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Original Article

Pravastatin improves renal progression in patients with chronic glomerulonephritis

Shan Mou*, Qin Wang*, Zanzhe Yu, Xinghua Shao, Lei Tian, Yanhong Yuan, Beili Shi, Liang Ma, Xiajing Che, Minfang Zhang, Wei Fang, Zhaohui Ni

*Department of Nephrology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, P. R. China. *Equal contributors.*

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Abstract: Chronic kidney disease (CKD) progressively results in end-stage renal disease in most patients. It has been suggested that statins may slow the progression of CKD in general. This trial aims to assess the effect of pravastatin treatment on kidney function, urinary protein excretion and inflammation in the patients with diagnosed chronic glomerulonephritis. This is a randomized controlled open-label clinical trial conducted in a teaching hospital in Shanghai. Forty-eight patients with chronic glomerulonephritis were randomized into the control group (n = 23) or to receive oral pravastatin treatment with 20 mg/day for 96 weeks (n = 25). The primary endpoint was absolute estimated glomerular filtration rate (eGFR) alteration. The secondary end points were an eGFR decrease of up to 50%, ESRD requiring RRT, all-cause mortality, number of hospitalization events during the 2-year follow-up or composite secondary endpoints. There were significant (P < 0.05) differences in kidney function and urinary protein excretion between groups over the 2 years and a significant fall in high reactive C-reactive protein and total serum cholesterol in pravastatin-treated patients (P = 0.029). Taking pravastatin (20 mg/day, oral) for 2 years had a significant effect on kidney function and urinary protein excretion in patients with chronic glomerulonephritis. Pravastatin could help in improving inflammation in these patients. However, whether such limited improvements can lead to better clinical outcomes requires further investigation.

Keywords: Chronic kidney disease, kidney function, pravastatin

Introduction

For over 10 years, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors have been widely used to reduce cardiovascular risk [1]. Statins are known to reduce inflammation and oxidative stress and to improve vascular dysfunction in the general population as well as in chronic kidney disease (CKD) patients prior to dialysis [2]. However, in patients undergoing hemodialysis, statin therapy failed to decrease all-cause mortality and cardiovascular events [3]. Nevertheless, few trial data were available to evaluate treatment efficacy in patients with milder CKD who are not receiving dialysis.

CKD is a worldwide common disease that can progress to end-stage renal disease (ESRD). Hyperlipidemia has been hypothesized to play an important role in the progression of chronic glomerulonephritis, through toxic effects of lipids on mesangial cells or by promoting intrarenal atherosclerosis [4]. In addition, there is emerging evidence that chronic glomerulonephritis may be associated with chronic inflammation [5, 6]. It has been found that statins appear to have some beneficial effect on the rate of renal function decline [1]. Moreover, there have been a few studies on the effect of statins on inflammation and urinary protein excretion in early-stage CKD patients. The effect of statins on kidney function may relate not only to their cholesterol-lowering properties, but also to their pleiotropic effects, including their ability to reduce inflammation and fibrosis [7].

Given CKD especially chronic glomerulonephritis is mainly responsible for the generation of oxidative stress and inflammation, which is the major cause of proteinuria pathology [8-10], we hypothesized that pravastatin can improve

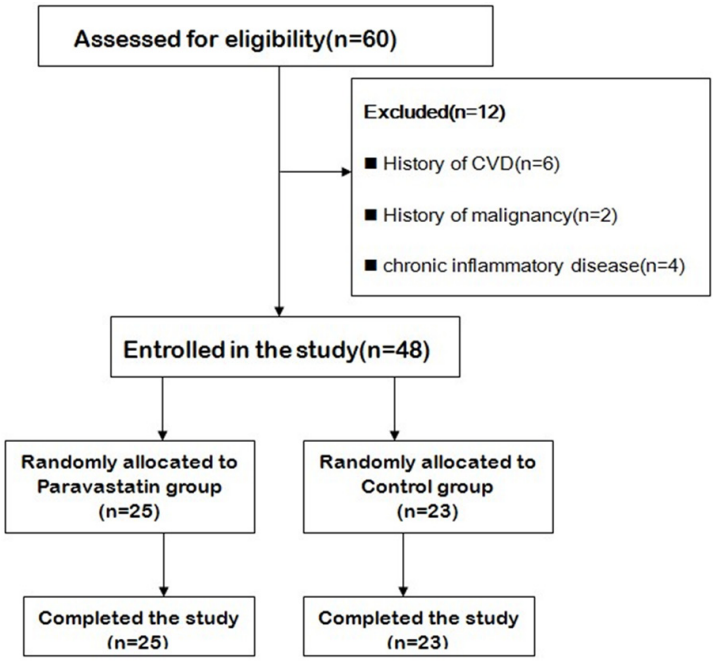

Figure 1. Flow Diagram.

inflammation and confer better kidney function protection in chronic glomerulonephritis patients and thus carried out this trial. This study also evaluated the efficacy and safety of statins in treatment of adults with chronic glomerulonephritis.

