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Efficacy comparison of atorvastatin versus rosuvastatin on blood lipid and microinflammatory state in maintenance hemodialysis patients

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ABSTRACT

Introduction: To investigate the effect of Atorvastatin (ATO) and Rosuvastatin (ROS) on blood lipid, high sensitivity CRP (hs-CRP), interleukin-6 (IL-6), albumin (ALB), prealbumin (PA), and transferring (TF) in maintenance hemodialysis (MHD) patients.

Methods: Eighty MHD patients were enrolled and divided into two groups: ROS and ATO. Patients in Group ROS ($n = 38$) received ROS (10 mg/day), and those in group ATO ($n = 42$) received ATO (20 mg/day) for 12 weeks, respectively.

Findings: Administration of ROS and ATO both significantly reduced the concentrations of TC, LDL-C, TG, hs-CRP, and IL-6, but increased high-density lipoproteincholesterol (HDL-C), ALB, PA, and TF levels. Furthermore, the level of LDL-C decreased more significantly with inhibited microinflammation and improved nutrition situation in ROS group compared with ATO group. ATO and ROS not only decreased blood lipid levels but also inhibited the microinflammatory state and improved nutrition situation in MHD patients.

Discussion: The results have shown that ROS is better than ATO in the treatment of MHD patients.

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Atorvastatin; rosuvastatin; lipid; microinflammatory; malnutrition; hemodialysis

Introduction

In recent years, with the continuous development of hemodialysis therapy, the long-term survival rate of maintenance hemodialysis (MHD) patients has significantly increased, but the prognosis of end stage renal disease (ESRD) patients is still poor. The five-year survival rate is only 33.0–54.3%.[1] Malnutrition Inflammation Atherosclerosis (MIA) Syndrome is a common complication of hemodialysis, regarded as an important factor affecting the long-term survival rate of MHD patients. The cardiovascular events are the leading cause of death for ESRD patients and account for nearly half of the total mortality rate.[2] In recent years, the relationship between atherosclerosis and microinflammation as well as malnutrition has aroused great attention.

Microinflammation can lead to malnutrition and atherosclerosis. Malnutrition and atherosclerosis can also aggravate the microinflammation.[3] Microinflammation may be the central feature of the pathogenesis of MIA syndrome.[4] Therefore, it is critical to reduce the microinflammatory state in hemodialysis patients. However, there are currently no effective drugs against microinflammation in dialysis patients. Macromolecular inflammatory cytokines such as CRP, IL-1, interleukin-6 (IL-6), and TNF-alpha, are difficult to be cleared by regular hemodialysis. High flux hemodialysis and hemodialysis perfusion can partially remove them, but are expensive. In the past, most researches were focused on the relationship between microinflammation, malnutrition, and atherosclerosis in patients with chronic renal failure. Special attention was paid to the evaluation of these indexes while few reports were related with the treatment of MIA with medications.

Statins have been demonstrated to exert anti-oxidant and anti-inflammatory effects independent of lipid reduction.[5] In terms of this situation, the present study aims to investigate the efficacy of atorvastatin (ATO)

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and rosuvastatin (ROS) on blood lipid, microinflammatory state and nutritional status in MHD patients. We set to explore the clinical application significance of ATO and ROS and search for new targets for the improvement of life qualities and survival rate for ESRD dialysis patients.

