Effects of Valsartan in Combination with Febuxostat on Serum Uric Acid, high-sensitivity C-reactive protein and Cardiac Function of Patients with Chronic Kidney Disease Plus Hyperuricemia

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We aimed to evaluate the effects of valsartan in combination with febuxostat on serum uric acid, high-sensitivity C-reactive protein and cardiac function of patients with chronic kidney disease plus hyperuricemia (HUA). A total of 144 patients with chronic kidney disease and hyperuricemia treated from June 2014 to June 2018 were retrospectively analyzed. They were divided into group A and group B according to treatment regimen. Both groups were given high-quality low-protein diet, and comprehensive treatments such as decrease of blood pressure, correction of anemia, supplementation of α-ketoacid, and correction of water, electrolyte and acid-base balances. Group A was administered 80 mg/d valsartan, based on which group B was given 40 mg/d febuxostat. Serum uric acid and high-sensitivity C-reactive protein levels were measured on the 2nd day after enrollment and after 2 mo of treatment, respectively. Echocardiographic examination was conducted. Before treatment, the two groups had similar serum levels of uric acid and high-sensitivity C-reactive protein ($p>0.05$). After treatment, such levels significantly decreased ($p<0.05$), and the levels of group B were significantly lower than those of group A ($p<0.05$). The two groups had similar cardiac function indices, including left anterior descending artery, left ventricular end diastolic diameter, thickness of inter ventricular septum, thickness of left ventricular posterior wall, left ventricular end-diastolic volume, left ventricular end-systolic volume, ejection fraction and fraction shortening ($p>0.05$). After treatment left atrial diameter, left ventricular end diastolic diameter, left ventricular end-diastolic volume and left ventricular end-systolic volume significantly reduced, and ejection fraction and fraction shortening significantly increased ($p<0.05$), with the changes of group B being more obvious. Febuxostat can relieve the microinflammatory status of patients with chronic kidney disease complicated with hyperuricemia, and protect endothelial and cardiac functions, exerting more evident effects after being combined with valsartan.

Key words: Valsartan, febuxostat, chronic kidney disease, hyperuricemia

With lifestyle changes, chronic renal failure (CRF) has affected global public health[1]. A global epidemiological investigation showed that the prevalence rate of chronic kidney disease (CKD) was about 8 %-16 %[2]. The prevalence rate of CKD in adults is 14.0 % in the United States[3], 10.2 % in Norway[4], and about 14.3 % in Australia[5]. In China, the overall prevalence rate of CKD is 10.8 %[6], with the rate of rural areas being slightly higher than that of urban ones (13.3 % vs. 12.9 %). However, the awareness rate is only 12.5 %. CKD not only elevates the risk of cardiovascular diseases, but also eventually develops into uremia requiring long-term renal replacement therapy, which greatly psychologically and economically burdens patients and their families. Uric acid, as the final product of purine metabolism, is mainly excreted by the kidneys. Patients with renal insufficiency have decreased glomerular filtration rate and uric acid excretion disorder, inevitably causing hyperuricemia (HUA) in the long run[7]. The prevalence rate of HUA in CKD patients is 33.6 %-50 %, which increases along with the deterioration of renal function[8]. Clinically, xanthine oxidase inhibitors (XOIs) are mainly used to reduce uric acid production. Allopurinol, the first used XOI in

