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Original article

Telaprevir is effective given every 12 hours at 750 mg with peginterferon-alfa-2b and ribavirin to Japanese patients with HCV-1b IL28B rs8099917 TT

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Abstract

Background: The aim of this study is to explore the efficacy, safety and pharmacokinetics of 750mg telaprevir (TVR) given at 8 or 12 hour intervals during triple therapy with peg-interferon-alfa-2b (PEG-IFN) and ribavirin (RBV) for patients with chronic hepatitis C virus (HCV) infection.

Methods: 52 patients with high viral loads of genotype 1b who were expected to respond well to therapy (rs8099917 TT genotype or relapse to previous therapy) were randomly assigned to two groups who were given 750mg TVR at either 8 or 12 hour intervals (q8h or q12h) in combination with PEG-IFN and RBV for 12 weeks, followed by an 12 additional weeks of treatment with PEG-IFN and RBV alone. The primary end point of the study was undetectable HCV RNA at 12 weeks after the end of treatment (SVR_{12}).

Results: SVR_{12} rates were 92.3% (24/26) for both q8h and q12h. The changes in mean log_{10} HCV RNA levels and viral response were also similar in q8h compared to q12h, whereas pharmacokinetic properties such as C_{max}, AUC0-24h and C_{trough} of TVR were slightly higher in q8h than in q12h (P>0.2). The frequency of TVR discontinuation due to anemia or renal damage was significantly higher in q12h than in q8h (6/26(23%) vs. 0/20, respectively; P=0.02).

Conclusions: TVR given at 12 hour intervals should be considered for patients with lower body weight, especially patients with prior relapse and with IL28B polymorphisms at rs8099917 TT (interferon lambda 4 ss469415590 polymorphism TT/TT) genotype in patients with genotype 1b HCV infection.

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Running head: Trial of 750 mg of telaprevir given at 8 versus 12 hour intervals

Introduction

There are estimated to be 170 million hepatitis C virus (HCV) carriers worldwide [1,2]. About 30% of carriers develop serious liver diseases, such as decompensated cirrhosis and hepatocellular carcinoma [3,4]. Eradication of the virus is necessary to prevent the development of severe liver damage in these patients.

Telaprevir (TVR), an HCV NS3/4A serine protease inhibitor, has recently been approved in the United States (US), Canada, the European Union (EU) and Japan for treatment of patients with chronic HCV genotype 1 infection. In Phase 3 studies, sustained viral response (SVR) rates increased significantly in both treatment-naïve as well as previously treated patients when TVR was administered in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) compared to PEG-IFN and RBV alone [5–7]. High SVR rates were also observed in Phase 3 studies in Japan [8,9]; however, side effects of triple therapy in the Japanese studies were so severe that many patients were forced to discontinue therapy due to adverse events, such as anemia and fatigue [5–9]. Anemia, in particular, is commonly associated with triple therapy. The frequency of anemia ranged from 15% to 19% [5,6] in patients treated with PEG-IFN and RBV alone, whereas in patients treated with triple therapy, the frequency of anemia increased to between 30% and 37% [5,6]. In addition, RBV dose-reduction rates and discontinuation rates of TVR treatment due to severe adverse events are higher in Japan than in the USA and EU [5–9]. The higher discontinuation rate may result from taking the same standard prescription dosage of TVR in spite of the lighter body weight of Japanese patients compared with patients in other countries. Japanese patients also tend to be relatively older, and may therefore be at greater risk of severe side effects due to poorer drug metabolism rates. The aim of this study is thus to compare effects and safety of triple therapy with TVR administered at 12 hour intervals compared with the standard 8 hour interval regimen. We also studied pharmacokinetics of TVR in both group of patients to see how the reduction of TVR affects the concentration of TVR.