Patients and methods

Study population

We started with 228 MHD patients in our single center from Department of Nephrology, the First Affiliated Hospital of Shantou Medical University, Shantou, Guangdong, PR China, from August 2011 to June 2013. The inclusion criteria were: (1) MHD patients; (2) the dialysis duration within 2–4 years. The exclusion criteria were: (1) patients who have familial hypercholesterolemia, infection, hepatitis, dysfunction of the heart, lung and liver, cancer, pregnancy, active rheumatoid and immunologic diseases, server malnutrition, use of hormones, critical illness and other major diseases, recent surgery or trauma, or recent cardiovascular events; (2) patients who have not taken any lipid regulating drugs, aspirin, ACEI or ARB, and immunosuppressive agents within the one month period before the study. One hundred and forty-eight patients were excluded and a total of 80 patients were selected for analysis. There were 40 male and 40 female patients, including 34 cases of chronic glomerulonephritis, 24 cases of obstructive nephropathy, 13 cases of diabetic nephropathy, seven cases of hypertensive renal damage, and two cases of adult polycystic kidney disease. The dialysis treatment for these patients lasted four hours each time for two to three times every week. The average treatment time was 36.3 ± 15.7 months. F-6 polysulfone membranes and bicarbonate dialysate were used. Blood flow and dialysate flow was 180–280 mL/min and 500 mL/min, respectively. The vascular access was a dynamic and static internal fistula. Common heparin or low molecular weight heparin was used for systemic heparin anticoagulation.

Eighty MHD patients were divided into ROS group (20 males and 18 females) and ATO group (20 males and 22 females) according to the random number table. There were no significant difference between ROS and ATO group both in clinical characteristics (age, duration of dialysis, lipid level) and basis of kidney disease. On the basis of conventional drugs (including ossification alcohol, erythropoietin, L-carnitine, nitrate ester, beta-blockers, and CCB antihypertensive drugs), patients were treated with either ATO (20 mg/day Pfizer) or ROS (10 mg/day AstraZeneca) for 12 weeks, at equivalent standard doses. The patients maintained their dietary habits, life styles and use of additional medications during the treatment.

Ethics statement

This study protocol was approved by the Ethics Committee from Shantou Medical University, Guangdong, China and the study conformed to the Declaration of Helsinki. Written informed consent was obtained from all patients before the procedure.

Blood sampling

Blood samples were obtained before treatment and at the time of 12 weeks after treatment. Fasting venous blood was drawn and centrifuged. The plasma was stored at $-70\,^{\circ}C$ until assay. All samples are pre-dialysis blood.

Measurement of blood lipid, high sensitivity CRP (hs-CRP), IL-6, albumin (ALB), prealbumin (PA), and transferring (TF)

Blood lipid (TC, LDL-C, TG, and high-density lipoprotein-cholesterol (HDL-C)) and serum ALB were measured using a Toshiba Automatic Biochemistry Analyzer (Toshiba, Tokyo, Japan). Analysis of hs-CRP, PA, and TF in serum was performed using immunoturbidimetry (Cobas 6000/8000, Roche Diagnostics, Shanghai, China) and IL-6 was measured by Elisa (R&D Systems, Shanghai, China).

Statistical analysis

Measurement data are presented as mean ± SD and enumeration data are expressed as the proportion. Student *t*-test and chi-square test were used to test statistical significance between two groups. Independent sample *t*-test was used to test statistical significance between groups. Paired sample *t*-test was used to test statistical significance within groups. All statistical tests were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL). The significance level is set at .05 to indicate statistical significance.

Results

Clinical characteristics of ROS and ATO patients

As is shown in Table 1, there were no differences in age, dialysis frequency, duration of HD, body mass

index (BMI), underlying diseases between the patients treated with ROS or ATO ($p > .05$).

Serum lipid levels were alleviated in ROS and ATO groups

Patients in the two groups follow the routine medications with good compliance. As is shown in Table 2, there were no differences in TC, TG, LDL-C, and HDL-C in patients before treatment ($p > .05$). In ROS and ATO groups, parameters of serum lipid were remarkably alleviated after therapy with significant difference ($p < .05$). There were no differences in TC, TG, and HDL-C after treatments in the two groups ($p > .05$). But LDL-C was decreased significantly in the ROS group compared with the ATO group ($p < .05$).

