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Progress in the Study of the Therapeutic Effects of Roxarestat

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Abstract: ***Hypoxia-inducible factor has a wide range of roles in the human body and is involved in pathophysiological processes including erythropoietin production, iron uptake metabolism and energy metabolism. Roxarestat is a small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase, which can stabilize the level of hypoxia-inducible factor to participate in systemic biological functions. Roxarestat is widely used in the treatment of renal anemia. With the deepening of research, it is found that roxarestat has therapeutic potential for renal fibrosis, cardiovascular disease, retinopathy, etc. This article summarizes the current status of roxarestat in the treatment of renal anemia, and its therapeutic effects on other therapies.***

Keywords: Roxarestat, Hypoxia-inducible factor, Chronic kidney disease, Anemia**.**

1. Introduction

In the course of chronic kidney disease, renal anemia is one of the most common complications in the patient population with a prevalence of 10.8% [1]. Renal anemia not only increases the rate of progression of chronic kidney disease, but also decreases the cognitive level of patients and elevates the incidence of adverse cardiovascular events [2]. HIF (hypoxia inducible factor) plays an important role in the progression of chronic kidney disease, which is a heterodimeric protein complex consisting of HIF -α subunit and HIF-β subunit, respectively. It stimulates increased expression of erythropoietin and also increases expression of erythropoietin receptor proteins, and its function is largely dependent on the oxygen-sensitive HIF-α. In a normoxic environment, the proline residues of HIF-α are hydroxylated by prolyl hydroxylase (PHD), and the hydroxylated HIF-α is subsequently recognized by the p von Hippel Lindau tumor suppressor accurately recognized by ubiquitin-proteasome mediated degradation. In contrast, in a hypoxic environment, HIF-α cannot be successfully degraded by PHD, and a large amount of intracellular HIF-α accumulates and forms a heterodimer with HIF-β, which binds to the hypoxia response element (HRE) of the gene, leading to the initiation of transcription of downstream target genes, which participate in a wide range of pathological processes, for example, encompassing erythropoietin, vascular endothelial growth factor, and connective tissue growth factor activation [3]. Roxarestat, a small molecule hypoxia-inducible factor-prolinyl hydroxylase inhibitor (HIF-PHD) analog, is capable of rapidly stabilizing HIF by mimicking intermittent hypoxia, and elevating erythropoiesis in a positive dose-related manner. Since the release of roxarestat, efficacy in the treatment of renal anemia has been well established. A growing body of research suggests that its therapeutic effects are not limited to renal anemia, and this article will summarize the current therapeutic effects of roxarestat.

2. Roxarestat for Renal Anemia

Prior to the first approval of roxarestat, erythropoiesis-stimulating agents were used in the treatment of renal anemia. Erythropoietin-stimulating agent (ESA) and iron supplementation are the main treatment options for renal anemia, but ESA has the risks of being difficult to store, being administered by injection, causing cardiovascular adverse events, and the efficacy of ESAs varies significantly among individuals [4], and roxarestat is a better solution to the therapeutic needs of patients. The efficacy and tolerability of roxarestat in non-dialysis CKD-associated anemia was evaluated in a global study in which 922 patients with stage 3-5 CKD who were not receiving dialysis were treated with oral roxarestat or placebo. At weeks 28-52, the roxarestat group showed a more significant change in mean hemoglobin value from baseline compared with the placebo group, demonstrating the efficacy of roxarestat in correcting anemia and maintaining hemoglobin levels. Moreover, the proportion of patients receiving resuscitation at week 52 was reduced compared to the placebo group, indicating that it was well tolerated [5]. In an investigative study from China, 129 patients with anemia in the peritoneal dialysis state were randomly divided into roxarestat-treated and erythropoiesis-stimulating agent-treated groups, and after 24 weeks of intervention, the hemoglobin level and the change in hemoglobin level from baseline in the roxarestat group were 11.5g/dL and 2.5g/dL, respectively, and in the erythropoiesis-stimulating agent-treated group, they were 11. 2 g/dL and 2. 2 g /The reduction in total and LDL cholesterol was greater in the roxarestat group than in the erythropoiesis-stimulating agent group. The results showed that rosastat could also effectively increase and maintain hemoglobin levels in peritoneal dialysis patients compared with erythropoiesis-stimulating agents [6]. LIU Mengjun et al. divided 60 hemodialysis patients with HIV/AIDS combined with erythropoietin resistance into rosastat-treated group and erythropoietin-treated group according to their willingness to be treated, and after 8 weeks of treatment, the rosastat group's After 8 weeks of treatment, hemoglobin level, serum iron, and total iron binding capacity increased significantly compared with before, and the comparison of the two groups found that hemoglobin level and total iron binding capacity of roxarestat group were higher than that of erythropoiesis-stimulating agent group, which indicated that roxarestat could significantly improve hemoglobin and iron metabolism level of the patients [7].

