Hyperuricemia and hyperlipidemia have attracted attention as progression factors for chronic kidney disease (CKD). In the drug treatment of hyperuricemia and hyperlipidemia complications, Atorvastatin (ATV), which inhibits urinary protein, increases glomerular filtration rate (GFR) and has renal protective effects, and Rosuvastatin (ROS) were found to be suitable because they promote serum uric acid (SUA) excretion. However, these drugs were administered at very high doses in previous studies. For example, the dose of the ATV group exceeded the maximum dose of 20mg/d in Japan. In this study, we have investigated the effects of ATV or ROS on renal protective effects and their SUA levels before and three months after each drug administration in CKD patients. We retrospectively investigated outpatients presenting with CKD (stages 3) on the basis of their electronic medical records as subjects. Estimated GFR (eGFR) was significantly increased after ATV administration, whereas no change in eGFR was observed following ROS administration. Furthermore, SUA levels significantly decreased after ATV administration, whereas no change in eGFR was observed following ROS administration. Therefore, it may be not necessary to administer drugs that lower the SUA levels to patients presenting with hyperuricemia and hyperlipidemia complications associated with moderate renal failure, such as patients with at least stage 3 CKD. We consider that, by selecting ATV, the renal protective effects and SUA-lowering effect would be sufficient.

Key words chronic kidney disease (CKD) stages 3; hyperuricemia; hyperlipidemia; Atorvastatin; Rosuvastatin

Subjects Among the 268 CKD patients who were outpatients in Yokosuka Kyousai Hospital from 2006.11 to 2011.10, we included 29 CKD patients (stage 3) as subjects. These patients had hyperuricemia and hyperlipidemia complications and were administered ATV or ROS (Fig. 1). We considered losartan, irbesartan, loop diuretics, thiazide diuretics, drugs that lowering the uric acid level, and fenofibrate as drugs that affect the uric acid levels3-15; thus, we excluded the patients who were administered a combination of these drugs. This study complied with the Declaration of Helsinki and we paid sufficient attention to the “Ethical Guidelines for Clinical Research.” 13 patients (male: 8, female: 5), aged 57–87 years old (mean: 67.5±8.4 years old), were included in the ATV group. On the other hand, 16 patients (male: 9, female: 7), aged 41–77 years old (mean: 64.8±11.5 years old), were included in the
ROS group. Average doses of ATV and ROS were 8.8±2.2 and 2.7±0.7 mg/d, respectively.

**Materials and Methods** The research items were age, sex, systolic and diastolic blood pressure (SBP, DBP) clinical laboratory values (hemoglobin (Hb), TC, TG, LDL-C, SUA, and serum creatinine (SCr) levels and estimated GFR (eGFR)), combination drugs (immunosuppressants or anti-platelet agents), and the presence or absence of diabetes. We collected information from medical records retrospectively. For each patient, we compared the measured values of TG, LDL-C, TC, SBP, DBP, SUA levels, and eGFR before and three months after ATV or ROS administration. In addition, we analyzed the patients in whom the SUA levels decreased to less than 6.0 mg/dL after the administration of ATV or ROS, and we compared and investigated the achievement rate of less than 6.0 mg/dL SUA levels.

**Statistical Analysis** The results are given as mean±standard deviation (S.D.). We carried out the normality test to compare the data volume between the two groups. We used the unpaired *t*-test after we confirmed that it showed a normal distribution. We used the *χ*² test or Fisher’s exact test to compare the categorical data and we used paired *t*-test to compare the results obtained before and after drug administration for each group. The significance level was 5% (*p*<0.05). In addition, the statistical analysis was performed using JMP® (Version 10, SAS Institute Inc.).

**Ethics Regulation** This study was conducted with the approval of the Yokosuka Kyousai Hospital Ethics Committee (Approval number: 12–10).

**RESULTS**

**Subjects** Figure 1 shows the flow chart of the selection of subjects in this study. Among them, 27 patients took a combination of losartan and irbesartan, 102 patients took a combination of loop and thiazide diuretics, 114 patients took drugs that lower the SUA levels, and 3 patients took fenofibrate. When we categorized the patients by CKD stage, 29 patients (10.8%) belonged to stage 3 and 48 patients (17.9%) were non-CKD stage 3 patients. There are reports that lipid-rich plaque formation progresses easily in patients presenting with CKD equivalent to stage 316,17); thus, we surveyed the stage 3 CKD patients.

**Comparison of Patient Characteristics before ATV or ROS Administration**

![Figure 1. Flow Chart of the Trial Selection Process](image)

* A total of 246 patients were included in the combinations.