Plasma inflammatory cytokines hs-CRP, IL-6 were reduced in ROS and ATO groups

There were no differences in hs-CRP and IL-6 before treatment between the two groups ($p > .05$). As is shown in Table 3, in ROS and ATO groups, the concentration of hs-CRP and IL-6 was significantly reduced after therapy ($p < .05$) and was decreased more obviously in the ROS group compared with the ATO group ($p < .05$).

Table 1. The clinical characteristics of ROS and ATO group patients.

Clinical characteristics	ROS group	ATO group	t (χ^2)	p Values
Age (years)	46.37 ± 11.43	43.26 ± 11.78	1.194[a]	.236
Gender (male/female), n	20/18	20/22	–	–
Dialysis frequency (times/week)	2.71 ± 0.46	2.79 ± 0.41	0.769[a]	.444
Duration of HD (months)	37.55 ± 9.85	37.90 ± 9.47	0.163[a]	.871
BMI (kg/m^2)	23.59 ± 2.15	24.45 ± 3.82	1.252[a]	.215
CGN, n (%)	16 (42.1)	18 (42.9)	0.050	.946
ON, n (%)	11 (28.9)	13 (31.0)	0.038	.845
DN, n (%)	6 (15.8)	7 (16.7)	0.011	.951
HN, n (%)	4 (10.5)	3 (7.1)	0.286	.593
Polycystic kidney, n (%)	1 (2.6)	1 (2.4)	0.050	.943

BMI: body mass index; CGN: chronic glomerulonephritis; ON: obstructive nephropathy; DN: diabetic nephropathy; HN: hypertensive nephropathy.
[a]t value.

Serum ALB, PA, and TF were increased in ROS and ATO groups

There were no differences in ALB, PA, and TF before treatment between the two groups ($p > .05$). As is shown in Table 4, in ROS and ATO groups, the concentration of ALB, PA, and TF was significantly increased after therapy ($p < .05$) and was increased more dramatically in the ROS group compared with the ATO group ($p < .05$).

Discussion

Hemodialysis is an important strategy for the treatment of uremic patients. Eighty percent of MHD patients in China are receiving hemodialysis therapy. The microinflammatory state represents a clinically infectious sign without systemic or local acute symptoms. But the inflammatory state is low and sustained, characterized by a mild elevation of inflammatory factors, features of continuous and relative concealment.[6] Microinflammation commonly exists in hemodialysis patients. The increase of CRP (>8 mg/L), evidence of the inflammatory activity, were confirmed in 30–50% predialysis, hemodialysis, and peritoneal dialysis patients. Chronic persistent inflammation was found in approximately 35–65% regular hemodialysis ESRD patients.

Microinflammation is an important cause in the development of atherosclerosis, and the degree of inflammation in the body can determine the incidence and mortality of cardiovascular events in uremic

Table 3. Comparison of hs-CRP and IL-6 between two groups before and after treatment ($\bar{x}\pm s$).

		hs-CRP (mg/L)		IL-6 (pg/mL)	
Group	n	Before	After	Before	After
ROS	38	5.08 ± 1.17	2.45 ± 1.35[b]	16.29 ± 4.29	7.18 ± 3.28[b]
ATO	42	5.24 ± 2.19[a]	3.34 ± 2.02[b,c]	15.08 ± 4.79[a]	9.17 ± 4.39[b,c]
t	–	0.35	0.08	0.47	0.14
p	–	0.72	0.03	0.24	0.03

Before: before treatment; After: after 12 weeks of treatment; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin 6.
[a]$p > .05$, compared with ROS group before treatment.
[b]$p < .05$, compared with before treatment.
[c]$p < .05$, compared with ROS group after 12 weeks of treatment.

Table 2. Comparison of lipid parameters between two groups before and after treatment ($\bar{x}\pm s$ mmol/L).

