei et al., 2021).

2.2.3 Exclusion criteria

(1) Persons with severe infection or severe malnutrition or incomplete clinical information. (2) Persons with chronic active bleeding, hypersensitivity to the drugs used in this study. (3) Persons with mental abnormalities. (4) Those with malignant tumors or serious illnesses such as heart or liver disease (Ichii et al., 2021). This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University.

2.3 Methodology

In response to the athletic patients' anemia, both groups were treated with regular hemodialysis. rHuEPO group patients were given Recombinant Human Erythropoietin for Injection (CHO cells) (Yibao) (NDC S19991025(4000IU), Shanghai Chemo Wanbang Biopharma Co., Ltd) treatment at a starting dose of 100-150 IU/kg per week in three injections, with the dose gradually reduced according to the improvement of the athletic patients' Hct and Hb levels until the Hct and Hb in the body were maintained at normal levels.

In the treatment group, after the end of hemodialysis, Roxadustat capsules (NDC H20180024，50mg x 3 capsules/box, FibroGen (China) Medical Technology Development Co., Ltd) were given orally, the starting dose was given according to the athletic patient's body weight, 100mg/time for 45-60kg, 120mg/time for ≥60kg, 3 times a week, both before and after meals, and adjusted according to the Hb level. The dose was adjusted every 4 weeks until normal levels were maintained. Both groups were treated for 6 months.

2.4 Follow-up visits

A post-hemodialysis return visit was conducted to investigate the post-dialysis living conditions of athletic patients based on their hemoglobin and the improvement of their anemia symptoms.

2.5 Observation indicators

Before and after treatment, blood tests were taken from two groups of athletic patients to determine Hb, Hct, SF, and serum transferrin (TRF), and to compare the occurrence of adverse reactions and allergic reactions in each group during the drug administration. The results of the treatment were compared with those of the athletic patients in terms of coagulation, ALT, creatinine clearance (CCr), liver and kidney function, efficacy, and the cost-effectiveness of the two treatments.

Costing: including direct costs, indirect costs, and intangible cost. a) Direct cost are related to the treatment costs incurred during the treatment period. B) Indirect costs are the financial losses incurred by athletic patients and their families during RA treatment, including daily transport costs during treatment and lost wages, which are calculated based on the average daily wage of local worker’s x the number of days of treatment. c) Intangible cost such as the cost of emotional distress due to RA illness.

2.6 Methodology for assessing the effectiveness of treatment

Significantly effective: significant reduction in symptoms caused by RA,

with Hb values more than 20g/L higher than the values tested before treatment. Effective: the symptoms caused by RA are reduced and the Hb value is more than 10 g/L higher than the value tested before treatment. Ineffective: no change in the symptoms caused by RA and no significant fluctuations in Hb values. The total treatment efficiency of the different treatments in both groups are the apparent efficiency + the effective rate. The cost of treating RA, enhancing quality of life, and the total cost of achieving efficacy were investigated using cost-effectiveness analysis approaches. The cost-effectiveness ratio (CER), which represents the cost per unit effect, was seen to achieve efficacy. The incremental cost-effect ratio ICER was calculated using incremental analysis to determine the ratio of the difference between the relative cost and impact of Roxadustat and rHuEPO. In this study, WTP values were used to assess the drug's economics, while ICER values were utilized to assess the drug's economics. When ICER < GDP per capita, the increased cost is completely worth it; When per capita GDP <icer<3 times per capita GDP, the increased cost is acceptable; When icer>3 times per capita GDP, the increased cost is not worth it. When ICER < patient WTP, it means that the drug is more economical for athletic patients.

2.7 Evaluation of sensitivity

(1) One-way sensitivity analysis: The major indicators throughout this study were medical expenses and clinical efficiency, and various costs were modified upward or downward with a 15% movement, respectively, to examine changes in ICERs. The study used GDP per capita as the baseline and 3 times GDP as the criterion. The effective rate was computed and the change in ICER was compared after adjusting the Hb value range from 100-130 g·L-1 to 90-130 g·L-1 and 110-130 g·L-1.

(2) Probabilistic sensitivity analysis: Using the single-factor analysis above, the two factors having the largest impact on ICER were chosen as variables, which were simulated 1000 times using MonteCarlo simulation, and an acceptable cost-effect curve was created.