3. Roxarestat for Other Kidney Diseases

With the in-depth study of roxarestat, the potential of its application in the treatment of hypoxia-related diseases, including chronic inflammation, fibrosis, etc. Menqiu Wu et al, based on the literature that transient activation of hypoxia-inducible factor (HIF) can protect the kidneys from acute ischemic injury, so they carried out a study on unilateral renal ischemia/reperfusion injury (UIR) model mice, and 3 days after UIR, the The mice were given roxarestat, and it was found that roxarestat may significantly slow down the fibrotic process of the kidney and enhance the regeneration of renal vasculature by activating the HIF-α-related pathway, preventing the transition from AKI to CKD [8]. Also in hypoxia-mediated renal ischemia-reperfusion injury, detection of CD73 protein and melanoma deficiency factor 2 in mice revealed that roxarestat could enhance CD73 synthesis in the kidney and inhibit melanoma deficiency factor 2 inflammatory vesicles to exert a protective effect on the kidneys, which provided a new idea for the treatment of acute renal injury caused by renal ischemia-reperfusion [9]. A study on the effect of intestinal biofunctional barrier in rats with chronic kidney disease found that blood creatinine urea nitrogen levels were decreased and hemoglobin levels were significantly increased in the roxarestat group compared to the sham-operated group of rats. It can delay the pathological changes of renal fibrosis, reduce the levels of TGF-β1 and α-SMA, and improve the microinflammatory state [10]. Huo Dongmei gave rats gavage with low, medium and high doses of roxarestat, respectively, and constructed a rat model of contrast-induced acute kidney injury using iopromide 2 days later, and waited for 1 day to detect renal fibrosis by using real-time fluorescent quantitative PCR (RT-PCR, RT-PCR) and immunoprotein blotting (Western Blot, WB). Western Blot (WB) was used to detect the expression levels of Bax, Bcl-2 and HIF-1α in renal tissues and the ROS index of oxidative damage in renal tissues. After control with the model group, it was found that the level of Bax index was significantly reduced, the expression of Bcl-2 and HIF-1α was significantly increased, and the ROS content was significantly reduced. It indicates that roxarestat can play a role in protecting the kidney by increasing the expression of Bcl-2 and HIF-1α, down-regulating the expression of Bax, and decreasing the content of ROS, thus reducing the model renal tissue and oxidative stress injury [11]. In a study targeting chronic tubulointerstitial nephritis, roxarestat was found to be attenuated for adenine-induced renal tubulointerstitial injury, including proximal and distal tubular injury, tubular dilatation, and renal crystal deposition in a model mouse [12]. Roxarestat may improve HIF by stabilizing it The above studies are all animal experimental studies, and there are no clinical studies on other clinical applications of roxarestat.

4. Roxarestat and Lipid Metabolism

Lipid metabolism is a complex biochemical reaction process of digestion, synthesis and catabolism in the presence of relevant enzymes. It has been found in studies prior to 2019 that roxarestat reduced LDL cholesterol and triglyceride levels and increased the ratio of HDL cholesterol to LDL cholesterol, whereas after discontinuation of the drug cholesterol levels returned to pre-treatment levels [13-14]. Alcoholic liver disease, as a disease characterized by lipid metabolism, reactive oxygen species production and inflammation, in a recent study on the relationship with alcoholic liver disease and rosarestat, an 8-week intervention was conducted in both long-term and short-term alcoholic fatty liver mouse models, and the results showed that rosarestat improved liver morphology and serum aminotransferase activity indexes significantly, inhibited the expression levels of inflammatory factors such as IL-1β and TNF-α, and reduced the accumulation of lipids [13-14]. expression levels and attenuated the level of lipid accumulation [15]. In a retrospective study of hemodialysis patients, roxarestat was found to significantly alleviate anemia in hemodialysis patients, inhibit the secretion of thyroid-stimulating hormone and free thyroxine, and reduce the levels of total cholesterol and LDL cholesterol, suggesting that the lipid-lowering mechanism of roxarestat may be to regulate the gene expression of LDL and to increase the clearance of LDL [16].

5. Roxarestat and Cardiovascular Disease

Adverse cardiovascular events often coexist with the progression of chronic kidney disease, and in the course of cardiovascular disease, ischemia and hypoxia are important factors leading to the deterioration of the condition, and HIF plays an indispensable role in the process, and its function is mainly dependent on HIF-α. The most studied of HIF-α can be divided into 2 different isoforms, HIF-1α, HIF-2α, which have different roles. Currently, HIF-1α is the most intensively researched, which exists in a wide range of areas, is regulated by oxygen concentration, and is the main regulator of hypoxic conditions in tissue cells, whereas HIF-2α is mainly found in vascular-rich organs, such as the heart, lungs, liver, kidneys, and brain. It contributes to vascular remodeling, catecholamine stabilization, iron level stabilization and is also a mediator of erythropoiesis [17]. In an earlier study on myocardial infarction model mice, it was found that HIF-1α was involved in myocardial remodeling and periportal vascularization of the lesions, effectively reducing the extent of myocardial infarction [18]. In obesity-associated atherosclerosis where adipose dysfunction is a major factor, Zhang X et al. found that in mice HIF-2α was able to be activated in adipose tissue under moderate cold conditions and prevented atherosclerosis by lowering plasma cholesterol levels and enhancing thermogenesis. Roxarestat exerted similar preventive effects on atherosclerosis through its own pharmacological actions, and further studies revealed that the preventive mechanism of roxarestat was closely related to the metabolic regulation of HIF-2α and ceramides in adipocytes, providing potential therapies against atherosclerosis [19]. Hypertension and chronic kidney disease are often causative of each other, and current treatment strategies for hypertension are still very limited. To observe the effects of rosastat on hypertension, the investigators induced the formation of a hypertensive model using angiotensin II. The blood pressure of the mice was significantly elevated during the 16 days of drug administration, and then decreased after the use of rosastat. Analysis of aortic and cardiac tissues using HE staining showed that aortic wall thickening was significantly attenuated and cardiomyocyte hypertrophy was alleviated in mice after roxarestat administration. In the kidney tissues of mice, the proliferation of mesangial cells was attenuated in the roxarestat group with no significant

effect on glomerular size. The expression of the proteins AGTR1 and AGTR2 that bind to angiotensin II and regulate vasoconstriction was detected by protein immunoblotting, and it was found that rosastat could enhance the expression of AGTR1 and reduce the expression of AGTR2, and also enhance the expression of eNOS, p-eNOS and HIF-1α. The results suggest that the eNOS/p-eNOS pathway regulated by HIF-1α may be a therapeutic pathway for roxarestat in angiotensin II-induced hypertension [20]. In terms of clinical studies, a rationale has been provided for the reduction of cardiovascular adverse events in the treatment of chronic kidney disease with roxarestat. A 2021 phase III clinical study of roxarestat versus erythropoiesis-stimulating agent in dialysis-dependent patients demonstrated that the relative baseline hemoglobin values of the roxarestat versus the erythropoiesis-stimulating agent groups at weeks 28-36 were essentially comparable, and that the incidence of cardiovascular adverse events was essentially comparable between the two groups. comparable. 2022 The same phase III clinical study of the cardiovascular safety of anemia treatment in dialysis-dependent patients was conducted on 2, 133 patients randomized to the roxarestat group versus the epoetin α group, with a 52-week intervention focus, and the overall event rate for adverse events was numerically higher for the roxarestat group than for the epoetin α, although the rates of individual and common adverse events were essentially similar between the treatment groups [21-22]. The In a Chinese clinical study of elderly hemodialysis patients, the efficacy of rosastat and recombinant human erythropoietin was compared, and the results showed that hemoglobin values were significantly higher in both groups, but rosastat was superior to the recombinant human erythropoietin group. There was no significant difference in iron metabolism indexes between the two groups, while systolic blood pressure, diastolic blood pressure, amino-terminal brain natriuretic peptide (NT-proBNP), and troponin (cTnI) indexes were significantly lower in the roxarestat group than in the recombinant human erythropoietin group. no cardiovascular adverse events occurred in the roxarestat group in the 12-week treatment period. This indicates that roxarestat has less effect on the cardiovascular system and has a good safety profile [23].