Patients and methods

Study design

This is a prospective, single-center, randomized, controlled, open-label trial conducted in the Renji Hospital, Shanghai Jiaotong University School of Medicine, in Shanghai. The Scientific and Ethics Committee of Renji Hospital has approved the study protocol and informed consents were obtained from all patients before the study. The allocation ratio was 1:1. Simple randomized grouping method was used. The study design was achieved and was not compromised throughout the trial.

Patients

Between April 2009 and March 2012, 60 patients who were over 18 years of age, proteinuria ≥ 0.5 g/24 h and ≤ 3.5 g/24 h, and with biopsy-proven chronic glomerulonephritis were assessed for this study. Because we mainly focused on the effect of statin on renal function in chronic glomerulonephritis patients with low-risk profiles for CVD, patients were considered eligible if they had no previous history of cardiovascular comorbidities. Additionally, we excluded patients with overt infection during the last 3 months prior to the study and a history of malignancy or other chronic inflammatory disease, such as systemic lupus erythematosus or rheumatoid arthritis. Among the screened patients, 48 patients who met the criteria and gave informed consent were enrolled in this study (**Figure 1**).

Randomization

The simple randomized grouping method was used, and the power was 80%. Randomization was performed by a researcher not involved in the recruitment and treatment of the participants and conducted via computer-produced random numbers. Random numbers were placed in sealed opaque envelopes.

Intervention

All patients received basic therapy throughout the study including dietary and life style instruction as well as anti-hypertension. Other than that patients were randomly assigned to the control group (n = 23) or to receive oral pravastatin treatment with 20 mg/day for 96 weeks (n = 25). No other intervention was implemented.

Outcome variables

The primary outcome was kidney function measured by Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) and secondary outcomes included C-reactive protein, and urinary protein excretion measured with a 24-hour urine collection.

Primary and secondary end points

The primary end point was absolute eGFR alteration. The secondary end points were an eGFR decrease of up to 50%, ESRD requiring RRT, all-cause mortality, number of hospitalization events during the 2-year follow-up or composite

Table 1. Demographic features of the CKD patients

	Total/Overall	Pravastatin group	Control group
Patient number	48	25	23
Number of the CKD stage III-IV patients	18	10	8
Age (year)	50.83±14.25	53.16±11.05	47.61±17.62
BMI (kg/m^2)	23.62±3.30	23.69±3.41	23.61±3.49
Systolic blood pressure (mmHg)	132.46±8.78	131.78±8.26	132.89±8.72
Diastolic blood pressure (mmHg)	75.27±8.84	75.53±8.13	75.14±8.93
Fasting blood-glucose (mmol/L)	5.47±0.93	5.66±1.07	5.17±0.55
TC (mmol/L)	5.62±1.08	5.73±0.86	5.38±1.46
TG (mmol/L)	2.33±1.28	2.17±1.03	1.85±0.75
LDL-C (mmol/L)	3.53±0.78	3.56±0.74	3.48±0.91
HDL-C (mmol/L)	1.20±0.38	1.18±0.35	1.26±0.45
CPK (IU/L)	81.05±28.59	82.07±28.36	78.50±31.71
sAlb (g/L)	40.85±3.65	40.79±2.95	40.96±4.85
Scr (umol/L)	81.75±23.88	82.11±23.51	80.46±22.18
hsCRP (mg/L)	3.31±3.62	3.46±3.49	3.18±3.37
24-h urinary protein (g/24 h)	1.41±0.98	1.14±1.01	1.26±0.95
eGFR (ml/min/1.73 m^2)	74.63±35.65	70.13±38.77	75.87±30.57
ACEI or ARB medication case	22	13	9
Number of patients with diabetes	4	3	1

No significant difference was observed between the two groups. CKD, chronic kidney disease; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CPK, creatine kinase; sAlb, serum albumin; Scr, serum creatinine; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

secondary end points. Hospitalization events were ascertained by electronic medical records obtained from the medical institution. All patients were followed up for 24 months.