2.8 Statistical methods

The new version of SPSS 26.0 software was used to process the data of each index. t-test was used for Hb, Hct, SF, TRF, duration of illness, weight, age, APTT, TT, PT, and FIB, and$\chi 2$ test was used for gender, efficacy, adverse effects, and cost-effectiveness. $P<0.05$ indicated that the difference was statistically significant.

3. Results

Basic information (gender, duration of illness, weight, and age) was compared between the two groups *at P*> 0.05. Fig.1.

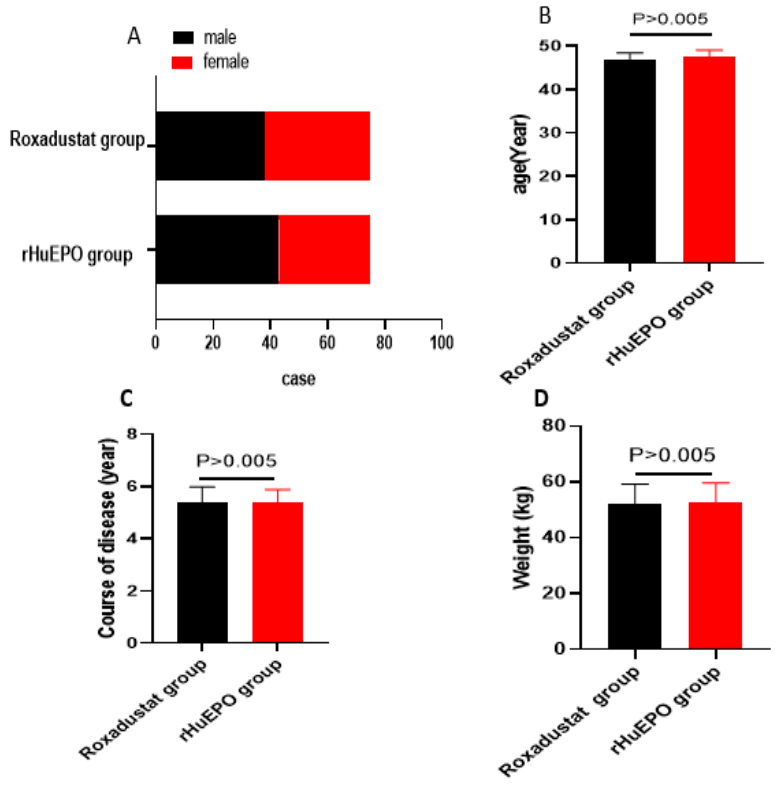

Figure1: Basic information

The total effective rate in the Roxadustat group was significantly higher (92.00) % than that in the rHuEPO group (74.67) %. p<0.05. Fig.2.

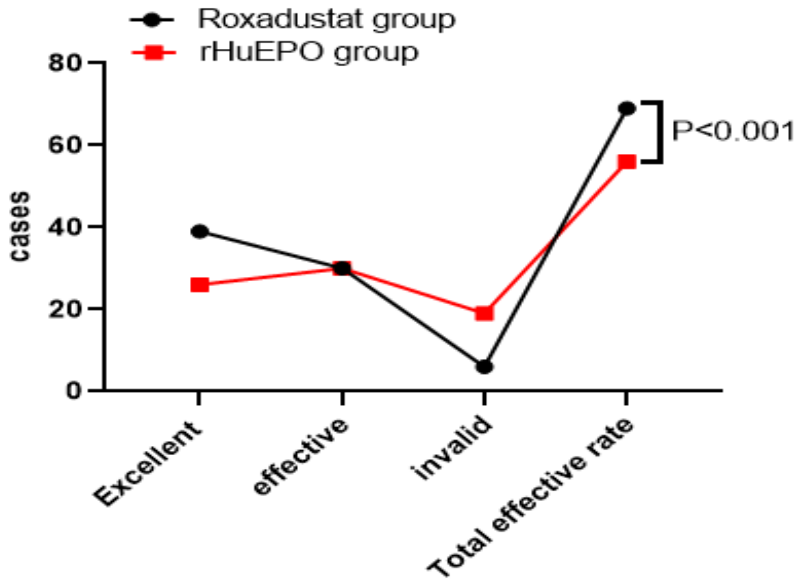

Figure 2: Comparison of the efficacy of different therapeutic drugs in the two groups

Before treatment, Hb, Hct, SF, and TRF were compared between the two groups, *P*> 0.05. After treatment, Hb, Hct, SF and TRF were better in both groups than before treatment, and Hb, Hct, SF and TRF were better in the Roxadustat group than in the rHuEPO group, P<0.05. Fig.3.

