

Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C

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SUMMARY. We aimed to examine the relationship between renal dysfunction and anaemia that may develop during combination therapy involving pegylated interferon, ribavirin and telaprevir (PEG-IFN/RBV/TVR) for the treatment of chronic hepatitis C. Sixty-eight patients with genotype 1b high viral loads were treated with PEG-IFN/RBV/TVR. Peg-IFN and RBV doses were administered according to body weight. TVR was prescribed at 2250 mg/day for 44 patients and at 1500 mg/day for 24 patients who had low haemoglobin level (<12 g/dL). When anaemia had developed, the RBV dose was decreased. The serum TVR concentration at day 8 was measured, and the serum RBV concentration was measured serially. The estimated glomerular filtration rate (eGFR) was estimated to assess renal function. At week 1, serum TVR concentration was not correlated with a decrease in eGFR; however, the TVR

dose, on a weight basis (mg/kg), and eGFR were correlated ($r = 0.2691$; $P = 0.0265$). Moreover, there was a negative correlation between eGFR and RBV serum concentration ($r = -0.3694$; $P = 0.0025$), and the serum RBV concentration and decrease in the haemoglobin were significantly correlated from week 1 to week 8. In triple therapy, the TVR dose per weight is correlated with a decline in renal function. Thus, the serum concentration of RBV increases, with a concomitant decrease in haemoglobin. It is important to adjust the doses of TVR and RBV to avoid excessive serum RBV levels and the development of severe anaemia, to achieve a good clinical effect.

Keywords: anaemia, estimated glomerular filtration rate, hepatitis C virus, ribavirin, telaprevir.

INTRODUCTION

An estimated 170 million people are chronically infected with hepatitis C virus (HCV) worldwide [1]. Approximately 30% of the patients with chronic HCV develop life-threatening liver disease, such as decompensated cirrhosis and hepatocellular carcinoma [2,3]. Since Hoofnagle *et al.* [4] first reported the effectiveness of interferon (IFN) in the treatment of the so-called non-A non-B chronic hepatitis, IFN has played a central role in the antiviral therapy for chronic hepatitis C. Until recently, combined therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV), for 48 weeks, has been the standard-of-care for patients infected with HCV genotype 1 (HCV-1), which is the most

prevalent genotype worldwide. However, sustained virological response (SVR) is achieved in only 42–52% of the patients treated with this regimen [5–7].

To achieve a better antiviral effect, investigators have developed several direct-acting antivirals, represented by NS3/4A protease inhibitors and NS5B polymerase or NS5A inhibitors [8]. Of these, telaprevir (TVR), an inhibitor of the NS3/4A serine protease, in combination with PEG-IFN and RBV (triple therapy), has been most promising and has been reported to achieve an SVR of up to 70% [9–13]. However, adverse events develop more frequently in patients treated with protease inhibitors than in those treated only with PEG-IFN and RBV. In TVR trials, rash, anaemia, pruritus, nausea and diarrhoea were found to develop more frequently in individuals who received PEG-IFN and RBV along with TVR than in those individuals who received PEG-IFN and RBV only [11]. In addition, a renal functional disorder associated with TVR therapy became evident in Japan after the Ministry of Health, Labour and Welfare approved the use of TVR [14]. RBV is excreted in the urine, and diminished renal function can interfere with its metabolism [15]. In this

Abbreviations: eGFR, estimated glomerular filtration rate; IL28B, interleukin 28B; ITPA, inosine triphosphatase; RBV, ribavirin; Scr, serum creatinine; SNP, single-nucleotide polymorphism; TVR, telaprevir.

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study, we aimed to examine the relationship between renal dysfunction and anaemia in patients undergoing triple therapy for HCV.