<table>
<thead>
<tr>
<th></th>
<th>ATV (n=13)</th>
<th>ROS (n=16)</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.5±8.4</td>
<td>64.8±11.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/5</td>
<td>9/7</td>
<td>0.78</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.7±21.6</td>
<td>132.9±15.7</td>
<td>0.58</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.2±10.8</td>
<td>80.0±15.4</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes number (%)</td>
<td>6 (46.2%)</td>
<td>7 (43.8%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Immunosuppressants use</td>
<td>2 (15.4%)</td>
<td>2 (12.5%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Anti-platelet agents use</td>
<td>6 (46.2%)</td>
<td>5 (31.3%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Hb (mg/dL)</td>
<td>14.0±1.8</td>
<td>13.6±1.8</td>
<td>0.51</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>233.1±19.8</td>
<td>330.5±186.6</td>
<td>0.95</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>217.9±171.5</td>
<td>219.2±90.2</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>141.3±29.7</td>
<td>200.2±122.6</td>
<td>0.95</td>
</tr>
<tr>
<td>SUA (mg/dL)</td>
<td>6.4±1.1</td>
<td>6.7±1.2</td>
<td>0.40</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.0±0.2</td>
<td>1.1±0.2</td>
<td>0.22</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>51.4±7.8</td>
<td>46.5±7.7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Mean±S.D. or number (percentage).
ROS Administration  Patient characteristics before ATV or ROS administration are shown in Table 1. We investigated 13 patients in the ATV group and 16 patients in the ROS group. When we compared the two groups, there were no significant differences in TG, LDL-C, SUA levels, eGFR, and so on.

Effects of ATV and ROS on Serum Lipids and Blood Pressure  Changes in clinical laboratory values, TG, LDL-C, TC, SBP and DBP before and after ATV or ROS administration are shown in Table 2. For ATV group, TG, LDL-C, and TC levels significantly decreased from 217.9±171.5, 141.3±29.7, and 233.1±19.8 mg/dL to 114.5±50.4, 91.7±32.1, and 174.2±30.8 mg/dL, respectively. For ROS group, TG, LDL-C, and TC levels significantly decreased from 219.2±90.2, 200.2±122.6, and 330.5±186.6 mg/dL to 153.8±73.6, 93.7±21.9, and 175.6±29.6 mg/dL, respectively. We did not observe significant differences in TG, LDL-C, and TC levels after administration between ATV and ROS administration. SBP and DBP were also not observed to have significant differences before (136.7±21.6 and 78.2±10.8 mmHg) and after (135.8±26.4 and 77.2±13.9 mmHg, respectively) ATV administration as well as before (132.9±15.7 and 80.0±15.4 mmHg) and after (127.1±16.1 and 77.2±13.9 mmHg, respectively) ROS administration.

Effects of ATV and ROS on Renal Function  In this study, we have investigated eGFR as a marker of renal function. For ATV group, eGFR was significantly increased from 51.1±7.82 mL/min/1.73 m² to 61.8±13.3 mL/min/1.73 m², whereas no significant change was observed before (47.7±7.04 mL/min/1.73 m²) and after (52.5±18.4 mL/min/1.73 m²) ROS administration (Fig. 2).

Effects of ATV and ROS on SUA Levels  For ATV group, SUA levels significantly decreased from 6.38±1.11 mg/dL to 5.48±1.44 mg/dL (Fig. 3), whereas no change was observed before (6.69±1.25 mg/dL) and after (6.71±1.36 mg/dL)

Table 2. Effects of ATV and ROS on Serum Lipids and Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>ATV (n=13)</th>
<th></th>
<th></th>
<th>ROS (n=16)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-drug</td>
<td>Post-drug</td>
<td>p Value</td>
<td>Pre-drug</td>
<td>Post-drug</td>
<td>p Value</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>217.9±171.5</td>
<td>114.5±50.4</td>
<td>0.018</td>
<td>219.2±90.2</td>
<td>153.8±73.6</td>
<td>0.045</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>141.3±29.7</td>
<td>91.7±32.1</td>
<td>0.001</td>
<td>200.2±122.6</td>
<td>93.7±21.9</td>
<td>0.001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>233.1±19.8</td>
<td>174.2±30.8</td>
<td>&lt;0.001</td>
<td>330.5±186.6</td>
<td>175.6±29.6</td>
<td>0.011</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.7±21.6</td>
<td>135.8±26.4</td>
<td>0.500</td>
<td>132.9±15.7</td>
<td>127.1±16.1</td>
<td>0.128</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.2±10.8</td>
<td>77.2±13.9</td>
<td>0.373</td>
<td>80.0±15.4</td>
<td>77.2±13.9</td>
<td>0.201</td>
</tr>
</tbody>
</table>

Pre-drug and post-drug show laboratory data before and three months after administration of ATV and ROS.