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clinical practice, has a similar structure to those of purines. It is mainly excreted by the kidneys, and its main metabolite, hydroxysterol, is active and can accumulate to a toxic level in patients with renal insufficiency, so its dose should be reduced for those with impaired renal function. Allopurinol should not be used when creatinine clearance is <10 ml/min[9]. The serious side effects of allopurinol also limit its use for patients with CRF. In contrast, febuxostat is a newly marketed XOI with inhibitory effects on both oxidized and reduced xanthine oxidases[10]. Although febuxostat can significantly reduce uric acid levels in patients with CRF and HUA, there is still controversy on whether it can protect their renal function. Therefore, 144 patients with CKD complicated with HUA were enrolled in this study, and treated with febuxostat for 2 mo to observe the changes in serum uric acid and high-sensitivity C-reactive protein (hs-CRP) as well as cardiac function. Febuxostat was also combined with valsartan to assess the protective effects on cardiac and renal functions and the possible mechanism. This study has been approved by the ethics committee of our hospital, and written consent has been obtained from all patients. A total of 144 patients with CKD and HUA treated in our hospital from June 2014 to June 2018 were retrospectively analyzed, including 78 males and 66 females aged 35-68 y old, (51.3±8.4) on average. Inclusion criteria: Stage I to III CKD, serum creatinine level>130 μmol/l, endogenous creatinine clearance >30 ml/min, serum uric acid level >480 μmol/l, and history of gout episode. Exclusion criteria: Severe water, electrolytes and acid-base balance disorders; history of active peptic ulcer in the past year; history of chronic respiratory diseases; severe heart failure; active liver disease or obviously abnormal liver function (alanine aminotransferase and aspartate aminotransferase levels exceeded the upper limits of normal values by over two-fold); blood system diseases; immune diseases and using immunosuppressors; history of using losartan, thiazide diuretics and theophylline; pregnant or lactating women. According to the treatment regimen, the patients were divided into group A and group B (n=72). There were 40 males 32 females in group A, who were aged 35-67 y old, (51.2 ± 8.6) on average. There were 8 diabetic patients (11.11 %) in this group. There were 38 males and 34 females in group B, who were aged 35-67 y old, (51.1 ± 8.3) on average. There were 9 diabetic patients (12.50 %) in this group. The baseline clinical data of the two groups were comparable. Both groups were given high-quality low-protein diet, and comprehensive treatments such as decrease of blood pressure (calcium channel blocker and/or β receptor antagonist), correction of anemia (erythropoietin), supplementation of compound α-keto acid tablets (Hebei Tiancheng Pharmaceutical Co., Ltd., China) and correction of water, electrolyte and acid-base balances (sodium bicarbonate). Group A was administered 80 mg/d valsartan, based on which group B was given 40 mg/d febuxostat (fig. 1). Fasting venous blood was taken in the morning on the 2nd day after enrollment and after 2 mo of treatment respectively for blood routine and biochemical index tests (serum creatinine, urea nitrogen, blood glucose, serum uric acid, blood lipids, serum albumin, etc.). Blood samples were retained to measure hs-CRP levels with Hitachi 7600-120 automatic biochemical analyzer (Japan). Hs-CRP detection kit was purchased from Ningbo Ruiyuan Biotechnology Co., Ltd. (China) to perform latex-enhanced immunoturbidimetry. Echocardiographic examination was performed on the 2nd day after enrollment and after 2 mo of treatment respectively. With Philips iE33 echocardiography system (USA), S4 cardiac ultrasound probe was used at a frequency of 2 to 5 MHz. The M-type, two-dimensional and color Doppler and pulsed Doppler (PW)/continuous Doppler (CW) ultrasound was carried out. Left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), thickness of interventricular septum (IVS), thickness of left ventricular posterior wall (LVPW), left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV), fraction shortening (FS) and ejection fraction (EF) were measured. All data were analyzed by SPSS 16.0 software. The categorical data were expressed as x±s. Pairwise comparisons for means were performed by the t test. $p<0.05$ was considered statistically significant. Before treatment, there were no significant differences in the serum levels of uric acid and hs-CRP between the two groups ($p>0.05$). After treatment, the levels significantly decreased ($p<0.05$), and the levels of group B were significantly lower than those of group A ($p<0.05$) (Table 1). There were no significant differences in the cardiac function indices

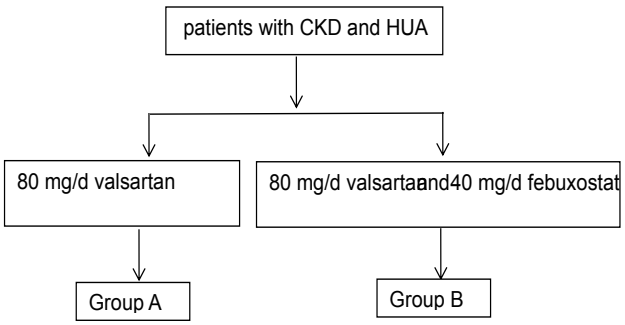

Fig. 1: Flow diagram for treatment regimens

TABLE 1: SERUM LEVELS OF URIC ACID AND HS-CRP BEFORE AND AFTER TREATMENT

	Group A (n=72)		Group B (n=72)	
	Before treatment	After treatment	Before treatment	After treatment
Serum uric acid (μmol/l)	514.76±45.67	462.78±34.56*	515.81±46.71	310.19±44.32*,#
hs-CRP (mg/l)	5.46±0.89	4.02±0.76*	5.49±0.92	1.75±0.43*,#

*Intragroup comparison before and after treatment, p<0.05; #intergroup comparison, p<0.05