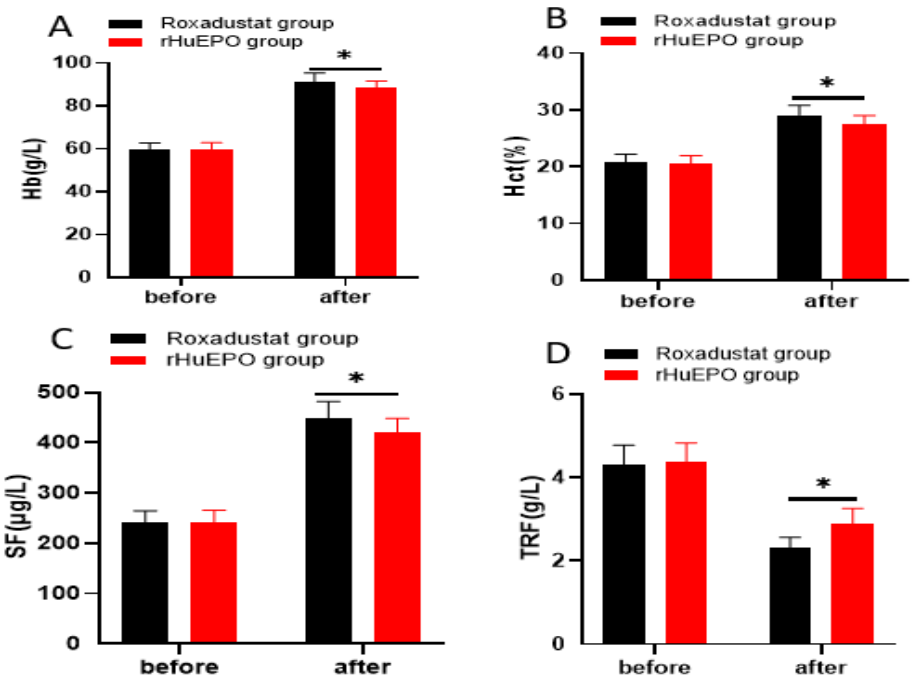

Figure 3: Comparison of Hb, Hct, SF, TRF before and after different treatments in both groups ***Note：****P<0.05*

The incidence of adverse reactions was better in the Roxadustat group (9.33) % than in the rHuEPO group (24.00) %, p<0.05. Fig.4.