PATIENTS AND METHODS

Patients

We enrolled 68 patients with HCV-1 who were treated with PEG-IFN/RBV/TVR at the Sapporo Kosei General Hospital. All participants provided written informed consent according to the process approved by the hospital's ethical committee, and the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients were excluded if they had evidence of autoimmune hepatitis; alcoholic liver disease; congestive liver failure; hepatitis B virus infection; markers for human immunodeficiency virus; hepatocellular carcinoma or other malignancies; or hepatic decompensation, associated with jaundice, ascites, encephalopathy, or gastrointestinal bleeding. The patient characteristics are shown in Table 1.

All patients were treated with PEG-IFN-a-2b, RBV and TVR triple therapy. PEG-IFN-a-2b (MSD, Tokyo, Japan) was injected subcutaneously at a median dose of 1.5 µg/kg per week. TVR and RBV doses were adjusted according to guidelines for the treatment of hepatitis B and C, established in 2012 by the Japanese Ministry of Health, Labour

and Welfare [16]. Usually, 750 mg of TVR (Mitsubishi Tanabe Pharma, Tokyo, Japan) was administered orally every 8 h after meals. The dose of RBV (MSD) was adjusted according to the individual's body weight (600 mg for individuals weighing ≤60 kg; 800 mg for individuals weighing <60 to ≤80 kg; and 1000 mg for individuals weighing >80 kg) and was orally administered after breakfast and dinner. If the initial haemoglobin (Hb) level was <14 mg/dL in women, or <13 mg/dL in men, the RBV dose was reduced by 200 mg. Triple therapy with TVR was administered for 12 weeks, followed by an additional 12 weeks of PEG-IFN-a-2b and ribavirin therapy (combination therapy). If severe anaemia was present, the dosage of RBV, followed by that of TVR, was adjusted, as determined by the chief physician.

Hepatitis C virus genotype

Hepatitis C virus genotype was determined by analysis of the sequence in the NS5B region.

Hepatitis C virus RNA levels

Hepatitis C virus RNA levels were determined using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The linear dynamic range of the assay was 1.2–7.8 log₁₀ IU/mL.

Table 1 Characteristics of study patients in each telaprevir (TVR) dose

| | Total | 1500 mg/day | 2250 mg/day | <i>P</i> |
|--|-------------|-------------|-------------|----------|
| Number | 68 | 24 | 44 | |
| Sex (M/F) | 34/34 | 4/20 | 30/14 | <0.0001 |
| Age (years old) | 55.8 ± 10.5 | 59.6 ± 9.4 | 53.7 ± 10.6 | 0.0023 |
| Height (cm) | 161.4 ± 7.8 | 157.1 ± 6.8 | 163.8 ± 7.4 | 0.0023 |
| Weight (kg) | 62.1 ± 10.2 | 57.9 ± 9.0 | 64.5 ± 10.2 | 0.0090 |
| rs12979860 (CC/TC/TT) | 43/23/2 | 16/8/0 | 27/15/2 | 0.5186 |
| rs1127354 (CC/CA/AA) | 51/16/1 | 18/5/1 | 33/11/0 | 0.7695 |
| WBC (/mm ³) | 4663 ± 1271 | 4107 ± 1101 | 4934 ± 1288 | 0.0074 |
| Haemoglobin (g/dL) | 13.6 ± 1.2 | 12.9 ± 1.0 | 14.0 ± 1.1 | 0.0005 |
| Platelet (×10 ⁴ /mm ³) | 16.6 ± 4.6 | 15.8 ± 4.1 | 17.1 ± 4.8 | 0.3521 |
| ALT (IU/L) | 57.1 ± 47.4 | 51.3 ± 39.8 | 60.3 ± 51.3 | 0.2905 |
| GGTP (IU/L) | 52.1 ± 53.7 | 44.7 ± 44.9 | 56.1 ± 58.0 | 0.1902 |
| estimated glomerular filtration rate (mL/min/1.73 m ²) | 85.6 ± 15.2 | 81.5 ± 11.7 | 88.1 ± 16.4 | 0.1902 |
| Viral genotype (1b/others) | 68/0 | 24/0 | 44/0 | |
| Virus titre (log IU/mL) | 6.5 ± 0.6 | 6.2 ± 0.7 | 6.5 ± 0.7 | 0.2456 |
| Pegylated interferon (µg/kg) | 1.52 ± 0.11 | 1.54 ± 0.13 | 1.52 ± 0.10 | 0.5004 |
| TVR (mg/kg) | 32.5 ± 6.8 | 26.5 ± 3.9 | 35.8 ± 5.7 | <0.0001 |
| Ribavirin (RBV) (mg/day) (400/600/800/1000) | 19/19/27/3 | 14/9/1/0 | 5/10/26/3 | <0.0001 |
| RBV (mg/kg) | 10.2 ± 2.0 | 8.5 ± 1.2 | 11.2 ± 1.7 | <0.0001 |