		TC		TG		LDL-C		HDL-C	
Group	n	Before	After	Before	After	Before	After	Before	After
ROS	38	6.62 ± 1.13	5.29 ± 0.76[b]	1.75 ± 0.15	0.82 ± 0.18[b]	3.40 ± 0.67	2.18 ± 0.73[b]	0.92 ± 0.22	1.41 ± 0.24[b]
ATO	42	6.42 ± 1.08[a]	5.37 ± 1.07[b,c]	1.71 ± 0.16[a]	0.80 ± 0.17[b,c]	3.69 ± 0.78[a]	2.73 ± 0.78[b,d]	0.95 ± 0.20[a]	1.45 ± 0.20[b,c]
t	–	0.81	0.41	1.08	0.50	1.81	3.23	0.67	0.82
p	–	0.42	0.67	0.28	0.62	0.75	0.00	0.51	0.42

Before: before treatment; After: after 12 weeks of treatment; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoproteincholesterol.
[a]$p > .05$, compared with ROS group before treatment.
[b]$p < .05$, compared with before treatment.
[c]$p > .05$ and [d]$p < .05$, compared with ROS group 12 weeks post treatment.

Table 4. Comparison of ALB, PA, TF between two groups before and after treatment ($\bar{x}\pm s$ g/L).

		ALB		PA		TF	
Group	*n*	Before	After	Before	After	Before	After
ROS	38	28.4 ± 4.6	32.2 ± 4.3^{b}	0.33 ± 0.06	0.38 ± 0.06^{b}	2.13 ± 0.48	2.53 ± 0.47^{b}
ATO	42	27.8 ± 5.3^{a}	$30.0\pm5.5^{b,c}$	0.31 ± 0.05^{a}	$0.34\pm0.05^{b,c}$	2.09 ± 0.47^{a}	$2.31\pm0.49^{b,c}$
t	–	0.32	0.55	0.72	0.27	0.80	0.95
p	–	0.58	0.04	0.07	0.00	0.67	0.04

Before: before treatment; After: after 12 weeks of treatment; ALB: albumin; PA: prealbumin; TF: transferrin.
[a]$p>.05$, compared with ROS group before treatment.
[b]$p<.05$, compared with before treatment.
[c]$p<.05$, compared with ROS group after 12 weeks of treatment.

patients.[6] Previous studies have revealed that cardiovascular disease (CVD) is the most common cause of mortality in MHD patients with about 40–50% of patients dying from CVD.[7] The causes of microinflammation are closely related to many factors, including accumulation of advanced glycation end products, oxidative stress, and uremia toxin, types of dialysis membranes, dialysis technology and quality.[8,9] Microinflammation was mainly reflected in the change of acute phase proteins (plasma C reaction protein, fibrinogen, and serum amyloid protein) and pro-inflammatory cytokine activation such as interleukin (IL) and tumor necrosis factor-α (TNF-α). Previous studies have demonstrated that the plasma levels of hs-CRP, IL-1, IL-6, IL-8, and TNF-α were predictors of microinflammation and correlated with coronary heart disease, heart failure, and atherosclerosis.[3,10–13] Among these factors, hs-CRP is the most reliable, precise and acknowledged inflammatory biomarker, recognized as an independent risk factor for predicting the survival rate of ESRD patients.

Additionally, inadequate diet and persistent catabolism play major roles in uremic malnutrition. Malnutrition is a common pathological condition for MHD patients leading to significantly increased morbidity and mortality of CVDs. It has been reported that the incidence of malnutrition is 18–75% in MHD patients. Malnutrition elevates the level of circulating cytokines, further aggravating the oxidative and inflammatory characteristics of uremia. It has been suggested that abnormalities of nitric oxide (NO) bioactivity, coupled with malnutrition and inflammation may contribute to increased incidence of atherosclerosis in uremia. The earliest indications of malnutrition are low concentrations of plasma amino acids, such as L-arginine, the precursor of NO synthesis. The deficiency of plasma amino acid increased arterial thrombosis. It has been widely accepted by the nephrology community that malnutrition is defined by reduced levels of serum ALB or PA or TF. Microinflammation causes the protein synthesis rate to decrease obviously. Hypoalbuminemia, ascribed to malnutrition, has been one of the most powerful risk factors predicting all-cause and cardiovascular mortality in MHD patients. Inflammation alters lipoprotein structure, function as well as endothelial structure and function to favor atherogenesis and increases the concentration of atherogenic proteins in serum, such as fibrinogen and lipoprotein. Therefore, the interaction between microinflammation and malnutrition leads to aggravated atherosclerosis.