Definitions

CR was defined as when return of proteinuria to normal range (< 0.3 g/day) was obtained. Nonnephrotic proteinuria (0.3-3.5 g/day) with loss of oedema was considered to be partial remission (PR). Persistence of proteinuria was considered as no response (NR).

Follow-up and data collection

We performed weekly follow-up in the first four weeks, and then by every three months. At each visit, we obtained complete blood counts, serum levels of creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose, urine dipsticks and daily proteinuria. We estimated serum creatinine (Scr) levels and urinary creatinine levels. Serum creatinine was measured by standard laboratory procedure, and estimated glomerular filtration rate (eGFR) was calculated and corrected for a standard body surface area of 1.73 m^2 by the MDRD formula. Demographic and clinical data were recorded in the beginning of the study including age, gender, body mass index (BMI) calculated as weight/(height)^2, primary renal disease and previous history of CVD. CVD was defined as a history of coronary, cerebrovascular or peripheral vascular disease. Following laboratory data were measured from blood samples: hemoglobin, blood urea nitrogen, creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol and triglyceride. High-sensitive C-reactive protein (hs-CRP) was determined using a latex-enhanced immunonephelometric method on a BN II analyzer (Dade Behring, Newark, DE).

Statistical analysis

Statistical analysis was performed with SPSS version 13.0 (SPSS, Inc., Chicago, IL). Data were expressed as mean ± SD or median with range for the skewed data. Comparisons between the two groups were made by the chi-square test and Student's *t*-test for normally

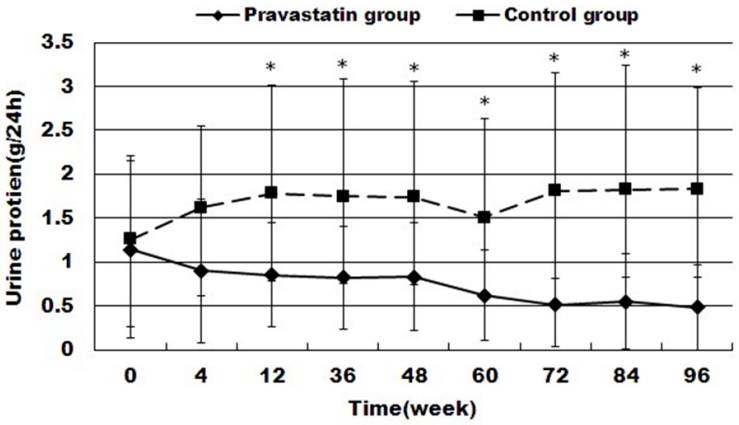

Figure 2. The urine protein levels of the two groups. *P < 0.05 compared with the control group. The bars represent 95% confidence interval.

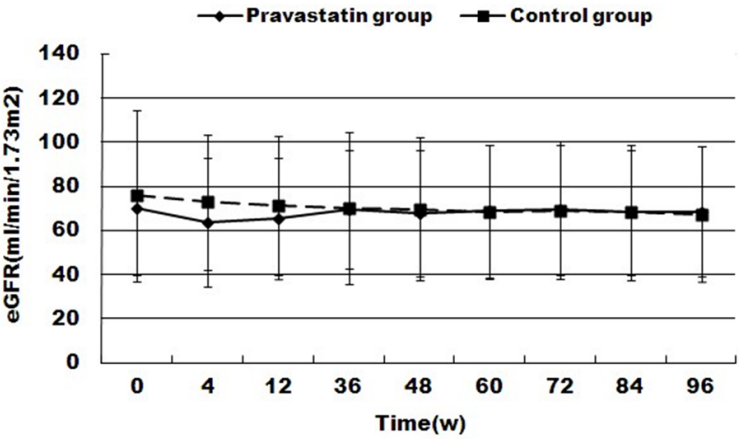

Figure 3. The eGFR levels of the two groups. The bars represent 95% confidence interval.

distributed variables. For skewed variables, the Mann-Whitney *U*-test was conducted. The levels of urine protein, eGFR, TC, LDL-c and hs-CRP were analyzed by two-way repeated-measures analysis of variance (ANOVA) with Bonferroni post hoc test. A value of $P < 0.05$ was considered significant. All analyses were performed on an intention-to-treat basis.