Patients and Methods

Patients

We enrolled patients at Hiroshima University Hospital, Toranomon Hospital and Sapporo Kosei General Hospital. Patients were enrolled from August 2012, and the last patient completed follow-up in May 2013. Criteria for inclusion were age between 20 and 70 years, chronic infection with HCV genotype 1b, and plasma HCV RNA level of 100,000 IU per ml or greater. We selected patients who were expected to respond well to triple therapy based on one of the following criteria: 1) patients with the treatment-

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favorable rs8099917 TT genotype in the IFN lambda 3 (IL28B) locus, or 2) patients who experienced relapse during prior treatment with PEG-IFN and RBV combination therapy. In order to avoid poor response to reduction of TVR, we excluded patients who were expected to have poor response to the therapy, including prior non-responders to PEG-IFN and RBV therapy (i.e., patients who failed to become negative for HCV RNA) and patients with rs8099917 T/G or G/G genotypes. Exclusion criteria also included liver disease due to other causes, decompensated cirrhosis, presence of liver cancer, HBV or HIV infection, renal insufficiency, history of heart disease or cerebral infarction, and pregnancy or current breastfeeding. IL28B rs8099917, IFN lambda 4 (IFNL4) ss469415590 and inosine triphosphate pyrophosphatase (ITPA) polymorphism (rs1127354) were genotyped using the Invader assay, TaqMan assay or by direct sequencing, as described elsewhere [10–12]. Amino acid substitutions in the HCV core were determined using direct sequencing of polymerase chain reaction products after extraction and reverse transcription of HCV RNA. Core amino acid substitutions at positions 70 and 91 (core 70 and core 91, respectively) were determined as in Akuta et al [13,14]. The demographic and baseline characteristics of patients are shown in Table 1. Median body weight was 62.3 kg, and 25 patients (48%) had body weight lower than 60 kg. IFNL4 ss469415590 and IL28B rs8099917 genotypes were completely linked, except in one patient (Supplementary Table 1).

Study design and randomization

This was an exploratory, prospective, multicenter, randomized study. Experimental procedures were approved by the institutional review boards at participating hospitals, and informed consent was obtained from all participants. Sample size was not based on hypothesis testing other than the precision estimate of SVR. If we assume that 80%, 85%, and 90% of subjects will have undetectable HCV RNA 12 weeks after the end of therapy (SVR_{12}), then 25 subjects per arm would yield two-sided 95% confidence intervals of 64.3 to 95.7%, 71.0 to 99.0% and 78.0 to 100%, respectively. The study was conducted in accordance with the Declaration of Helsinki, and the trial was registered with UMIN Clinical Trials (UMIN000006758). Randomization was stratified according to the combination of prior treatment experience and amino acid substitution at HCV core amino acid 70 (treatment-naïve and wild type, naïve and mutant, transient response and wild, transient response and mutant, non-response and wild or non-response and mutant), age (<60 or ≧60), gender (male or female) and baseline Hb level (<13 or ≧13 g/dl). As shown in Table 1, the demographic and baseline characteristics were well balanced in the two groups of patients.

Mythos (Osaka, Japan), a third party institute that was not involved in the conduct of the study, randomly allocated the two groups of patients to different doses of TVR by means of computer-generated randomization codes.

Study procedures

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TVR was administrated at a randomized dose of 750mg after meals at q8h or q12h intervals. PEG-IFN alfa-2b (PegIntron; MSD, Tokyo, Japan) was administered subcutaneously at a dose of 1.5 μg per kilogram of body weight once weekly, and oral RBV (Rebetol; MSD) was administered at a total dose of 600 to 1200 mg per day based on body weight. Patients received 12 weeks of treatment with TVR plus PEG-IFN/RBV followed by PEG-IFN/RBV alone for an additional12 weeks. Follow-up observation was performed for 24 weeks. RBV dosage was reduced or discontinued as required, based on reduction of hemoglobin levels or the development of adverse events. When hemoglobin decreased below 10 g/dL, the daily dose of RBV was reduced from 600 to 400 mg, from 800 to 600 mg and from 1000 to 600 mg, depending on the initial dose of each patient. RBV was withdrawn when hemoglobin decreased below 8.5 g/dL. Decrease of TVR dose was not permitted, but administration was stopped if necessary due to the development of adverse events.

Efficacy assessments

Serum HCV RNA levels were measured using COBAS TaqMan HCV RNA 2.0 assay (Roche Diagnostics), with a lower limit of quantification of 25IU/ml and a lower limit of detection of 10 IU/ml. The lower limit of detection was used in the determination of undetectable HCV RNA at week 4. HCV RNA levels were measured on day 1 and at the following times: weeks 2, 4, 8, 12, 16, 20, and 24 and every 4 weeks until the end of treatment; and every 4 weeks after the end of treatment until 12 weeks after the end of treatment.

