Analysis of renal function during telaprevir-based triple therapy for chronic hepatitis C

MOTOYUKI KOHJIMA[1], MIHO KUROKAWA[1], MUNECHIKA ENJOJI[2], TSUYOSHI YOSHIMOTO[1], TSUKASA NAKAMURA[1], TOMOKO OHASHI[1], KUNITAKA FUKUIZUMI[1], NAOHIKO HARADA[1], YUSUKE MURATA[2], KAZUHISA MATSUNAGA[2], MASAKI KATO[3], KAZUHIRO KOTOH[3] and MAKOTO NAKAMUTA[1]

[1]Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka 810-8563; [2]Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka 814-0180; [3]Department of Medicine and Bioregulatory Science, Kyushu University, Fukuoka 812-8582, Japan

Abstract. Telaprevir (TVR) is used for the treatment of chronic hepatitis C in a combination therapy with pegylated-interferon and ribavirin. Although renal dysfunction is one of the critical adverse outcomes of this treatment, little is known regarding the mechanism of its onset. The present study assessed the association of renal function with TVR dose and viral response. Hematological, biochemical, urinary and virological parameters of renal function were examined during the TVR-based triple therapy of patients infected with hepatitis C virus (HCV) genotype 1b. Serum creatinine levels were increased and the estimated glomerular filtration rate (eGFR) was decreased in every patient during TVR administration, but these values recovered to normal levels following cessation of TVR. Fractional excretion of sodium was <1% at days 3 and 7, appearing similar regardless of baseline renal function. Urinary β_2-microglobulin levels were elevated and were significantly higher in patients with renal dysfunction, as compared with those not exhibiting renal dysfunction (P<0.05). The reduction in renal function was milder in patients treated with a reduced TVR dose, and these patients had a significantly lower risk of developing renal dysfunction (P<0.05). Using a multivariate analysis, TVR dose and eGFR at the initiation of treatment were identified as significant contributory factors in the development of renal dysfunction. Reduction in TVR dose did not lead to a significant increase in the viral kinetics of HCV or detrimental effects on the sustained viral response (SVR) rate. It is hypothesized that renal dysfunction during TVR treatment is caused by damage of the renal tubule, in addition to pre-renal dysfunction, and that reduction in TVR dose reduces the rate of renal dysfunction without causing a significant decrease in the SVR rate.

Correspondence to: Dr Munechika Enjoji, Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Fukuoka 814-0180, Japan
E-mail: enjoji@adm.fukuoka-u.ac.jp

Introduction

Worldwide, ~170 million individuals are infected with the hepatitis C virus (HCV) and cirrhosis is estimated to develop in 5-20% of patients ~20 years after acquiring the infection (1). In Japan, >70% of cases of chronic hepatitis C are caused by HCV genotype 1b (HCV-1b) in high viral loads (>5.0 log IU/ml) (2). A maximum of 50% of patients infected with HCV-1b attain a sustained viral response (SVR) following pegylated-interferon (peg-IFN)-α and ribavirin (RBV) combination therapy (2,3). Telaprevir (TVR), an inhibitor of HCV NS3/4A protease, has been approved for the treatment of patients infected with HCV-1b (4-7). Although TVR-based triple therapy, combining TVR with peg-IFNα and RBV, has improved the SVR rate to >70%, critical adverse effects, including anemia, skin rashes and renal dysfunction, may lead to a dose reduction or treatment discontinuation, resulting in a reduced SVR rate (4-7).

Renal toxicity as a side-effect to medication occurs through alterations to plasma filtration and the maintenance of metabolic homeostasis (8). According to a previous study, the incidence of drug-associated acute tubular necrosis or acute interstitial nephritis may be as high as 18.3% (8). In the majority of cases, renal dysfunction was reversible and the blood test parameters normalized when the causal drug was discontinued; however, a number of medications induced chronic renal injury (8). Drugs may affect renal perfusion or injure vascular, tubular, glomerular and interstitial cells directly (9). As the TVR-based triple therapy is administered over a period of 3-6 months, the authors of the present study hypothesized that the renal damage may be chronic. However, little is known regarding the mechanism of the onset and development of renal dysfunction during HCV therapy. The present study therefore aimed to analyze

Table I. Patient background.