Results

Forty eight adult patients met the enrollment criteria and agreed to participate. Twenty-five patients were enrolled to the pravastatin group and twenty-three were to the control group. There were no differences between the two groups in the main baseline characteristics (**Table 1**). All of the patients completed the 96-week therapy and were included in the subsequent evaluation of pravastatin efficacy. No patients from each group discontinued treatment because of severe drug-related adverse effects.

Demographic features of the CKD patients

The average age of CKD patients was 50.83±14.25 years. Most patients were over 50 years old. Male and smoker accounted for 46.51% and 9.3%, respectively. Diabetes mellitus (n = 6, 13.5%) and hypertension (n = 9, 20.93%) were the common comorbid condition in these patients. Most patients (60.42%) were at CKD Stages I-II according to the eGFR evaluated by the simplified Modification of Diet in Renal Disease equation. The mean eGFR was 74.63±35.65 mL/min/1.73 m^2 and the mean serum creatinine level was 81.75±23.88 umol/L. The demographic data here reflected the common characteristics of Chinese CKD patients. There were no significant differences between control group and pravastatin group in age, gender, diabetes mellitus prevalence, hypertension prevalence, initial renal function and CKD stage.

Therapy outcome

We evaluated the outcome of the patients who completed the 96-week therapy. Among them, 49.36% in the pravastatin group and 20% in the control group achieved CR and PR. The patients in the pravastatin group tended to have higher cumulative CR and PR rates after 24 weeks of therapy. Twelve Patients in the pravastatin group and 7 patients in control group were still in PR after 24-week of treatment. No response was seen in two (15.4%) patients of the control group after 24-week treatment. The mean serum albumin levels (sALB) after 2, 4 and 12 weeks of treatment were significantly higher in the pravastatin group than that in the control group (P = 0.012, P = 0.002 and P = 0.005, respectively. Data not shown). In addition, the pravastatin group had

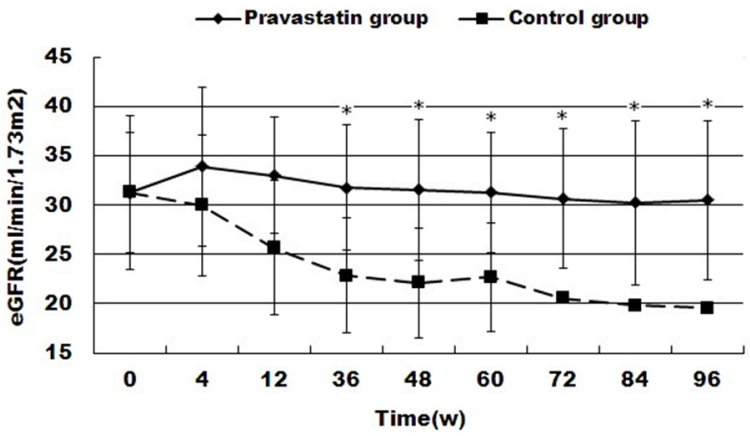

Figure 4. The eGFR levels of the CKD stage III-IV patients in the two groups. *P < 0.05 compared with the control group. The bars represent 95% confidence interval.

significantly lower daily proteinuria after eight weeks of therapy (all P < 0.05; **Figure 2**).

Effects of pravastatin on renal function

The differences of eGFR between the two groups during the period of therapy and follow-up were not statically significant (**Figure 3**). However, we found that Scr and eGFR were significantly different between the two groups in CKD stage III-IV patients (**Figure 4**). At the last observation, no patient in either group showed significant deterioration of renal function. Meantime, pravastatin treatment (**Table 2**) significantly decreased the total cholesterol (4.73±0.86 to 4.17±0.25 mmol/L, P < 0.001) and LDL cholesterol levels (3.56±0.74 to 2.46±0.66 mmol/L, P < 0.001).

Effects of pravastatin on inflammation

In addition, serum hs-CRP level (1.63±1.10 to 1.24±0.87 mg/L, P = 0.003) further decreased in the patients receiving pravastatin treatment (**Figure 5**). We calculated the differences in hs-CRP levels during this period and compared these values between the two groups. Compared to control group, the inter-group differences in hs-CRP levels [-0.39 (95% CI, -0.61 to -0.17) versus -0.02 (-0.23 to 0.19) mg/L, P = 0.02] were greater in the pravastatin group.

Adverse effects

No patient suffered from any serious adverse event during the follow-up. In the pravastatin group, reported adverse event was hepatotoxicity, presented as an elevation of ALT (85-252 IU/l) and AST (84-186 IU/l). All patients were alive and dialysis-free at the end of the study. No patients developed diabetes or new-onset hypertension.