End points

The primary end point was the proportion of patients who had undetectable plasma HCV RNA 12 weeks after the end of treatment (SVR_{12}). The secondary end point was the rate of discontinuation of the therapy due to adverse events.

Pharmacokinetic assessments

Blood samples were collected immediately prior to administering the morning dose, and at week 2 at 1, 2.5, 4, 6, 8 and 12h after the first dose to determine the concentration of TVR (750mg q8h or 750mg q12h) in the plasma. Plasma concentrations of TVR were determined using a high-performance liquid chromatographic apparatus fitted with a mass spectrometer. AUC24h was calculated by multiplying AUC8h by 3 or AUC8h by 2. The maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}) were directly determined from the observed values at week 2. Ribavirin concentration was measured prior to the morning dose at week 2.

Safety assessments

Safety assessments including physical examinations, clinical laboratory tests and evaluation of adverse events were performed at each hospital visit during and after treatment at least every 4 weeks until 12 weeks after cessation of the therapy.

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Statistical analysis

Analysis was performed on the intention-to-treatment population, defined as all randomly assigned patients who received one dose of the study medication. Categorical variables between groups were compared using Fisher's exact test and continuous variables using the Mann-Whitney test. All analyses were performed using R version 2.15.3.

Results

Efficacy

SVR12 rates were 92.3% (24/26) for both q8h and q12h. The percentage of patients with undetectable HCV RNA at weeks 2, 4, 12, 24, end of treatment (EOT) and at 12 weeks after EOT (SVR12) was not statistically different between the two groups of patients (Supplementary Fig. 3). Similar decreases in mean log10 HCV RNA levels were observed in both groups of patients (Fig. 1). The SVR12 rate did not differ when the patients were divided by response to previous therapy, age, gender and platelet count (Supplementary Table 2). These results show that the anti-viral effect of triple therapy is nearly equivalent between the two patient groups.

Four patients did not achieve SVR_{12}.The patient characteristics (age [range], gender [male/female], viral load [range] and platelet count [range]) of four patients were 64 years [62-65], 3/1, 6.9 log IU/mL [5.8-7.2] and$17x10^4$/μL [12–22], respectively.

Pharmacokinetics

Mean pharmacokinetics parameters of TVR are shown in Table 2. Trough plasma concentration (C_{trough}) was slightly lower in the q12h group than in the q8h group. AUC24h was also slightly higher in the q8h group than in the q12h group. However, these differences were not statistically significant. The maximum plasma concentration (C_{max}) was similar in both groups of patients.

The mean (±SD) of ribavirin concentration (C_{trough}) at week 2 in the q8h and q12h groups was 1706 (±221) and 1562 (±222) ng/mL, respectively. Although the concentration was slightly higher in the q8h group than in the q12h group, the difference was not statistically significant (P=0.515).

Safety

There were no deaths or serious adverse effects. Adverse events with a frequency of more than 5% in total patients are listed in Table 3. The overall safety profile was similar in both groups of patients except for the frequency of renal damage. The ratios of discontinuation of all treatment due to adverse events were 12% (3/26) in the q8h group and 15% (4/26) in the q12h group (Supplementary Table 3a). Discontinuation of TVR occurred in 42.3% (11/26) of patients in the q8h group and 21.4% (6/28) of patients in the q12h group. Frequency of TVR discontinuation due to anemia or renal damage was

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significantly higher in q12h than in q8h (6/26(23%) vs. 0/20, respectively; P=0.02)(Supplementary Table 3b).

For anemia, decreases of mean hemoglobin levels were similar during the initial 6 weeks. Although mean hemoglobin levels continued to decrease in the q8h group, hemoglobin levels stopped decreasing in the q12h group after week 6 (Fig. 2a). Low hemoglobinemia (<8.5 g/dL) occurred in 8 patients (30.8%) in the q8h group and 6 patients (23.1%) in the q12h group. The genotype of the ITPA SNP had no significant effect on the frequency of anemia. In terms of renal damage, during the 12 weeks of the triple therapy, eGFR decreased significantly more in the q8h group than in the q12h group (Fig. 2b).

Adherence to pegylated IFN and ribavirin treatment was higher in the q12h group, although the difference was not statistically significant (Supplementary Table 4).