Factor	TVR dose		P-value
	2,250 mg/day	1,500 mg/day	
No. of patients	20	99	
Gender (male/female)	7/13	46/53	NS
Age, years	51.8±97.4	60.0±9.5	0.0003
History of IFN therapy (naive/IFN/IFN + RBV patients)	8/4/8	42/18/39	NS
HCV RNA, log IU/ml	6.45±0.61	6.27±0.61	NS
IL-28B (rs8099917) (TT/TG + GG)	6/14	34/65	NS
ITPA (rs1127354) (CC/CA + AA)	5/15	26/73	NS
Core 70 (WT/mutations)	11/9	65/34	NS
ALT, IU/l	123.6±110.3	86.5±77.0	NS
GGT, IU/l	98.1±85.6	60.3±47.3	0.0063
Neutrophils/μl	2721±1189	2254±815	0.034
Hemoglobin, g/dl	14.4±1.2	13.7±1.5	NS
Platelets/μl	17.1±5.5	16.0±6.0	NS
Creatinine, mg/dl	0.65±0.15	0.70±0.18	NS
eGFR, ml/min/1.73 m^2	94.7±19.0	80.1±15.2	0.0003
Uric acid	5.38±1.42	5.69±1.24	NS
TVR dose/body weight/day	34.0±6.5	24.7±4.6	<0.0001

TVR, telaprevir; IFN, interferon; RBV, ribavirin; HCV, hepatitis C virus; IL-28B, interleukin-28B; ITPA, inosine triphosphatase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; NS, not significant.

the pathogenesis of renal dysfunction in patients infected with HCV-1b during TVR-based triple therapy. Analysis of clinical parameters associated with renal injury, including urinary sediment presence, serum creatinine level, estimated glomerular filtration rate (eGFR), fractional excretion of sodium (FENa) and β_2-microglobulin level, were examined as potentially important metrics. A knowledge of FENa levels is useful for the evaluation of acute renal failure (10); low FENa (<1%) indicates kidney retention of sodium and exogenous renal dysfunction caused by pre-renal disease, whilst higher percentages (>2%) suggest leakage of sodium due to endogenous renal failure. Urinary β_2-microglobulin values were also used to evaluate renal filtration function.

Materials and methods

Study patients and drug regimen. A standard treatment regimen (5,6) was adopted for patients infected with HCV-1b at the Kyushu Medical Center (Fukuoka, Japan) between December 2011 and April 2013. A 12-week triple therapy was administered, including oral TVR (2,250 mg/day; Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan), weekly subcutaneous peg-IFNα2b (median dose, 1.5 μg/kg; range, 1.3-1.7 μg/kg; MSD Pharmaceuticals, Tokyo, Japan) and oral RBV (600-1,000 mg/day; MSD Pharmaceuticals), followed by a 12-week dual therapy of peg-IFNα2b and RBV. The dose of RBV was adjusted according to body weight; 600 mg was administered to patients weighing <60 kg, 800 mg to patients weighing 60-80 kg and 800 mg to patients weighing >80 kg. Although the standard dose of TVR

is 2,250 mg/day, the dose was reduced to 1,500 mg/day for small patients or aging women. The present study conformed with the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Ethics Committee of the National Hospital Organization (No. 13-72). The patients were provided with an explanation of the aims and outline of the study, and written informed consent was obtained from all. A total of 119 patients infected with HCV-1b were enrolled. The patient profiles and their baseline characteristics are reported in Table I. In all patients, the baseline HCV RNA levels in serum were >5.0 log IU/ml.