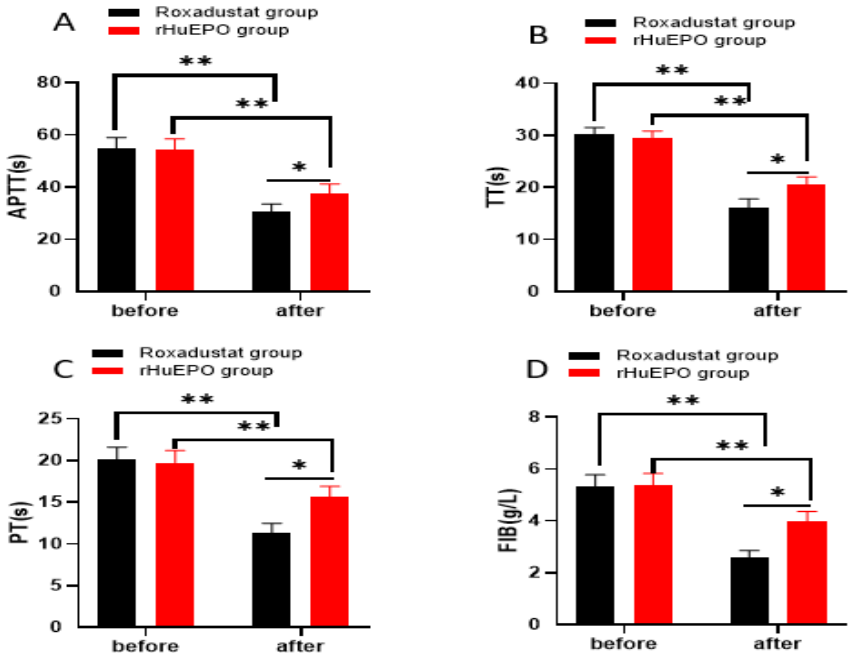

Figure 4: Comparison of coagulation-related indicators between the two groups before and after treatment with different methods. ***Note：****P<0.05，**P<0.05*

Before treatment, there was no statistically significant difference in the comparison of coagulation-related indexes APTT, TT, PT, and FIB between the

two groups, P>0.05. After treatment, both groups were better than before treatment, and coagulation-related indexes APTT, TT, PT, and FIB were significantly better in the Roxadustat group than in the rHuEPO group, P<0.05. Fig.5.

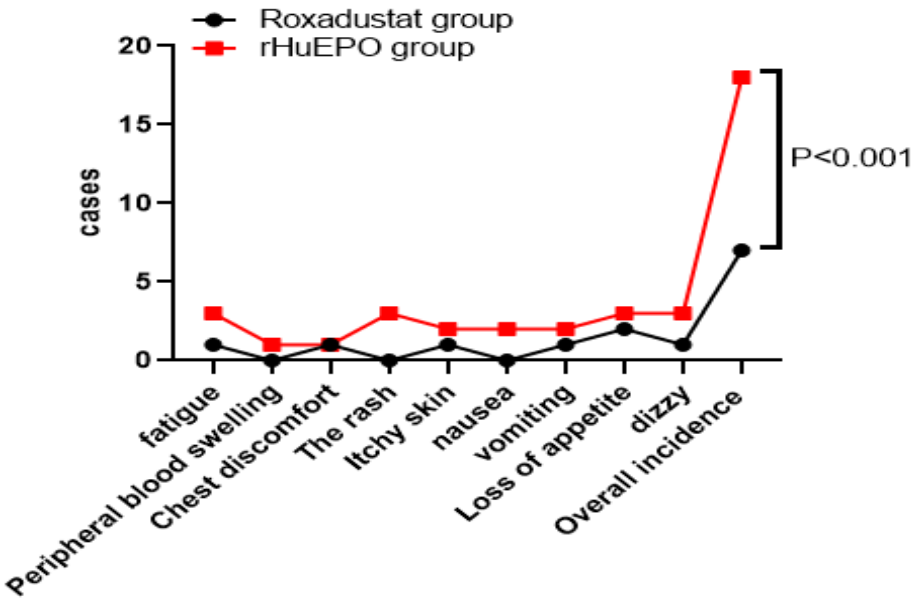

Figure 5: Occurrence of adverse reactions in the two groups treated by different methods

Before treatment, the ALT and CCr of the two groups were compared, *P*> 0.05. After treatment, the ALT and CCr of both groups were better than before treatment, and the ALT and CCr of the Roxadustat group were better than those of the rHuEPO group, P<0.05. Fig.6.

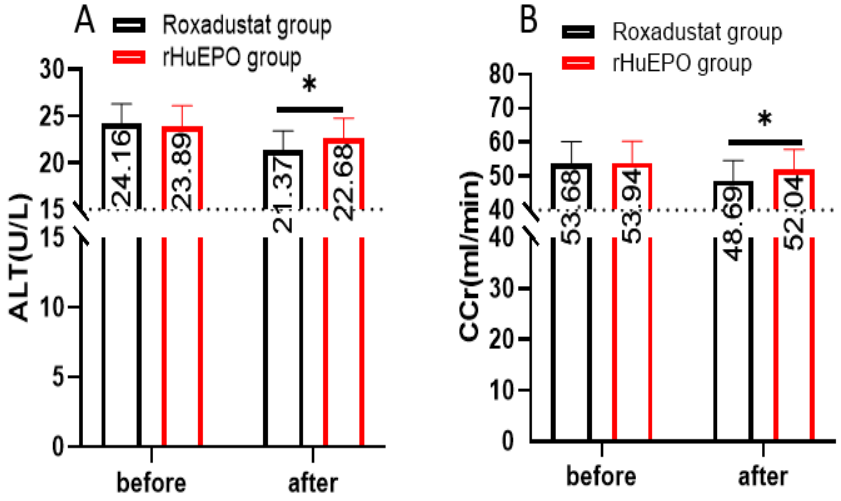

Figure 6: Comparison of liver and kidney function indicators before and after treatment by different methods in the two groups. ***Note:*** **P<0.05*