Discussion

With the introduction of TVR, the eradication rate of HCV has improved significantly [5–7]. However, severe adverse effects associated with TVR have also been reported, some or which occur more frequently in Japanese patients [8,9]. The dose of TVR for use in triple therapy was determined based on a dose-finding study conducted in the United States and Europe [15], which found that the q8h dosage regimen achieved the greatest reduction of HCV RNA. However, body weights of Japanese patients who were treated with TVR, peginterferon alfa-2b and ribavirin [9] were 61-63 kg compared to 79-91kg among American and European patients who were treated with boceprevir, peginterferon alfa-2b and ribavirin combination therapy [16]. As the dose of TVR is the same among countries where triple therapy is approved, we considered the possibility that the dose of TVR might be too high for smaller Japanese patients and could be reduced. Suzuki et al. previously reported that the anti-viral effect of triple therapy was similar when patients were given TVR at 1500mg/day (every 8 hours at 500mg) compared with those given at 2250mg/day (every 8 hours at 750mg) in the Japanese patients [17], suggesting that reduction of TVR might be possible. However, the treatment period of their study was only 12 weeks, and the study was a non-randomized controlled study with a small number of patients. Therefore, we conducted a randomized controlled trial to confirm that the dose reduction is as effective as the approved regimen. Therefore, we also attempted to test if TVR is as effective when administered at 12 hour intervals instead of 8 hour intervals, based on a pharmacokinetics study in which Marcellin et al. found no difference in viral response and safety profiles between patients treated with the triple therapy with TVR2250 mg (q12h) and TVR2250 mg (q8h) [18]. Furthermore, Buti et al. reported that the effectiveness and safety were similar between patients treated with triple therapy with 2250 mg TVR (q12h) and 2250 mg TVR (q8h) in the OPTIMIZE trial (Phase3b) [19].

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We showed in this study that the effect of TVR given every12 hours at 750mg with PEG-IFN alfa-2b and RBV is the same as TVR given every 8 hours among Japanese chronic hepatitis C patients. However, four patients failed to achieve SVR_{12}, and all treatment was discontinuation within four weeks in these patients. Safety profiles were similar except for differences in the frequency of anemia and renal damage. Hemoglobin levels continued to decline only in patients who received the larger 2,250mg dose, whereas hemoglobin levels plateaued by week 6 in patients who received the 1,500mg dose. We also found that the 1,500mg dosage was also accompanied with a lower frequency of renal damage (Fig. 2b). Incidence of TVR discontinuation was significantly less frequent in patients treated with the 1,500mg regimen. These results suggest that reduction of TVR to 1,500mg and administration of the drug every 12 hours is as effective as the approved 2,250mg dose and is less likely to result in premature termination of TVR therapy (Supplementary Table 3).

We assessed the effect of reduced TVR only in patients who relapsed under previous PEG-IFN/RBV therapy or had the IL28B SNP rs8099917 TT genotype that is associated with a good response to interferon therapy. Patients who had relapsed during previous PEG-IFN/RBV therapy have been reported to respond well to triple therapy [9]. The majority of patients with the rs8099917 TT genotype have also been reported to successfully eradicate the virus with triple therapy [20,21]. The effect of TVR reduction on patients who are expected to be difficult to treat should be further explored in a different trial.

Until recently it was unknown why SNPs near the IL28B locus, such as rs8099917 and rs12979860, are associated with the outcome of interferon therapy. However, the recent characterization of IFNL4 and its association with polymorphism ss469415590 (TT or ΔG) has shed light on this issue [22]. Genotype ss469415590 TT, which fails to express functional IFNL4, is associated with both eradication of HCV by peg-interferon plus ribavirin combination therapy as well as spontaneous clearance of the virus [22]. As this polymorphism is in strong linkage disequilibrium with rs8099917 and rs12979860 in Asian populations [22], it is assumed that in the majority of patients the IL28B and IFNL4 ss469415590 genotypes are in complete linkage disequilibrium, and in fact, there was only one patient who had a discrepancy between ss469415590 and rs8099917 genotypes (Supplementary Table 1). Taken together, patients with ss469415990 genotype TT/TT are expected to be successfully treated with the 1,500mg regimen.