Laboratory data. Hematological, biochemical, urinary and virological parameters were determined by the clinical laboratory at Kyushu Medical Center. Renal dysfunction was defined as elevated serum creatinine levels (>1.1 and 0.8 mg/dl for men and women, respectively), or as an eGFR level <60 ml/min/1.73 m^2. Severe renal dysfunction was defined as elevated serum creatinine levels (>1.3 mg/dl) or as decreased eGFR levels (<40 ml/min/1.73 m^2). Serum HCV RNA concentrations were determined using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). SVR was defined as no detectable HCV RNA, reported at weeks 12 and 24 after therapy completion. A number of patients were subject to genotyping of interleukin-28B (rs8099917) and inosine triphosphatase (rs1127354) polymorphisms, performed using TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, Inc., Waltham, MA, USA) by applying polymerase chain reaction (PCR)-based restriction fragment length polymorphism assays. To identify amino acid polymorphisms in the
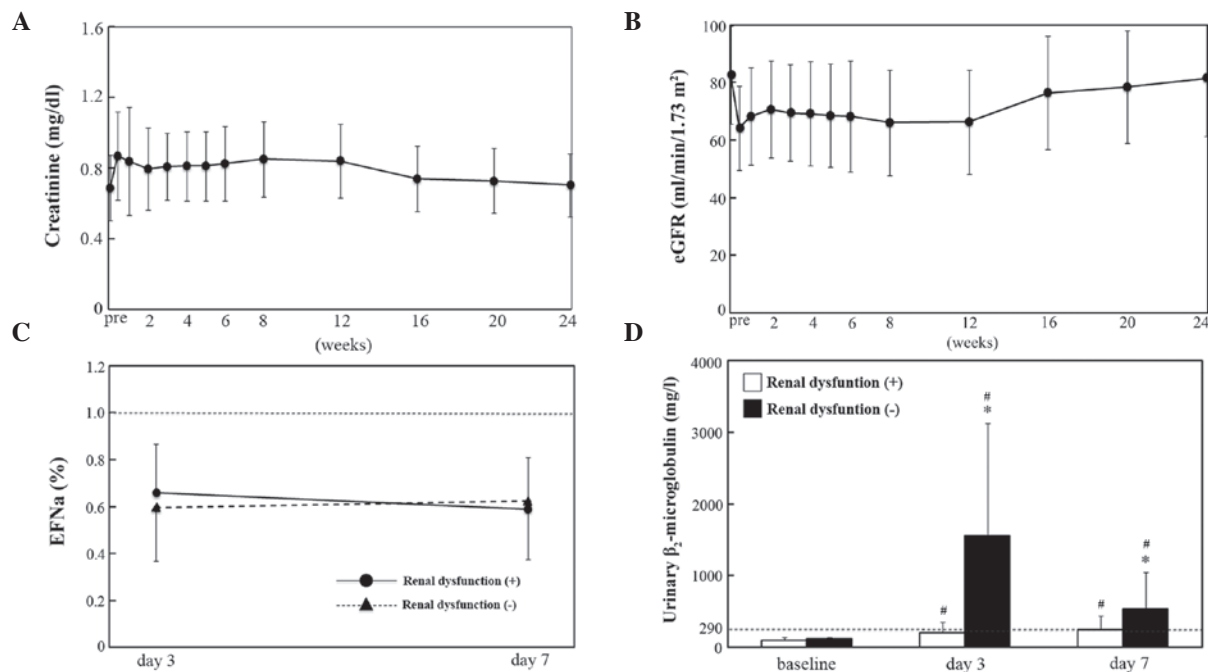
Figure 1. Renal dysfunction during telaprevir-based triple therapy. (A) Time course of serum creatinine values. (B) Time course of eGFR rate. (C) FENa on days 3 and 7 of the treatment. (D) Urinary β2-microglobulin values. Data are presented as the mean ± standard deviation. *P<0.01 vs. renal dysfunction (+) cases; #P<0.01 vs. the baseline. eGFR, estimated glomerular filtration; FENa, fractional excretion of sodium.

HCV core protein, PCR was conducted using primers specific to a polymorphism at core 70, in accordance with the previously reported methodology (11,12). Briefly, the PCR reaction system (25 μl) consisted of 2X Power SYBR Green PCR Master Mix (Applied Biosystems; Thermo Fisher Scientific, Inc.) and 2.5 pmol of each primer. The PCR cycling conditions were as follows: Denaturation at 95°C for 10 min, followed by 40 cycles at 95°C for 15 sec and 60°C for 1 min. A melting curve analysis was conducted to confirm their specificity. Peg-IFN, RBV and TVR were discontinued in various combinations, or their doses were reduced as required following a decrease in hemoglobin levels, neutrophil or platelet counts, or the development of other adverse side-effects. To appropriately evaluate therapeutic effects, SVR rates were examined with the intention to treat.