Rosuvastatin is an hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which can reduce the cholesterol biosynthesis and decrease blood cholesterol levels in patients. It can improve the patient's lipid metabolism and thereby reduce the incidence of CVDs and other complications. Rosuvastatin is one of the most effective, safe, and classical lipid-lowering drugs. A series of studies have confirmed that ROS not only has the function of lowering blood lipids, but protect the kidney independent of the lipid lowering effect. Statin drugs may reduce the inflammatory response by inhibiting the synthesis of pro-inflammatory mediators. The main way of ROS to improve the microinflammatory state is to reduce the expression of IL-6 messenger RNA and the synthesis of IL-6. It can also inhibit the activity of CoA-HMG reductase and block the formation of CRP through reducing the synthesis of IL-6.[14] In several studies, the effects of statins in renal protection have been related to their anti-inflammatory, antioxidant, and vascular protection.[15,16] We found that after 12 weeks of treatment in ROS or ATO, serum lipid (TC, LDL-C, and TG) levels were decreased significantly, but HDL-C was increased compared with that of before treatment. These results suggest that ROS and ATO can effectively regulate the serum lipid levels in MHD patients. LDL-C level reduced significantly in ROS group compared with ATO group. In addition, our results have shown that after 12 weeks of treatment with ROS or ATO, the concentration of hs-CRP and IL-6 was decreased significantly, but serum ALB, PA and TF was increased compared with that of before treatment. More significant increase was observed in ROS group than ATO group. These results suggest that ROS and ATO not only lower lipid levels, but also play critical roles in decreasing microinflammation and regulating

malnutrition. The effect of ROS has been proved better than ATO. In other words, ROS exerts a more beneficial reno-protective effect than that of ATO. This is in agreement with the previous study that ROS is more effective in preventing contrast induced nephropathy in patient with chronic kidney disease versus ATO.[17] In addition, in an experimental murine model of cigarette smoke-induced acute lung inflammation, ROS was proven to perform better than ATO or simvastatin because of better attenuation of both inflammation and oxidative stress parameters.[18] In the present study, we referred to the dosage of ATO or ROS used in the literature[19] and adjusted it according to the economy, compliance, and shape of the Chinese patients. We therefore chose the dose of ATO (20 mg) and ROS (10 mg) for the population in this study.

In conclusion, quality of life for MHD patients with microinflammation state was affected seriously when complicated with malnutrition and atherosclerosis. Prevention and treatment of MIA syndrome will reduce the occurrence of cardiovascular events and improve the survival rate and quality of life of patients. The present study has demonstrated that ROS and ATO have the potential in improving microinflammation and malnutrition. The effect of ROS is more obvious. As suggested in the guidelines of 2013 ACC/AHA treatment of lowering the risk of cardiovascular risk in adult patients with statins, clinicians should consider the potential benefits of drugs for the treatment of atherosclerotic cardiovascular disease (ASCVD), as well as adverse drug reactions, drug interactions, drug effects, and other effects.[20] This study may provide a clinical theoretical basis for improving microinflammation and malnutrition in MHD patients. Nevertheless, the present study has several limitations. (1) The relatively small sample size for analysis, which deserves further investigation in more cases in multi centers. (2) The trial approach warrants improvements with randomized and double-blinded manners. (3) Further studies are needed to determine the definite mechanisms of ROS and ATO in the treatment of MHD patients.

Disclosure statement

The authors report no conflict of interest.

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