Our results were obtained from Japanese patients with body weights between 61 and 63 kg in each group of patients (Table 1). Results obtained here should be confirmed in patients with a larger body weight. Alternatively, administration of TVR based on body weight should be considered in order to maintain high eradication rates while reducing the risk of adverse effects. However, it should be noted that the limitations of the study are the relatively small patient numbers and enrolling two main groups including prior relapsers and treatment-naïve patients with favorable INFL4 genotypes. A more comprehensive study is essential in the future.

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Disclosure statement

Kawakami Y., Suzuki F., Karino Y., Toyota J ., Kumada H. and Chayama K. are none to declare.

Figure Legends

Figure 1. Decrease of HCV RNA during the therapy.

Data are shown as mean (SD).

Figure 2a. Time course of hemoglobin levels during the triple therapy.

Change from base line hemoglobin concentrations are noted as mean (SD).

Figure 2b. Time course of eGFR levels from baseline during triple therapy.

Asterisks indicate statistically significant differences between patients treated with 1,500mg versus 2,250mg treated. *;P<0.05, **; P<0.01.

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Table 1. Baseline characteristics of patients

Characteristic	750mg q8h group (n=26)	750mg q12h group (n=26)	P-value
Male/Female	17/9	18/8	0.77
Age (years)	61 (24-68)	61 (37-70)	0.99
Body weight (kg)	61.4 (39-82)	63.3 (40-81)	0.76
Body mass index (kg/m^2)	23.5 (16.8-32.0)	22.5 (17.8-27.7)	0.61
White blood cell count ($/mm^3$)	4890 (3500-8920)	4995 (2970-11830)	0.67
Hemoglobin (g/dL)	14.2 (12.2-16.5)	15.2 (11.4-17.4)	0.17
Platelet count ($x\ 10^4/\mu L$)	15.9 (5.7-25.3)	16.9 (5.2-25.6)	0.74
ALT (IU/L)	36 (16-292)	40 (14-117)	0.62
γGTP (IU/L)	26 (13-125)	20 (10-192)	0.25
eGFR (mL/min)	80 (62-105)	80 (60-120)	0.61
HCV-RNA (log IU/mL)	6.8 (5.3-7.4)	6.9 (5.2-7.8)	0.26
Previous IFN therapy (naive/relapse/non-response)	14/9/3	11/11/4	0.42
rs8099917 (TT/TG)	25/1	26/0	0.32
ss469415590 (TT/TT/TT/ΔG)	24/2	26/0	0.49
rs1127354 (CC/non-CC/ND)	18/8	20/5/1	0.39
HCVcore70 (wild/mutant/ND)	17/6/3	20/4/2	0.67

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Table 2. Pharmacokinetic Parameters of Telaprevir at Week 2.

Pharmacokinetic parameter	750mg q8h group (n=10)	750mg q12h group(n=10)	P-value
C_{trough} (μ g/ml)	2.80±1.33	2.00±0.59	0.243
1hr(μ g/ml)	2.93±1.35	3.07±0.81	0.661
2.5hr(μ g/ml)	3.60±1.66	3.24±1.22	0.842
4hr(μ g/ml)	3.42±1.40	3.03±1.02	0.661
6hr(μ g/ml)	3.02±1.41	2.51±0.97	0.549
8hr(μ g/ml)	2.48±1.37	1.98±0.77	0.549
12hr(μ g/ml)	3.42±1.47	1.36±0.70	<0.001
C_{max} (μ g/ml)	3.90±1.50	3.74±0.99	0.720
AUC24h (μ g*h/ml)	74.91±32.91	57.16±18.12	0.243

All values are expressed as mean ± SD.
AUC24h calculated by multiplying AUC8h by 3 or AUC12h by 2.