Statistical analysis. Data are presented as the mean ± standard deviation. Statistical analyses were conducted using JMP software, version 8.0.2.2 (SAS Institute Inc., Cary, NC, USA). Differences between categorical variables were analyzed using Fisher's exact test or a χ^2 test. A Mann-Whitney U test was used to compare continuous variables. Multivariate analyses were conducted to identify factors independently associated with renal dysfunction. The odds ratio (OR) and 95% confidence intervals were also determined. P<0.05 was considered to indicate a statistically significant difference.

Results

Renal dysfunction during TVR-based triple therapy. Serum creatinine values were markedly elevated in all patients by ~0.2 mg/dl from the baseline from the third day, and remained elevated until after week 12 of triple-therapy administration

(Fig. 1A); however, this difference was not significant (P>0.05). The serum creatinine concentration in the patients progressively decreased after week 12, and baseline values were eventually restored following cessation of TVR (Fig. 1A). The mean eGFR values markedly decreased by 15 ml/min/1.73 m^2 during TVR administration, and improved following cessation of TVR (Fig. 1B); however, the mean eGFR values were not significantly different from the baseline throughout the 24-week treatment period (P>0.05). Treatment was discontinued in 2 patients due to the onset of acute renal failure. In order to evaluate the underlying mechanism of renal dysfunction, the presence of urinary sediment, granular casts and tubular epithelial cells was evaluated, but no abnormal findings were observed. The FENa values observed in the patients were ~0.6% at days 3 and 7 of the therapy, when serum creatinine and eGFR were markedly changed, in the renal dysfunction (n=17) and normal function groups (n=102) (Fig. 1C). FENa values were also similar between patients treated with TVR at 2,250 mg/day and those treated with a reduced TVR dose (1,500 mg/day) (data not shown).

The present study investigated urinary β_2-microglobulin, a marker of tubular damage, at days 3 and 7 of the treatment. Urinary β_2-microglobulin was elevated, but reached abnormal levels (>290 μg/l) in only half of the patients. Patients with renal dysfunction exhibited significantly elevated levels of urinary β_2-microglobulin on day 3 of the treatment, as compared with the baseline and patients without renal dysfunction (P<0.01; Fig. 1D). However, there was no significant difference in β_2-microglobulin levels between patients with renal dysfunction and those without renal dysfunction on day 7 of the treatment (P>0.05; Fig. 1D).

Predictive factors associated with renal dysfunction. Within the listed factors in Table II, predictive factors associated with

Table II. Factors involved in renal dysfunction.

Factor	Renal dysfunction(-)	Renal dysfunction(+)	P-value
No. of patients	102	17	
Gender (male/female), n	49/53	10/7	NS
Age, years	59.1±9.9	56.4±8.1	NS
History of IFN therapy (naive/IFN/IFN+RBV patients), n	42/20/40	8/2/7	NS
Staging (F0/F1/F2/F3/F4), n	1/12/16/11/20	0/1/3/3/0	NS
HCV RNA, log IU/ml	6.26±0.60	6.58±0.63	NS
IL-28B (rs8099917) (TT/TG + GG), n	67/35	12/5	NS
ITPA (rs1127354) (CC/CA + AA), n	76/26	12/5	NS
Core 70 (WT/mutations), n	66/36	10/7	NS
ALT, IU/l	74.6±86.2	81.5±71.5	NS
GGT, IU/l	67.1±56.4	64.2±61.5	NS
Neutrophils/μl	2302±842	2515±1205	NS
Hemoglobin, g/dl	13.8±1.5	14.0±1.3	NS
Platelets/μl	16.0±6.0	17.2±5.7	NS
Creatinine, mg/dl	0.65±0.13	0.72±0.16	0.048
eGFR, ml/min/1.73 m^2	85.3±15.4	80.1±12.8	NS
Uric acid, mg/dl	5.61±1.26	5.80±1.40	NS
Total cholesterol, mg/dl	141.8±27.4	151.5±34.8	NS
Triglycerides, mg/dl	89.9±40.3	87.9±74.2	NS
Diabetes mellitus, -/+	92/10	1/16	NS
TVR dose, 1,500/2,250 mg	94/8	5/12	<0.0001

TVR, telaprevir; IFN, interferon; RBV, ribavirin; HCV, hepatitis C virus; IL-28B, interleukin-28B; ITPA, inosine triphosphatase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; NS, not significant.

Table III. Multivariate analysis for predictive factors associated with renal dysfunction.