Data are presented as mean ± SD.

Single-nucleotide polymorphism genotyping

We genotyped each patient for two single-nucleotide polymorphism (SNP)s: rs12979860, an IL28B (interleukin 28B) SNP previously reported to be associated with therapeutic outcome [17], and rs1127354, an inosine triphosphatase (ITPA) SNP reported to be associated with ribavirin-induced anaemia [18]. Samples were genotyped using the Illumina HumanHap610-Quad Genotyping BeadChip (Illumina, San Diego, CA, USA) or the Invader or TaqMan assay, as described previously [19,20].

Drug concentrations

Blood samples were collected immediately prior to the administration of TVR or RBV in the morning on days 8, 15 and 29. Serum concentrations of TVR were determined at day 8 (week 1) using a high-performance liquid chromatographic (HPLC) apparatus fitted with a mass spectrometer (LC-MS/MS) (Mitsubishi Chemical Medience Corporation, Tokyo, Japan), and the serum concentration of RBV was measured at day 8 (week 1), day 15 (week 2) and day 29 (week 4) by HPLC (SRL, Inc. Tokyo, Japan) using serum stored at -80°C .

Renal function

To assess the renal function, we used the estimated glomerular filtration rate (eGFR), which was calculated according to the equation $[194 \times (\text{Scr}^{-1.094}) \times (\text{age}^{-0.287}) \times (0.739 \text{ for women})] (\text{mL}/\text{min}/1.73 \text{ m}^2)$ serum creatinine (Scr)], as established by the Japanese Society of Nephrology in 2008 [21].

Statistical analysis

Continuous variables between groups were compared using the Mann–Whitney *U*-test, and categorical variables were compared using the Fisher's exact test. The correlation between the two groups was calculated using Spearman's rank correlation coefficient. Statistical analyses were performed using the statistical software SAS version 9.1 (SAS Institute Inc., Cary, NC, USA); a *P* value of <0.05 was considered significant.

RESULTS

Telaprevir dose and patient background

The TVR dose was administered according to initial Hb level and gender. The dose per weight of TVR and RBV was significantly higher in the patients receiving the 2250-mg TVR dose; however, the dose per weight of PEG did not differ according to the TVR dose. With regard to background factors, an increased age, higher proportion of

women, decreased height and weight, lower white blood cell count and lower levels of Hb and eGFR were noted in the 1500-mg TVR dose group (Table 1).

Telaprevir serum concentration

The TVR serum concentration (trough value) at day 8 (week 1) of triple therapy was measured in 65 of 68 cases. The TVR concentration varied widely (1076–4598 ng/mL). The mean TVR serum concentration of patients receiving the 2250-mg TVR dose was higher than that of patients receiving the 1500-mg TVR dose (2739 ± 833 ng/mL vs 2361 ± 838 ng/mL, respectively); however, the difference was not statistically significant ($P = 0.075$). The patients' background factors were used as independent variables in the multiple regression analysis (Table 1), and the TVR serum concentration was estimated using the following formula: TVR concentration (ng/mL) = $56.2 \times \text{TVR (mg/kg)} - 37.6 \times \text{height (cm)} + 6878.4$ ($R^2 = 0.3500$, $P < 0.001$) (Fig. 1). In addition, the dose per weight of TVR (mg/kg) and the TVR serum concentration were significantly correlated ($r = 0.4795$, $P < 0.001$) (Fig. 2).