The total cost/efficiency of the Roxadustat group was lower than that of the rHuEPO group and the cost-effectiveness was better than that of the

rHuEPO group, p<0.05. Fig.7.Roxadustat ICER is 41,134.10 and based on China's per capita GDP of 80,976 yuan in 2021, the calculated 6-month per capita GDP is around 40,488 yuan, with per capita GDP ICER 3 times GDP.

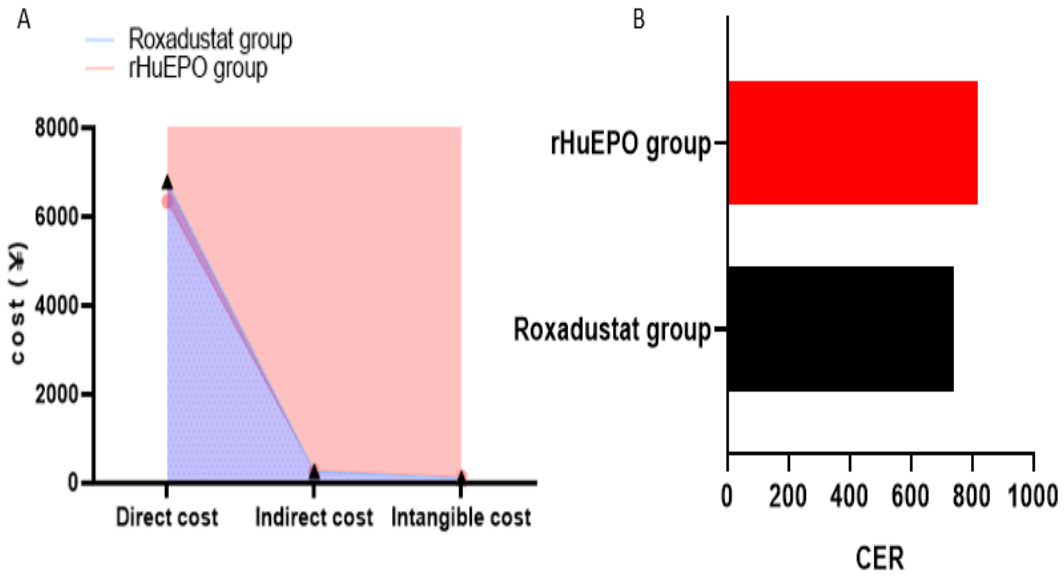

Figure 7: Cost-effectiveness comparison of 2 different treatments

3.1 Sensitivity analysis

(1) Single-factor sensitivity analysis: Among the various cost categories, direct costs have a greater impact on the results. Single-factor analysis of direct costs, using GDP per capita and 3 times GDP per capita as thresholds, respectively, shows that direct costs are linearly related to ICER, and ICER increases with the increase of direct costs. ICER < GDP per capita when direct costs were reduced by 20%. The lower limit of Hb in the efficacy criteria was adjusted, and the efficiency rate was recalculated for univariate analysis. The results showed that the ICER changed little when the lower limit of Hb changed from -10 to +10 g·L-1 and increased substantially when the change value was greater than 16 g·L-1.

(2) Probabilistic sensitivity analysis**:** It is assumed that the direct cost change obeys the triangular distribution and the efficiency change obeys the Beta distribution. The Monte Carlo simulation was performed according to the results in Fig.7, and the cost-effectiveness acceptable curve was obtained as shown in Fig.8.

When the WTP increased, the probability of economic of Roxadustat also increased. when the WTP was 22,000 yuan, the probability of economic of drug Roxadustat was less than 10%; when the WTP was 30,000 yuan, the probability of economic of drug Roxadustat was 50%; when the WTP > 40,000 yuan, the probability that Roxadustat has economy is close to 100%.