Factors	Odds ratio	95% confidence interval	P-value
TVR dose (2,250 mg/day)	102.6	11.3-1650	<0.0001
eGFR (<90 ml/min/1.73 m^2)	30.5	4.2-568	0.0003

TVR, telaprevir; eGFR, estimated glomerular filtration.

renal dysfunction were examined in patients undergoing triple therapy. Univariate analysis identified two parameters that were significantly correlated with renal dysfunction; these were serum creatinine (P=0.048) and TVR dose (P<0.0001) (Table II). From a multivariate analysis, TVR dose (2,250 mg/day; OR, 102.6; P<0.0001) and eGFR (<90 ml/min/1.73m^2; OR, 30.5; P=0.003) were demonstrated to be significant contributory factors for renal dysfunction (Table III). Creatinine was not shown to be a significant contributory factor in this multivariate analysis (P>0.05).

Effect of TVR dose on renal dysfunction and therapeutic outcome. The present study evaluated the association between TVR dose and pathogenesis, severity of renal dysfunction and therapeutic outcome. Although the serum creatinine levels were increased on day 3 of the treatment and had remained elevated

in patients treated with TVR at 1,500 mg/day, serum creatinine values were significantly higher in patients treated with TVR doses of 2,250 mg/day at days 3, 7 and 14 of the treatment (P<0.01; Fig. 2A). Although eGFR depression was induced by TVR administration (Fig. 1B), the decrease in eGFR was smaller in patients receiving a reduced TVR dose. However, no significant difference was observed in the decreasing rates of eGFR between the low- and high-dose groups (P>0.05; data not shown). Of the 20 patients treated with TVR at 2,250 mg/day, 13 patients developed renal dysfunction; of these, 12 patients exhibited severe dysfunction. Patients treated with TVR at 1,500 mg/day demonstrated a significantly lower incidence of renal dysfunction (P<0.01; Fig. 2B).

The therapeutic effects of TVR at 2,250 and 1,500 mg/day were assessed. SVR at 12 weeks was achieved in 17 patients (89.5%) treated with TVR 2,250 mg/day and 68 patients (78.2%)
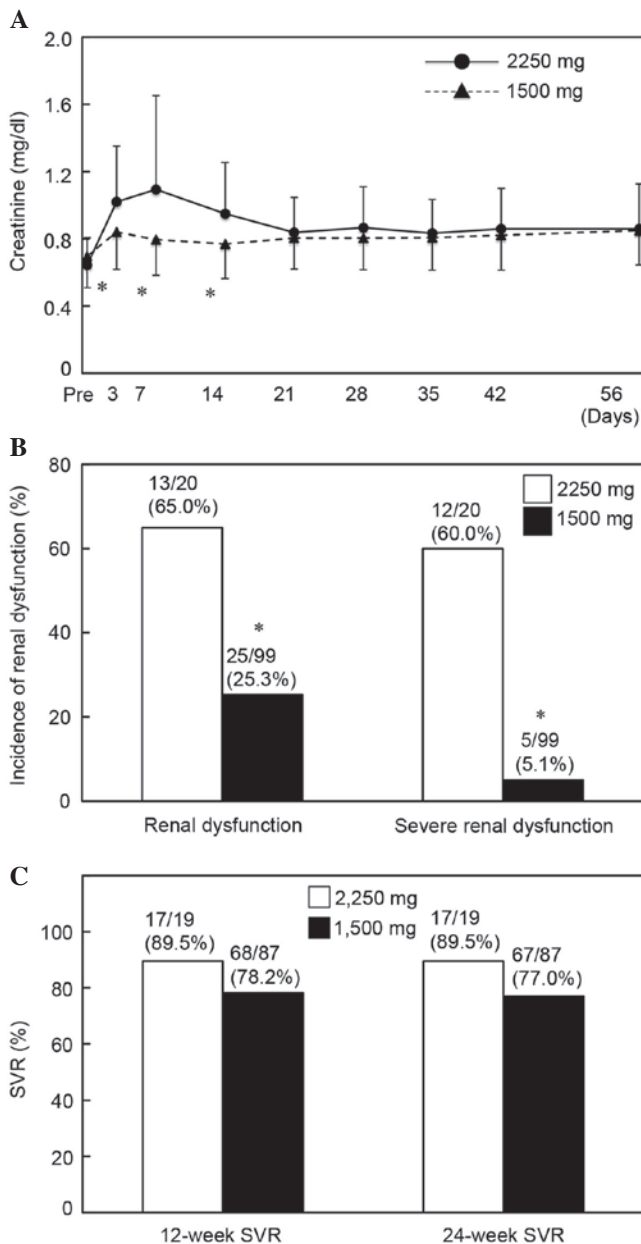
Figure 2. Effect of TVR dose reduction. (A) Time course of serum creatinine levels. (B) Incidence of renal dysfunction. (C) SVR rates in patients. Data are presented as the mean ± standard deviation. *P<0.01 following treatment with TVR at 2,250 vs. 1,500 mg/day. TVR, telaprevir; SVR, sustained viral response.