Discussion

Whether statins could improve deterioration of kidney function in chronic glomerulonephritis patients is controversial. The benefits of statins are potentially greater in persons with CKD because of the substantially higher incidence of occlusive vascular disease [1]. Unfortunately, the evidence that statins may have less efficacy in patients with CKD was suggested by two large trials in which the individual receiving hemodialysis was studied and no benefit of statins on mortality or cardiovascular events was found [3, 11], suggesting that the pathogenesis of vascular events in ESRD patients may be different from those without ESRD and that earlier statin therapy prior to initiating dialysis may be of benefit. In addition, a previous study indicated that the benefits of statin treatment for renal function and for cardiovascular disease were provided independent of each other [12]. In this study, we hypothesized that response to statins might be different between patients with and without evident CVD. Thus, we excluded patients with a history of CVD. Meanwhile, the patients in the present study were characterized by young age, normal range of BMI and relatively well-controlled BP.

This prospective, open-label, randomized, controlled study revealed that pravastatin may be advantageous to slowed renal progression in individuals with severe chronic glomerulonephritis. Among CKD stage I-II patients, pravastatin use was related to a clinically insignificant increase in the rate of subsequent renal progression. However, the rate of renal progression in patients with CKD stage III-IV who received pravastatin was significantly less rapid than that in those without oral pravastatin. In addition, pravastatin reduced proteinuria and improved inflammation in early stage chronic glomerulonephritis patients. The observed benefits of pravastatin were greater in

Table 2. Time-course study of the blood lipid level

(mmol/L)	Group	0 week	4 weeks	12 weeks	36 weeks	48 weeks	60 weeks	72 weeks	84 weeks	96 weeks
TC	Pravastatin	5.73±0.86	4.90±1.02	4.39±0.43	4.35±0.36[a]	4.25±0.23[a]	4.23±0.25[a]	4.35±0.27[a]	4.21±0.3[a]	4.17±0.25[a]
	Control	5.38±1.46	5.44±1.16	5.28±1.39	5.15±046	5.33±0.41	5.45±0.52	5.56±0.63	5.36±0.29	5.43±0.57
TG	Pravastatin	1.85±0.75	1.69±0.61	1.58±0.42	1.38±0.28[b]	1.33±0.29[b]	1.27±0.34[b]	1.3±0.36[b]	1.32±0.29[b]	1.29±0.25[b]
	Control	1.97±0.93	1.93±0.44	2.04±0.50	1.96±0.49	1.84±0.44	1.97±0.55	1.95±0.53	1.86±0.49	1.82±0.49
LDL-C	Pravastatin	3.56±0.74	3.24±0.57	2.88±0.70	2.52±0.69[b]	2.61±0.70[b]	2.54±0.63[b]	2.59±0.71[b]	2.49±0.62[b]	2.46±0.66[b]
	Control	3.48±0.91	3.37±1.04	3.37±1.05	3.54±0.70	3.57±0.76	3.5±0.69	3.61±0.74	3.34±0.72	3.39±0.75
HDL-C	Pravastatin	1.26±0.45	1.36±0.52	1.32±0.47	1.39±0.54	1.42±0.49	1.59±0.32	1.56±0.4	1.62±0.36	1.65±0.39
	Control	1.18±0.35	1.29±0.36	1.25±0.24	1.24±0.25	1.19±0.28	1.17±0.25	1.09±0.23	1.13±0.29	1.08±0.25

[a]P < 0.01 and [b]P < 0.05 compared with that of the control group. TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

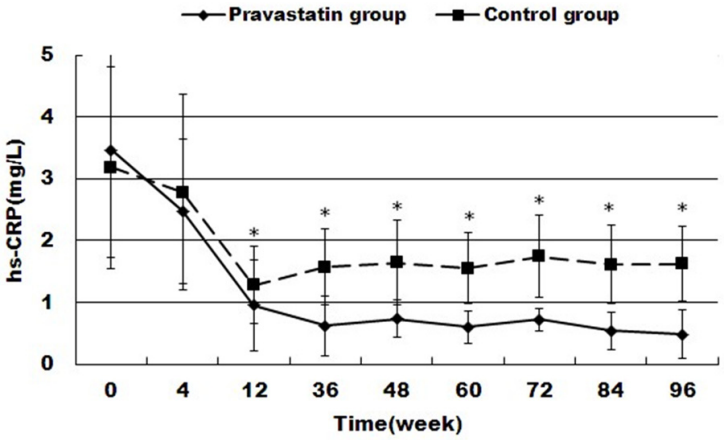

Figure 5. The hs-CRP levels of the two groups. *P < 0.05 compared with the control group. The bars represent 95% confidence interval.