Correlation of telaprevir serum concentration, dose per weight of telaprevir (mg/kg) and decline in renal function

The patients' eGFR declined at an initial stage during triple therapy, and the decline continued for the duration of TVR treatment [baseline: 85.8, week 1: 69.6, week 2: 70.2, week 4: 69.2, week 8: 66.6, week 12: 72.5 (mL/min/1.73 m²)] (Figure S1). The total TVR serum concentration (trough value) at week 1 of the triple therapy was not correlated with the delta eGFR; however, the dose per body weight of TVR (mg/kg) was significantly correlated with delta eGFR at week 1 and week 4, but not at week 8 (Fig. 3).

Correlation of renal function and ribavirin serum concentration

There was no correlation between the dose per weight of RBV (mg/kg) and eGFR or delta eGFR at week 1 ($P = 0.6422$ and $P = 0.1152$, respectively). However, at week 1, there was a significant negative correlation between eGFR and RBV serum concentration, and a significant positive correlation between delta eGFR and RBV serum concentration ($r = -0.3694$, $P = 0.0025$; $r = 0.3189$, $P = 0.0096$, respectively) (Fig. 4). By multiple regression analysis, the serum concentration of RBV at week 1 was estimated using the formula: RBV concentration (ng/mL) = $413.5 \times \text{sex (male = 1, female = 2)} + 12.8 \times \text{age (years)} + 163.5 \times \text{RBV (mg/kg)} - 5.9 \times \text{eGFR (1 week)} - 1291.6$ ($R^2 = 0.4631$, $P < 0.001$) (Fig. 1). Thus, in addition to age, sex and the dose per weight of

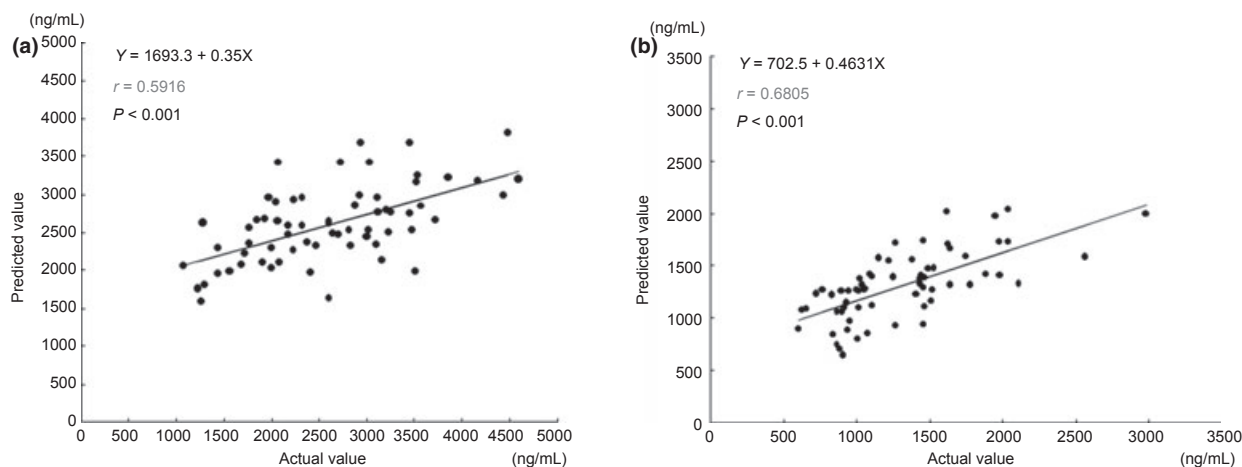


Fig. 1 (a) Correlation of TVR serum concentration actual value and predicted value. The actual TVR serum concentrations and predicted values, calculated by the formula derived from multiple regression analysis, are significantly correlated; (b) correlation of RBV serum concentration actual value and predicted value. The actual values of RBV serum concentration and the predicted values, calculated by the formula derived from multiple regression analysis, are significantly correlated.