treated with TVR 1,500 mg/day, but no statistically significant difference was revealed between the groups (P>0.05; Fig. 2C). Concordantly, the 24-week SVR rate in patients receiving a reduced dose of TVR was lower than that of patients with TVR at 2,250 mg/day (77.0 and 89.5%, respectively); however, this difference was not statistically significant (P>0.05; Fig. 2C). SVR was undetermined in four patients due to discontinuation of treatment (2 patients) and hospital visiting (2 patients).

Discussion

In the present study, a combination therapy comprising peg-IFN, RBV and TVR was demonstrated to cause markedly increased SVR rates, as compared with a dual therapy of peg-IFN and RBV. However, critical adverse effects, including anemia and dermatopathy, have previously been reported (4-7). Additionally, renal dysfunction is recognized as a significant adverse effect of TVR-based triple therapy, and may lead to discontinuation of the treatment (6). IFN is an established causative agent of renal impairment, including proteinuria, glomerular minimal damage, cellular hyperplasia and focal segmental glomerulosclerosis, which are predominantly observed in patients with malignancy. This renal damage predominantly occurs within the first 4 weeks or several months of IFN therapy (13-16). In patients with chronic hepatitis C, renal impairment during dual therapy with peg-IFN and RBV is relatively rare, and not recognized as a central element of the adverse event profile (17). In the present study, deterioration of renal function, which was recognized only during TVR administration, occurred in all patients, suggesting that TVR is responsible for renal dysfunction during the treatment.

Although renal dysfunction has not been listed as a safety concern in multiple previous clinical trials of TVR and serious renal adverse events have not been noted, TVR-induced renal dysfunction has been previously reported (18-23). Renal dysfunction is now recognized as a critical complication of TVR-based triple therapy (18-23). Higher incidences of serious impairment of eGFR (<60 ml/min) were previously observed in patients receiving TVR or boceprevir with peg-IFN and RBV (6.6 and 4.7%, respectively) when compared with those receiving dual therapy with peg-IFN and RBV only (0.9%) (19). The risk factors associated with eGFR <60 ml/min in this previous study were age, increased baseline serum creatinine level, arterial hypertension and receiving triple therapy with TVR or boceprevir (19). In the present study, renal dysfunction was not significantly associated with age, gender, liver fibrosis, HCV RNA, alanine aminotransferase, uric acid, total cholesterol or diabetes mellitus. Age and co-morbidity were not established as significant contributory factors to renal dysfunction, but the eGFR baseline level, in addition to the TVR dose, contributed to renal dysfunction during treatment. Typically, Japanese patients with HCV infection are older, and have a lower height and body weight compared with patients in the United States and Europe (24-26). Furthermore, a higher frequency of treatment discontinuation due to laboratory abnormalities and adverse side effects has been reported in older patients (24-26). TVR dose reduction in aging patients or smaller women is a common practice in the department in which the present study was conducted; this reduction may have been linked to the difference in the risk factors reported during TVR treatment. Mauss et al (19) analyzed the temporal concentration of eGFR in patients receiving TVR-based triple therapy; a decrease in eGFR was reported within the first 12 weeks, which was followed by a marked improvement subsequent to the termination of TVR treatment in the majority of patients. In the present study, renal function was also evaluated; the decrease in eGFR concentration and an increase in serum creatinine were only observed during the 12 weeks of TVR administration, but these improved following cessation of TVR treatment. It may, therefore, be concluded that renal dysfunction during TVR treatment is reversible in the majority of treated patients.