patients with CKD stage III-IV than those in the group with eGFR > 60 mL/min/1.73 m^2 despite the drug's exerting similar reductions of TG, TC and LDL-c in both groups. In contrast, a meta-analysis conducted by Palmer et al. [1] found that the effects of statin therapy on creatinine clearance or glomerular filtration rate were uncertain. Further investigation is needed to clarify whether statins either individually or as a class exert differing benefits in patients with various stages of CKD.

During the follow-up, the uric protein level significantly reduced after eight weeks, while the eGFR significantly improved after 36 weeks. We found that the benefit of pravastatin appeared early during the follow-up, which is consistent with some previous trials that have examined the cardiovascular effects of these drugs in patients with mild and moderate CKD [13-15]. The earliest reduction of uric protein level observed here also suggests that the effect of pravastatin on proteinuria may promote the improvement of renal function, since proteinuria, a well-known marker of renal disease that initiates or aggravates tubulointerstitial injury, is an independent risk factor for progressive renal diseases [16].

Our study found that pravastatin may improve renal function in patients with CKD stage III-IV. Similar results have been previously reported. In the CARE study [17], among individuals with a baseline GFR < 60 mL/min/1.73 m^2, there was a slightly slower loss of renal function in those who were treated with pravastatin compared with those on placebo. In the pravastatin pooling project, significantly less acute renal failure and fewer patients with decreasing GFR were noted in the active treatment group [18]. Moreover, a meta-analysis of 27 studies with 39,370 patients included showed significantly slower loss of renal function in patients receiving statins versus control groups [19]. Our findings suggested that pravastatin use in patients with moderate renal function may be better than in patients with mild renal function.

In this study, we further investigated parameters associated with kidney function. During the first 12-week statin treatment, hs-CRP levels significantly decreased by 72.5% from baseline. Statin further decreased hs-CRP levels by 87% after 96 weeks. Evidence indicates that persistent inflammation is present early in patients with failing kidney function. Several studies have reported that kidney disease is associated with low-grade inflammation as

measured by elevated CRP levels, even among patients with moderate renal impairment [20-22]. In addition, the studies from the African American Study of Kidney Disease and Hypertension revealed that CRP level is a marker of risk for CKD progression [23]. In line with these studies, our study showed pravastatin improved renal function along with the decreased levels of the abovementioned markers. Therefore, it can be presumed that pravastatin delays renal progression by inhibiting inflammation.

This prospective analysis also confirmed pravastatin's safety in the setting of patients with CKD stage I-IV, with no difference of serious adverse events and abnormal laboratory tests. The issue of drug safety is especially important in patients with renal dysfunction, because patients with CKD need for chronic treatment.

In addition, patients maintained BP at stable levels during the study period. During the washout period, other antihypertensive medications were prescribed to control BP, thus no significant changes in BP were observed during the follow-up. Therefore, the improvement of renal function in this study was unlikely to be attributed to the influence of these factors.

Several shortcomings should be addressed in this study. Firstly, the limitations of this study are its small sample size, the limited 2-year follow-up period and that it was performed at a single medical center. Although our mean follow-up period was only 96.0 months, most patients continue to visit our medical center and we believe that longer follow-up periods will verify the results presented here. Secondly, we did not evaluate dose-dependent changes in renal function or proteinuria. In the present study, since serum lipid levels in our patients were not so high, 20 mg of pravastatin was selected. Whether proteinuria could be further improved by escalating the dose of statin is currently unknown. However, such effects can be expected because there is some evidence that inflammation is more ameliorated by a high dose of statin [24].

In conclusion, this study suggests that combination of statin with the standard therapy, stabilizes renal function and was more effective in improving inflammation and proteinuria in chronic glomerulonephritis patients. However, there was only a slight improvement by treatment with statins. Therefore, whether such limited improvements in renal dysfunction can lead to better clinical outcomes needs to be further investigated.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Qin Wang and Zhaohui Ni, Department of Nephrology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, 145 Shandong Middle Rd, Shanghai 200127, P. R. China. Tel: +86-21-68383121; Fax: +86-21-68383124; E-mail: qinwang_dr@126.com (QW); drzhni@sina.com (ZHN)

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