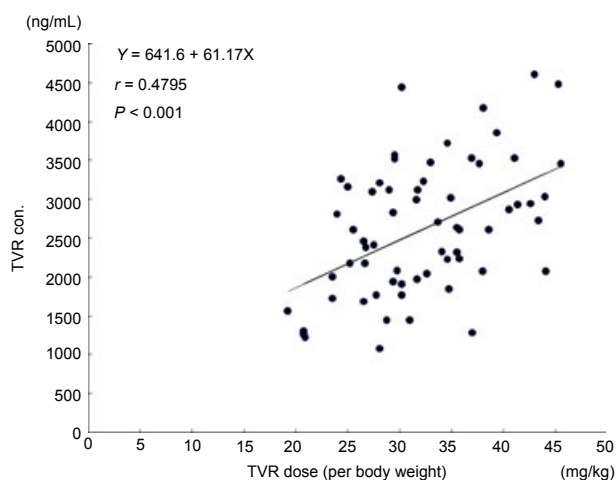


Fig. 2 Correlation of TVR serum concentration and quantity of TVR (mg/kg). The TVR serum concentration and dose per weight (mg/kg) are significantly correlated.

RBV (mg/kg), eGFR was also correlated with the RBV serum concentration.

Correlation of telaprevir, ribavirin serum concentration and haemoglobin level

The TVR serum concentration at week 1 was significantly negatively correlated with Hb levels at week 3, 6, 7 and 8 of treatment and was significantly positively correlated with the delta Hb level only at week 3 of treatment. The RBV serum concentration at week 1 showed a significant negative correlation with the Hb levels from week 2 to week 8 and a significant positive correlation with the delta Hb levels from week 1 to week 8. Moreover, the RBV

serum concentration at week 2 and week 4 showed a significant negative and positive correlation with the Hb levels and the delta Hb levels, respectively (Table S1).

DISCUSSION

As RBV is usually eliminated by renal filtration, the development of renal failure would result in the accumulation of RBV, particularly in red blood cells, and may induce haemolytic anaemia. Triple therapy that includes TVR has two well-known serious side effects: anaemia and dermatopathy. In addition to these side effects, a decline in renal function, which was noted in Japan after TVR was made commercially available, is now recognized as a significant problem; this decline in renal function was not noted with PEG-IFN and RBV combination therapy. Renal dysfunction has also recently been associated with boceprevir use [22,23]. The mechanism responsible for the decline in renal function caused by TVR remains unknown; however, the risk factors in Japanese patients include receiving a 2250-mg TVR dose, advanced age and low Hb levels at the start of the therapy.

The serum concentration of TVR reportedly reaches a steady state in 2–7 days of treatment [24,25]. In the present study, the trough serum concentration of TVR at day 8 of triple therapy was estimated through multiple regression analysis using the formula: $\text{TVR (ng/mL)} = 56.2 \times \text{TVR (mg/kg)} - 37.6 \times \text{height (cm)} + 6878.4$. The dose per weight of TVR (mg/kg) was the strongest determinant of the TVR serum concentration. The renal function impairment in patients treated with the TVR/PEG-IFN/RBV combination therapy was noted at an early stage in the treatment and persisted throughout the TVR treatment duration, but gradually improved after TVR treatment was