Carrier et al (23) reported a case of acute renal insufficiency occurring at week 36 of TVR-based triple therapy at standard

doses. Renal biopsy findings revealed membranous glomeru-lonephritis and prominent interstitial fibrosis with tubular atrophy. The glomerulonephritis was hypothesized to be due to peg-IFN, while possible involvement of TVR was described in the interstitial fibrosis. In the present study, 17 patients experienced severe renal dysfunction; 2 of these had their treatment discontinued as a result. All patients receiving TVR demonstrated a decline in renal function, initially occurring at the first or second week of treatment. These results suggested that the mechanism of renal impairment may differ from that illustrated by Carrier *et al* (23). All patients in the present study demonstrated low levels of FENa (<1%) within 7 days of receiving treatment, regardless of renal function; however, urinary β_2-microglobulin was only significantly elevated in patients with renal dysfunction. Furthermore, a number of patients with severe renal dysfunction demonstrated high values of urinary *N*-acetyl-β-D-glucosaminidase, a marker of tubular damage, although no significant difference was found. These results clearly suggest that renal dysfunction is associ-ated with a pre-renal mechanism, and additional damage to the renal tubule exacerbates renal impairment. Although inadequate blood flow into the renal arterioles and inhibition of renal drug transporters are assumed to be the origin of renal damage (27), the pathophysiological mechanism of renal toxicity caused by TVR is not completely understood, and additional study is necessary.

Multivariate analysis indicated that TVR dose, in addition to baseline eGFR levels, was a significant contributory factor to renal dysfunction in the present study. It has been previously reported that TVR impairs renal function and increases serum RBV concentration, which exacerbates anemia, emphasizing the importance of adjusting the dose of TVR in order to avoid an excessive elevation of serum RBV levels (21,22). Furthermore, dose reduction of TVR also restrains the pathogenesis of renal damage (21,22). However, it remains unclear whether TVR dose reduction affects the viral response to treatment. In the present study, 12- and 24-week SVR rates were lower in patients treated with 1,500 mg/day TVR than in those treated with 2,250 mg/day TVR, although this difference was not statistically significant. The TVR 1,500 mg/day group included older patients, a divi-sion established to have a poorer viral response compared with younger patients (6). It is therefore possible that the lower SVR rate observed in the present study does not result from the reduced TVR dose, but that these rates may be associated with patient age. Univariate and multivariate analysis indicated that the TVR dose as a proportion of body weight, in addition to initial TVR dose, was not associated with SVR in the patients treated with TVR-based triple therapy (data not shown). For a reliable assessment, additional clinical data is required to deter-mine the optimum dosage of TVR in order to achieve a higher SVR rate and a lower incidence of adverse side effects.

Acknowledgements

References

1. Alter HJ: HCV natural history: The retrospective and prospective in perspective. J Hepatol 43: 550-552, 2005.
2. Kumada T, Toyoda H, Honda T, Kuzuya T, Katano Y, Nakano I and Goto H: Treatment of chronic hepatitis C with interferon alone or combined with ribavirin in Japan. Intervirology 49: 112-118, 2006.
3. Aghemo A, Rumi MG and Colombo M: Pegylated IFN-alpha2a and ribavirin in the treatment of hepatitis C. Expert Rev Anti Infect Ther 7: 925-935, 2009.
4. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J and Muir AJ; PROVE1 Study Team: Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 360: 1827-1838, 2009.
5. Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K and Kumada H: Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. J Viral Hepat 19: e134-e142, 2012.
6. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H and Hayashi N: Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol 56: 78-84, 2012.
7. Rajani AK, Ravindra BK and Dkhar SA: Telaprevir: Changing the standard of care of chronic hepatitis C. J Postgrad Med 59: 42-47, 2013.
8. Kleinknecht D, Landais P and Goldfarb B: Drug-associated acute renal failure. A prospective collaborative study of 81 biopsied patients. Adv Exp Med Biol 212: 125-128, 1987.
9. Choudhury D and Ahmed Z: Drug-associated renal dysfunction and injury. Nat Clin Pract Nephrol 2: 80-91, 2006.
10. Prowle J, Bagshaw SM and Bellomo R: Renal blood flow, frac-tional excretion of sodium and acute kidney injury: Time for a new paradigm? Curr Opin Crit Care 18: 585-592, 2012.
11. Nakamoto S, Kanda T, Yonemitsu Y, Arai M, Fujiwara K, Fukai K, Kanai F, Imazeki F and Yokosuka O: Quantification of hepatitis C amino acid substitutions 70 and 91 in the core coding region by real-time amplification refractory mutation system reverse transcription-polymerase chain reaction. Scand J Gastroenterol 44: 872-877, 2009.
12. Kohjima M, Enjoji M, Yoshimoto T, Yada R, Fujino T, Aoyagi Y, Fukushima N, Fukuizumi K, Harada N, Yada M, *et al*: Add-on therapy of pitavastatin and eicosapentaenoic acid improves outcome of peginterferon plus ribavirin treatment for chronic hepatitis C. J Med Virol 85: 250-260, 2013.
13. Fahal IH, Murry N, Chu P and Bell GM: Acute renal failure during interferon treatment. BMJ 306: 973, 1993.
14. Jadoul M, Piessevaux H, Ferrant A, Cosyns JP and van Ypersele de Strihou C: Renal thrombotic microangiopathy in patients with chronic myelogenous leukaemia treated with interferon-alpha 2b. Nephrol Dial Transplant 10: 111-113, 1995.
15. Shah M, Jenis EH, Mookerjee BK, Schriber JR, Baer MR, Herzig GP and Wetzler M: Interferon-alpha-associated focal segmental glomerulosclerosis with massive proteinuria in patients with chronic myeloid leukemia following high dose chemotherapy. Cancer 83: 1938-1946, 1998.
16. Russo MW and Fried MW: Side effects of therapy for chronic hepatitis C. Gastroenterology 124: 1711-1719, 2003.
17. Willson RA: Nephrotoxicity of interferon alfa-ribavirin therapy for chronic hepatitis C. J Clin Gastroenterol 35: 89-92, 2002.
18. Gervasoni C, Milazzo L, Pezzani D, Fucile S and Cattaneo D: Telaprevir therapy, renal impairment, and their effects on the pharmacokinetics of tenofovir in HIV/hepatitis C virus coin-fected patients. AIDS 28: 285-287, 2014.
19. Mauss S, Hueppe D and Alshuth U: Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. Hepatology 59: 46-48, 2014.
20. Pariente A, Rémy AJ, Lesgourgues B and Hagège H; APROVVIE group of the Association Nationale des Gastroentérologues des Hôpitaux Généraux (ANGH): Risk factors for severe anaemia during telaprevir-based triple therapy: Is acquired renal dysfunction the missing link? Liver Int 34: e163-e164, 2014.
21. Tempestilli M, Lionetti R, D'Offizi G, Montalbano M, Giaffreda A, Fazio S and Pucillo LP: Increased plasma concentration of ribavirin as a result of renal dysfunction in hepatitis C virus patients treated with telaprevir. Hepatology 60: 1109-1110, 2014.

22. Karino T, Ozeki I, Hige S, Kimura M, Arakawa T, Nakajima T, Kuwata Y, Sato T, Ohmura T and Toyota J: Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C. J Viral Hepat 21: 341-347, 2014.
23. Carrier P, Chambaraud T, Vong C, Guillaudeau A, Debette-Gratien M, Jacques J, Legros R, Sautereau D, Essig M and Loustaud-Ratti V: Severe renal impairment during triple therapy with telaprevir. Clin Res Hepatol Gastroenterol 38: e69-e71, 2014.
24. Kainuma M, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Satoh T, Maruyama T, Nakamuta M, Kotoh K, et al; Kyushu University Liver Disease Study Group: Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C. World J Gastroenterol 16: 4400-4409, 2010.
25. Honda T, Katano Y, Shimizu J, Ishizu Y, Doizaki M, Hayashi K, Ishigami M, Itoh A, Hirooka Y, Nakano I, et al: Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. Liver Int 30: 527-537, 2010.
26. Furusyo N, Ogawa E, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, et al; Kyushu University Liver Disease Study (KULDS) Group: Telaprevir can be successfully and safely used to treat older patients with genotype 1b chronic hepatitis C. J Hepatol 59: 205-212, 2013.
27. Kunze A, Huwyler J, Camenisch G and Gutmann H: Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters. Biochem Pharmacol 84: 1096-1102, 2012.