Fig. 2. Change in eGFR by ATV and ROS
We compared the measured values of eGFR before and three months after ATV and ROS administration.

Fig. 3. Changes in SUA Levels by ATV and ROS
We compared the measured values of SUA before and three months after ATV and ROS administration.
In the GREek Atorvastatin and Coronary heart disease Evalu-
and vascular smooth muscle. Such as anti-platelet, anti-coagulation, and anti-inflammatory
sary to consider the involvement of a multifaceted action,
Concerning the mechanism of the improvement of renal func-
protective effects might be different between ATV and ROS.
In this study, we could obtain the result that was similar to
and after ROS administration was not significantly changed.
creased significantly by ATV. On the other hand, eGFR before
and ROS administration.
Results showed that eGFR was in-
also determined the change in eGFR before and after ATV
administration.
and ROS administration (Fig. 3).
Next, we compared ATV and ROS in terms of their
achievement rate of SUA levels of less than 6.0mg/dL. The
achievement rates of ATV (5–10mg/d) and ROS (2.5mg/d)
were 70 and 20%, respectively (Fig. 4).

DISCUSSION

The most valuable result obtained from this study is that we
could show renal protective effects in stage 3 CKD pa-
tients with hyperuricemia and hyperlipidemia complications
after ATV administration. We could also show a significant
decrease in SUA level after ATV administration. On the other
hand, we could not show significant changes in SUA levels
and eGFR after ROS administration.

In the meta-analysis by Sandhu et al., wherein the renal
protective effects of statin drugs were determined, eGFR improved to 3.1mL/min/1.73m² in one year for subjects with underly-
ing diseases such as glomerulonephritis, diabetes, and hypertension.18) In the subanalysis of the results of the Treat-
ing to New Target (TNT) trial that determined the second
prevention of cardiovascular disease, eGFR increased approxi-
mately 2% after one year of ATV administration (80mg/d) in
CKD patients.19) In this study, eGFR increased significantly in
comparison with the result of the previous study. In addition, it is known that the improvement degrees of eGFR are differ-
ent between statin drugs. In the PLANET study, in which the
renal protective effects of ATV and ROS were observed in
CKD patients, it was reported that ATV was superior to ROS
in improving urinary protein levels and renal function.20) We
also determined the change in eGFR before and after ATV
and ROS administration. Results showed that eGFR was in-
creased significantly by ATV. On the other hand, eGFR before
and after ROS administration was not significantly changed.
In this study, we could obtain the result that was similar to
that of the PLANET trial. We could demonstrate that the renal
protective effects might be different between ATV and ROS.
Concerning the mechanism of the improvement of renal func-
tion by ATV, we believe that it may be based on the effect of
lowering the LDL-C level. In addition, it may also be neces-
sary to consider the involvement of a multifaceted action,
such as anti-platelet, anti-coagulation, and anti-inflammatory
effects, and the favorable impact of statins on endothelial cells
and vascular smooth muscle.

The effect of ATV on lowering the SUA level was shown.
In the GREek Atorvastatin and Coronary heart disease Evalu-
ation (GREACE) study, 1600 patients with coronary heart
disease were administered ATV up to a maximum of 80mg/d.
As a result, SUA level decreased by 8.2% after 48 months
(end of study).21) In addition, Marais et al. administered ATV
(80mg/d) for 6 weeks to 22 patients with familial hypercholes-
terolemia, and reported that SUA levels decreased by approxi-
mately 10% from 4.87 to 4.36mg/dL.22) The SUA-lowering
effect of ATV in these patients is the result of a dose that far
exceeds the maximum daily dose of 20mg allowed in Japan.
In this study, we could demonstrate the SUA-lowering effect
of ATV at the average dose of 8.8mg/d, which is less than
the dose reported previously. We suggested that SUA level
decreased by renal protective effects of ATV. In this study, we
have shown that ATV has the significant effect of improving
hyperlipidemia and hyperuricemia complications. Moreover,
it has a renal protective effect and it may be able to suppress
the development of CVD. However, subjects who were taking
calcium channel blockers (CCBs) (cilnidipine and efonidipine)
and angiotensin-receptor blockers (ARBs) (telmisartan, valsar-
tan, and olmesartan) were also included in this study. There
are reports that these drugs increase eGFR. We consider the
possibility that these drugs have an effect on the findings
of this study. It is necessary to sufficiently lower the blood
pressure to show the renal protective effects. However, these
drugs were used in this study, and no significant difference
in blood pressure before and after ATV or ROS administra-
tion was found. Therefore, we hypothesize that there is little
effect of ARBs, except losartan and irbesartan, and CCBs.
Furthermore, the primary disease of subjects is mostly chronic
glomerulonephritis. Immunosuppressants and anti-platelet
agents are used for the treatment of chronic glomerulonephri-
tis. The excretion level of urinary protein decreases, and renal
function is maintained by the action of these drugs. In other
words, in some cases that eGFR increased significantly, we
hypothesized that there was a possibility that these drugs may
be related.