6. Roxarestat for the Treatment of Anemia in Myelodysplastic Syndromes

Myelodysplastic syndrome (MDS) is a neoplastic disease originating from hematopoietic stem cells, and the disease is characterized by abnormalities in hematopoietic function and blood cell development. Clinically, the disease is characterized by refractory hematopoiesis with a high risk of transformation to leukemia. Current treatment strategies for low-risk MDS focus on improving quality of life and hemopenia, while prolonging survival and delaying disease progression are the focus of treatment for high-risk MDS, but there is a lack of potent therapeutic options, including hypoxia-inducible factor stabilizers rosmarinostat, TP53 modulators, and other promising agents under development [24]. The difference in efficacy between roxarestat and placebo was evaluated in a clinical trial of very-low- to intermediate-risk-stage MDS in which both groups were treated with optimal supportive therapy, but without erythropoiesis-stimulating agents, for a total of 52 weeks of intervention, followed by 4 weeks of follow-up. Many clinical parameters improved in the roxarestat group compared with the placebo group, including a higher increase in hemoglobin concentration and a lower need for blood transfusions. The primary endpoint of treatment effect was not statistically significant for roxarestat compared with placebo, which may be related to the shorter duration of treatment and lower study completion rate in the roxarestat group [25]. Further subsequent studies of roxarestat may be useful in targeting the treatment of mild MDS anemia.

7. Roxarestat and Tumor Therapy

Tumors broadly refer to the abnormal proliferation of collective cells to form localized masses in the body, which can be classified as benign or malignant. Glioblastoma (GBM), a common primary malignant tumor in the cranium, currently has very limited therapeutic options. The difficulty in treating glioblastoma is the resistance to apoptosis-inducing regimens, and the iron death pathway has been identified as a possible new approach for treatment, characterized by the accumulation of free iron and lipid peroxidation leading to cell death [26-27]. A study on novel therapeutic targets of iron death in GBM found that roxarestat significantly inhibited GBM cell viability in a cell viability assay, induced GBM cell death with more pronounced potency in combination with the chemotherapeutic agent temozolomide alone or in combination with the chemotherapeutic agent temozolomide and did not show significant visceral toxicity. HIF-2α is a potential therapeutic target for the induction of iron death in chemo-resistant GBM, and reveals that roxarestat his potential as a new approach option for patients with refractory GBM [28].

8. Roxarestat for the Treatment of Retinopathy

In an earlier study in neonates, it was found that high oxygen concentrations may lead to retinal vascular growth slowing and vascular occlusion in neonates, leading to retinopathy of prematurity (ROP), by a mechanism closely linked to upregulation of HIF [29]. In a recent study also on ROP, it was found that the simulation of a hypoxic environment is the idea for the treatment of the disease, and that this protective effect requires carbonylglycine structures to be produced. roxarestat targets the retina, kidneys, and brain, and can reduce the ablation effect of the liver, and then increase the expression of glycolysis-related genes through the stabilization of the induced HIF-1α, which leads to the improvement of the retinal metabolism and the normalization of the angiogenesis. Rosastat also provides weak HIF-2α induction in retinal cells, increasing angiogenesis and enhancing the safety of drug therapy [30].

9. Discussion

At present, roxarestat, as a small molecule inhibitor of the hypoxia-inducible factor prolyl hydroxylase, has been widely used in the clinical treatment of renal anemia. In addition to its therapeutic effect on renal anemia, it also has therapeutic effects on renal fibrosis, oxidative stress, inflammatory response, angiogenesis, etc. Its wide range of effects suggests that roxarestat has the potential for the treatment of other diseases, but most of the studies are still in the animal

experiment stage and have failed to provide evidence for the effectiveness of roxarestat. However, most studies are still at the animal experiment stage and fail to provide strong evidence. Finally, roxarestat, like other drugs, has many adverse effects, and its wide range of action is a double-edged sword. In follow-up studies, the dose and duration of use should be strictly controlled to avoid the occurrence of unexpected side effects.

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