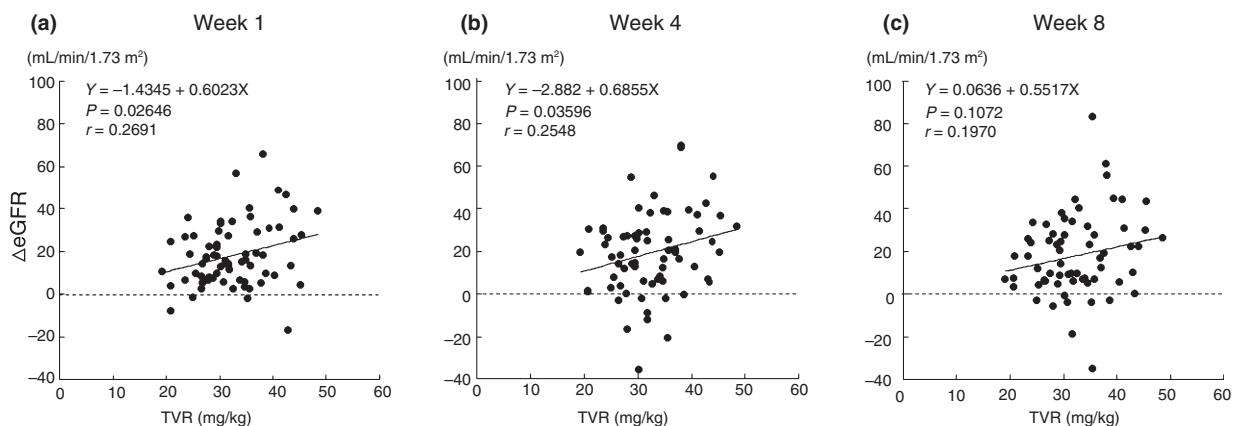


Fig. 3 Correlation between TVR (mg/kg) and delta eGFR. The dose per weight of TVR (mg/kg) is significantly correlated with the delta eGFR, indicating a decline in renal function from the baseline, at week 1 and week 4, but not at week 8 of triple therapy.

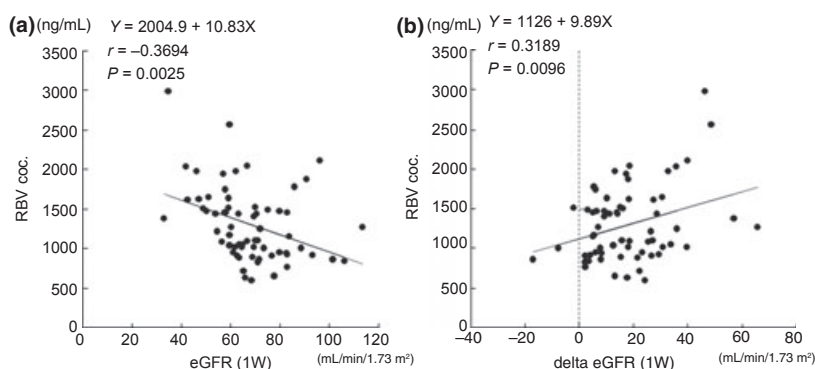


Fig. 4 Correlation between RBV concentration (Week 1) and eGFR (Week 1) and delta eGFR (Week 1). The eGFR at week 1 is negatively correlated with eGFR, whereas the serum RBV concentration at week 1 is positively correlated with delta eGFR.

discontinued. In patients receiving the TVR/PEG-IFN/RBV combination therapy, although the serum TVR concentration at week 1 was not significantly correlated with the decline in renal function during week 1, the dose per weight of TVR (mg/kg) showed a significant correlation with the decline in renal function during week 1. Thus, the degree of renal function impairment worsened with an increase in the dose per weight of TVR (mg/kg). Furthermore, because RBV is eliminated by renal filtration [15], it is expected that a decline in renal function will result in an increase in serum RBV concentration. In the present study, the serum concentration of RBV at week 1 showed a significant negative correlation with eGFR and significant positive correlation with delta eGFR. The RBV serum concentration was estimated through multiple regression analysis using the formula: RBV concentration (ng/mL) = $413.5 \times \text{sex}$ (male = 1, female = 2) + $12.8 \times \text{age}$ (years) + $163.5 \times \text{RBV}$ (mg/kg) - $5.9 \times \text{eGFR}$ (week 1) - 1291.6. In addition to sex, age and dose per weight of RBV, the eGFR at week 1 was a regulating factor for RBV serum concentration. After examining the relationships among TVR serum concentration, RBV serum concentration, and Hb level, the TVR serum concentration at week 1 was negatively corre-