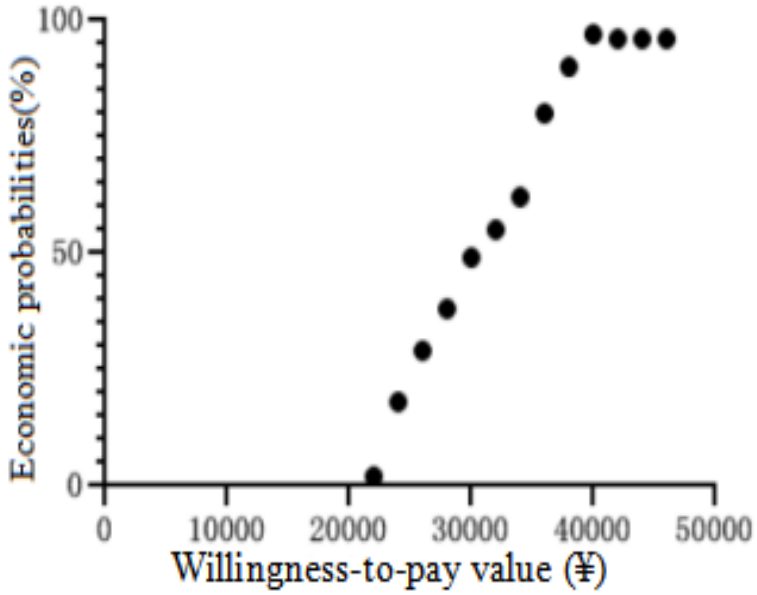

Figure 8: Cost-Effectiveness Acceptable Curve

4. Discussion

RA is a complication of CKD and is strongly associated with adverse clinical outcomes (Reza-Zaldivar et al., 2020). CKD is one of the fastest rising leading causes of death internationally, with an overall prevalence of 13% worldwide (Watanabe et al., 2016). Treating RA is essential to reverse this negative trend (Winkelmayer & Walther, 2022). The prevalence of renal anaemia increases as the estimated glomerular filtration rate (GFR) decreases (Provenzano et al., 2022). Anaemia occurs in about half of athletic patients with CKD stage G4 and in more than 90% of athletic patients with end-stage renal disease on dialysis (Fishbane et al., 2022). Correction of RA can reduce mortality, the Hospitalization rate, risk progression of CKD and improve health-related quality of life (Zhu, Zhang, Xu, Jiang, & Yao, 2021). The main mechanisms associated with the development of renal anaemia are inadequate EPO synthesis and a combination of EPO resistance (Precup et al., 2020). Other contributing factors include absolute and functional iron deficiency, chronic inflammation, uremic toxins, disturbances in iron homeostasis, shortened red blood cell lifespan, and vitamin deficiencies (vitamin B12 or folic acid). In addition, hemodialysis itself may contribute to blood loss and red blood cell damage (Hara et al., 2022). This study focuses on the efficacy of rHuEPO therapy versus Roxadustat as a treatment for RA and further investigates its cost-effectiveness, with the aim of improving patient outcomes while reducing the financial burden on athletic patients. Roxadustat is a novel oral hypoxia-proline-hydroxylase (HIF-PHD) inhibitor (Zheng et al., 2022). In hypoxic conditions, the hydroxylation of the HIF-α subunit by PHD is reduced through hydroxyl binding to the HIF-α subunit, and the hydroxylation of the HIF-α subunit is reduced in a hypoxic environment. HIF-PHD inhibitors inhibit hypoxic

metabolism in vivo, resulting in the inhibition of iron hormone, erythropoietin, erythrocyte receptor, and transferrin receptor activity genes into the body without hypoxia (Tang et al., 2021). In this study, by comparing the efficacy of rHuEPO and Roxadustat treatment, the results showed that Roxadustat was significantly more effective than rHuEPO due to the fact that Roxadustat inhibited HIF-PHD while promoting erythropoiesis and improving iron metabolism.