TABLE 2: CARDIAC FUNCTION INDICES BEFORE AND AFTER TREATMENT

	Group A (n=72)		Group B (n=72)	
	Before treatment	After treatment	Before treatment	After treatment
LAD (mm)	45.2±4.5	43.6±3.1*	45.1±4.4	33.7±4.3*,#
LVEDD (mm)	60.5±4.3	49.6±3.5*	59.9±4.2	46.4±4.0*,#
LVS (mm)	9.7±0.9	8.9±0.8	9.8±0.9	8.8±0.8
LVPW (mm)	10.7±0.9	10.3±0.9	10.8±0.8	10.4±0.8
EDV (mL)	134.7±11.6	118.7±9.8*	133.9±10.9	107.7±11.2*,#
ESV (mL)	58.4±5.3	46.9±4.3*	58.3±4.9	36.5±5.1*,#
EF (%)	40.2±5.8	45.7±6.2*	40.8±6.0	59.8±5.2*,#
FS (%)	17.4±2.9	21.7±3.0*	17.8±3.1	26.6±3.0*,#

*Intragroup comparison before and after treatment, p<0.05; #intergroup comparison, p<0.05

between the two groups before treatment, including LAD, LVEDD, LVS, LVPW, EDV, ESV, EF and FS (P>0.05). After treatment, LAD, LVEDD, EDV and ESV significantly reduced, and EF and FS significantly increased (P<0.05), with the changes of group B being more obvious (Table 2). Microinflammation is prevalent in patients with CRF, mainly characterized by changes in acute phase response proteins and activation of cytokines[11]. Microinflammation is the result of sustained activation of the mononuclear-macrophage system, and hs-CRP is currently a good indicator of subclinical inflammation[12]. Antioxidants, reduced glutathione, statins, angiotensin-converting enzyme inhibitors have been reported to alleviate the inflammatory state[13-15]. Febuxostat can reduce C-reactive protein levels, indicating that febuxostat has a certain inhibitory effect on inflammation[16]. In this study, both valsartan and febuxostat can improve the microinflammation status and reduce the hs-CRP level in patients with CKD plus HUA, but the combined effect is more obvious. HUA can aggravate arteriosclerosis and cause plaque instability. When blood uric acid is increased, the uric acid microcrystals precipitate easily, promote platelet adhesion and aggregation, and can also directly deposit in the vascular wall to damage the intima of the blood vessels, activate platelets and blood coagulation process[17]. Heart damage is a complication entailing death in the later stages of CRF and functional damage already occurring in the earliest stages of CRF[18]. It is well-documented that the ubiquitous microinflammation of CKD patients can accelerate the development of atherosclerosis[19-21]. High uric acid is an independent risk factor for cardiovascular events. Febuxostat is mainly metabolized and oxidized to acyl-glucuronide in the liver, and a small fraction is metabolized to active oxidation by cytochrome P450, and only 1 %-6 % is excreted from the urine by the prototype. Its pharmacokinetics are not affected by age, mild to moderate liver dysfunction or renal dysfunction; it does not affect CYP activity, or interact with non-steroidal anti-inflammatory drugs, thiazides or warfarin commonly used to treat gout. Curiel *et al.* conducted a study on uric acid lowering in patients with CRF and HUA[22]. The rate of uric acid recovery in patients taking 40-80 mg/day of febuxostat was higher than that of patient using 100-300 mg/day of allopurinol, i.e. febuxostat worked better than allopurinol did. A study of febuxostat for moderate to severe renal insufficiency showed a UC level reduction of >40 % in stage 3b of CKD, a >5 % reduction in uric acid levels in stages 4 and 5 of CKD, and more than 70 % of patients achieved uric acid ≤6.0 mg/dl[23]. The rate of compliance with febuxostat for uric acid reduction was 3.32 times that of allopurinol (uric acid compliance was defined as uric acid <6.0 mg/dl)[24]. Herein, after 12 mo of treatment with febuxostat, the blood uric acid level was significantly decreased, and the cardiac function indicators were improved. This change may be through angiotensin II receptor antagonist. The combination of the drug and febuxostat enhances the clearance of inflammatory mediators and the protection of endothelial cells.

In summary, paying attention to HUA complicated by CKD patients and early intervention is important to protect vascular endothelial function and important

target organ function, improve microinflammation in CKD patients, reduce the incidence of cardiovascular events, and delay further damage of renal function. The combination of angiotensin II receptor antagonist with febuxostat is expected to be an important clinical treatment for CKD with HUA.

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