lated with the Hb level at week 3, 6, 7 and 8 and was positively correlated with the delta Hb level at week 3. The RBV serum concentration was negatively correlated with the Hb level from week 2 to 8 and positively correlated with the delta Hb level from week 1 to 8. Similarly, the serum RBV concentration at weeks 2 and 4 was correlated with the Hb level and the delta Hb level, respectively.

In patients receiving TVR-containing triple therapy, the development of anaemia can lead to dose reduction or discontinuation of the drug. The administration of TVR or RBV alone can cause anaemia. However, the renal dysfunction caused by TVR can exacerbate this problem by increasing the serum concentration of RBV and thus increase the severity of haemolytic anaemia.

Because TVR was administered at a fixed dose of 2250 mg/day during the third phase of the clinical trial for TVR/PEG-IFN/RBV combination therapy in Japan, the dose per weight of TVR varied widely (25.7–55.3 mg/kg) [13]. Moreover, by multivariate analysis, we noted that the factor that contributed significantly to a decline in the Hb level to less than 8.5 g/dL – which necessitated the discontinuation of TVR/PEG-IFN/RBV combination therapy – was a relatively high dose per weight of TVR [26]. In the present

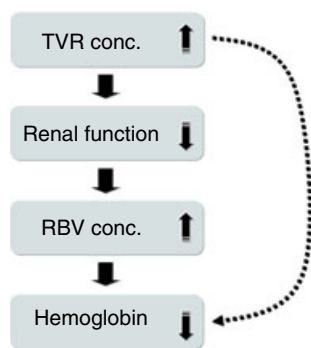


Fig. 5 Cascade reaction of RBV induced anaemia during triple therapy. In the triple therapy, as the TVR concentration increases, renal function (and consequent excretion of RBV) decreases; the RBV serum concentration increases, and the Hb level decreases. In addition, TVR has a mild direct hemolytic effect (interrupted arrow on the right), contributing to the decrease in Hb concentrations.

study, although the TVR dose was reduced to 1500 mg/day in a few female patients and in those with low baseline Hb level, the dose per weight of TVR varied widely (19.2–48.5 mg/kg). A decline in the eGFR at week 1 was related to the dose per weight of TVR, and the RBV serum concentration at week 1 was related to the decline in the eGFR at week 1; moreover, a higher RBV concentration at week 1 was related to a greater decline in Hb levels.

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In summary, we noted a certain sequence of events that can occur during anti-HCV treatment that includes TVR: (i) the starting dose of TVR, when not calculated on a per weight basis, may be high, (ii) TVR causes a reduction in renal function, with a reduction in the excretion of RBV, (iii) the blood concentration of RBV rises and (iv) the increased RBV concentration, in addition to the inherent tendency for TVR to lower Hb levels, leads to haemolytic anaemia (Fig. 5). The declining Hb levels may require discontinuation of the regimen or reduction in the anti-HCV drug doses and, consequently, may result in a reduced antiviral effect. For patients requiring TVR/PEG-IFN/RBV combination therapy, the interactions of TVR and RBV should be considered while determining the optimal doses of TVR and RBV.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Correlation between serum concentration of RBV or TVR and Hb,

as well as delta Hb levels. The reduction in the eGFR is evident as early as week 1 of therapy and persists for the duration of treatment.

Figure S1. The reduction in the eGFR is evident as early as week 1 of therapy and persists for the duration of treatment.