In athletic patients with RA, the diagnosis of anemia-related indicators Hb, Hct, SF, and TRF, suggests drug improvement of anemia in RA. Hb is the main substance that transports oxygen within red blood cells, Hct indicates the ratio of the volume of red blood cells in a specific volume of whole blood to a specific total volume, and an abnormality in Hct indicates an abnormal number of red blood cells. TRF is used in the diagnosis of anemia and in the monitoring of treatment. Haemoglobin F is one of the indicators used to detect thalassemia (Eager, 2016). The improvement of anemia with the two drugs was evaluated by comparing the Hb, Hct, SF, and TRF indicators between the two groups. The results showed that before receiving this treatment, the differences in the comparison of all indicators between the 2 groups of RA athletic patients were not statistically significant. After 6 months of treatment with rHuEPO and Roxadustat respectively, it was found that the improvement of Hb, Hct, SF, and TRF in athletic patients treated with Roxadustat was significantly better than that in athletic patients treated with rHuEPO, indicating that the effect of Roxadustat in improving anemia was better than that of rHuEPO. This is consistent with the findings of UGAWA T (Ugawa, Ashizaki, Murata, & Majikawa, 2021). who showed that Roxadustat promotes hemoglobin production, increases serum Hb levels, activates erythropoietin receptors, and increases iron use in the body, thus improving anemia. The potential clinical benefits of HIF-PHI treatment include achievement of Hb targets, a significant reduction in plasma EPO levels; and hypolipidemic, hypotensive, anti-inflammatory, protective, and ischaemic effects in CKD.

In addition, comparing the occurrence of adverse reactions and allergic reactions in the two groups, the results showed that the incidence of adverse reactions was lower in athletic patients treated with Roxadustat than in those treated with rHuEPO, indicating that Roxadustat has fewer side effects and is safer. (Cai et al., 2021) showed that Roxadustat was well tolerated, that it had relatively few side effects and that it caused fewer adverse reactions. APTT, TT, PT, and FIB are the four routine tests of coagulation function. Abnormalities in APTT indicate an increase or decrease in platelets, FIB is in an elevated state in RA athletic patients, and abnormalities in TT indicate abnormalities in anticoagulant substances (Wu et al., 2022). By analyzing the coagulation-related indicators APTT, TT, PT, FIB, and liver and kidney function-related indicators ALT and CCr in both groups, the APTT, TT, PT, FIB, ALT, and CCr were significantly better after 6 months of treatment with Roxadustat than after

6 months of treatment with rHuEPO. The aggravation of anemia in RA athletic patients will damage the liver and kidney functions to a certain extent, so the effect of the drug on the liver and kidney is also particularly important. Roxadustat promoted the recovery of coagulation in RA athletic patients and caused less damage to liver and kidney function. This was also confirmed in the study by (Yang et al., 2021). The APTT, TT, PT, and FIB in the observation group were significantly better than those in the control group. Also the study by (Li et al., 2022) showed that Roxadustat was able to compassionately promote recovery from renal injury by improving folic acid-induced mitochondrial dysfunction. This is consistent with the findings of the present study. To further clarify the cost-effectiveness of rosalsat and rHuEPO, the results showed that the benefit of rosalsat group was better than that of rHuEPO group, because the cost of rosalsat capsule was lower, and it was convenient and fast to take orally, with lower total cost, and its efficacy was higher than that of rHuEPO, so the cost-effectiveness was also higher than that of rHuEPO. When WTP of athletic patients >41134.10 yuan, Roxadustat was more economical.

5. Conclusion

This study underscores the efficacy of Roxadustat and rHuEPO in treating renal anemia, with a particular focus on athletic patients undergoing regular hemodialysis. Roxadustat emerges as the more effective treatment, showcasing a higher success rate in improving anemia-related metrics and a lower incidence of adverse reactions compared to rHuEPO. The convenience of oral administration with Roxadustat is a significant advantage, especially for athletes who require a straightforward, manageable treatment regimen alongside their training and competition schedules.

Economically, while Roxadustat is costlier, its cost-effectiveness becomes justifiable within the context of athletes. Athletes, often facing unique health and performance challenges, may find the higher efficacy and safety profile of Roxadustat to be a worthy investment, particularly if their willingness to pay aligns with the treatment costs. Therefore, Roxadustat stands out as the preferred choice for athletic patients with renal anemia, balancing the crucial aspects of efficacy, safety, patient convenience, and economic viability.

Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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