On the other hand, we could not show the SUA-lowering
effect of ROS. Nezami et al. reported no change in SUA levels
in 30 patients with type 2 diabetic nephropathy, who were ad-
ministered 20mg of ROS daily for 90d.23) The results of this
study support these previous findings. We suggested that ROS
has no SUA-lowering effect.

The reasons for the difference between the SUA-lowering
effects of ATV and ROS have been reported. Athyros et al.
reported that the SUA-lowering effect observed in the
GREACE study has been attributed to an increase in renal
blood flow owing to the improvement of endothelial function
by ATV, which exerts a variety of pleiotropic effects in addi-
tion to lowering lipid levels.24) In this study, we analyzed the
correlation between the rate of increase in eGFR and the rate
of decrease in SUA levels for patients with decreased LDL-C
levels. However, the significant difference was not found in
this study.

There are no reports on the target achievement rates of
statins for the reduction of SUA levels. Sarawate et al. re-
ported that a gout attack was unlikely to occur in patients
whose SUA levels were maintained at less than 6.0mg/dL.8) We
compared ATV and ROS in terms of their achievement
rate of SUA levels of less than 6.0mg/dL. As a result, that
of ATV was 3.5 times higher than that of ROS. Our results are
sufficient to indicate the effectiveness of ATV in lowering the

Fig. 4. Achievement Rate of Less than 6.0mg/dL SUA Levels of ATV
and ROS
Average doses of ATV and ROS were 8.8 and 2.5mg/d, respectively. The
achievement rate of ATV was significantly higher than that of ROS.

SUAs levels in patients with up to moderate renal failure such as stage 3 CKD.

There has been much discussion on drug therapy to prevent renal failure, and the selection and dose adjustment of drugs that lower the SUA levels have become important issues in the medical field. In this study, the renal protective effects and SUA-lowering effect of ATV were observed, and we confirmed the clinical utility of ATV in patients presenting with hyperlipidemia and hyperuricemia complications associated with moderate renal failure, such as patients with at least stage 3 CKD. We consider that, by selecting ATV, the renal protective effects and SUA-lowering effect would be sufficient. Due to this, the number of drugs to be taken will be reduced, and this will lead to compliance for the patients. Moreover, the possible side effects caused by drugs that lower the SUA levels will be eliminated, and we consider that there are good benefits from the viewpoint of medical economics. However, it is necessary to be careful about the side effects of rhabdomyolysis when we administer ATV. Most of the reported cases of rhabdomyolysis are renal function disorder patients. In addition, it is recognized that rapid renal dysfunction is aggravated by rhabdomyolysis. Therefore, we consider that it is necessary to administer ATV carefully after having considered its usefulness and risk in CKD patients.

This study is a cross-sectional study. There are few subjects than meta-analysis by Sandhu et al. and GREACE study and also is short during the target period in this study. In addition, there was a possibility that the drugs of subjects and the treatments for chronic glomerulonephritis may be related in eGFR. Furthermore, we did not consider the effects of diet and exercise. That is to say that we cannot deny the possibility those other factors may have affected the results of this study. We consider that it is necessary to confirm through observation period of one year or more by a large-scale prospective study to demonstrate the clinical utility of ATV. These are the limitations of this study.

In recent years, the number of patients with end-stage kidney disease (ESKD) has been increasing. Aggressive management and treatment of CKD in terms of reducing the risk of developing CVD and preventing the progression to ESKD should be carried out immediately.

In conclusion, we confirmed the clinical utility of ATV in CKD patients in a retrospective observational study. Through this study, we should consider the renal protective effects of ATV and the need for drugs that lower the SUA level to monitor the development of CVD.

REFERENCES

20) Clinical Trials. gov, Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive