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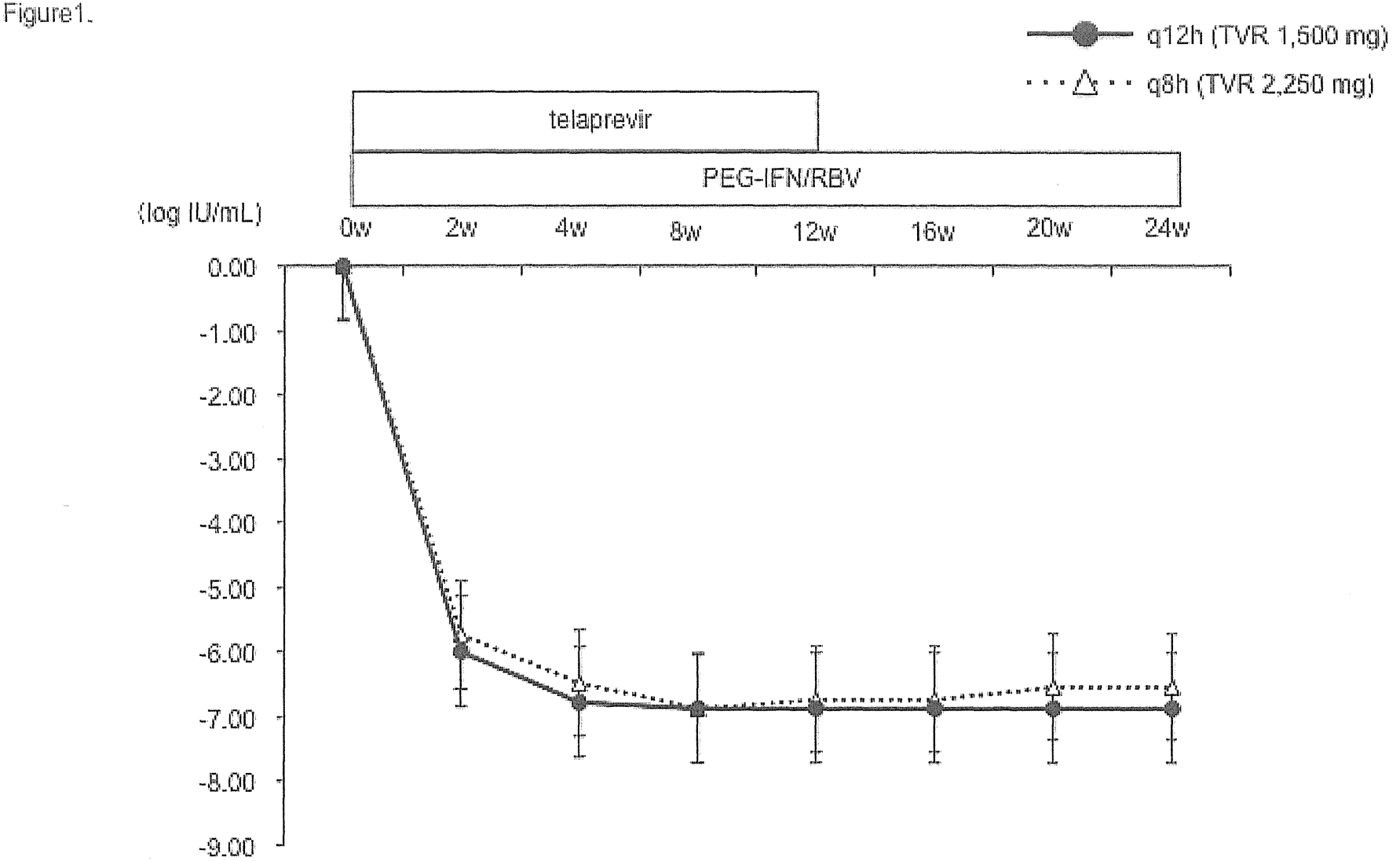
Table 3. Adverse events occurring in more than 5% of participants

	750mg q8h group (n=26)	750mg q12h group (n=26)	P value	All (n=52)
White blood cell count decreased	26(100)	26(100)	1.00	52(100)
Platelet count decreased	26(100)	26(100)	1.00	52(100)
Anemia	26(100)	26(100)	1.00	52(100)
Blood creatinine increased (eGFR decreased)	21(80.8)	12(46.2)	0.02	33(63.5)
Skin rash	11(42.3)	13(50)	0.59	24(46.2)
Blood uric acid increased	10(38.5)	6(23.1)	0.37	16(30.1)
Anorexia	4(15.4)	2(7.7)	0.67	6(11.5)
General fatigue	3(11.5)	1(3.8)	0.61	4(7.7)

Figure1.



Patients remaining on study

q12h (n)	26	24	24	22	22	22	22	22
q8h (n)	26	25	24	23	23	23	23	23

Figure2a.

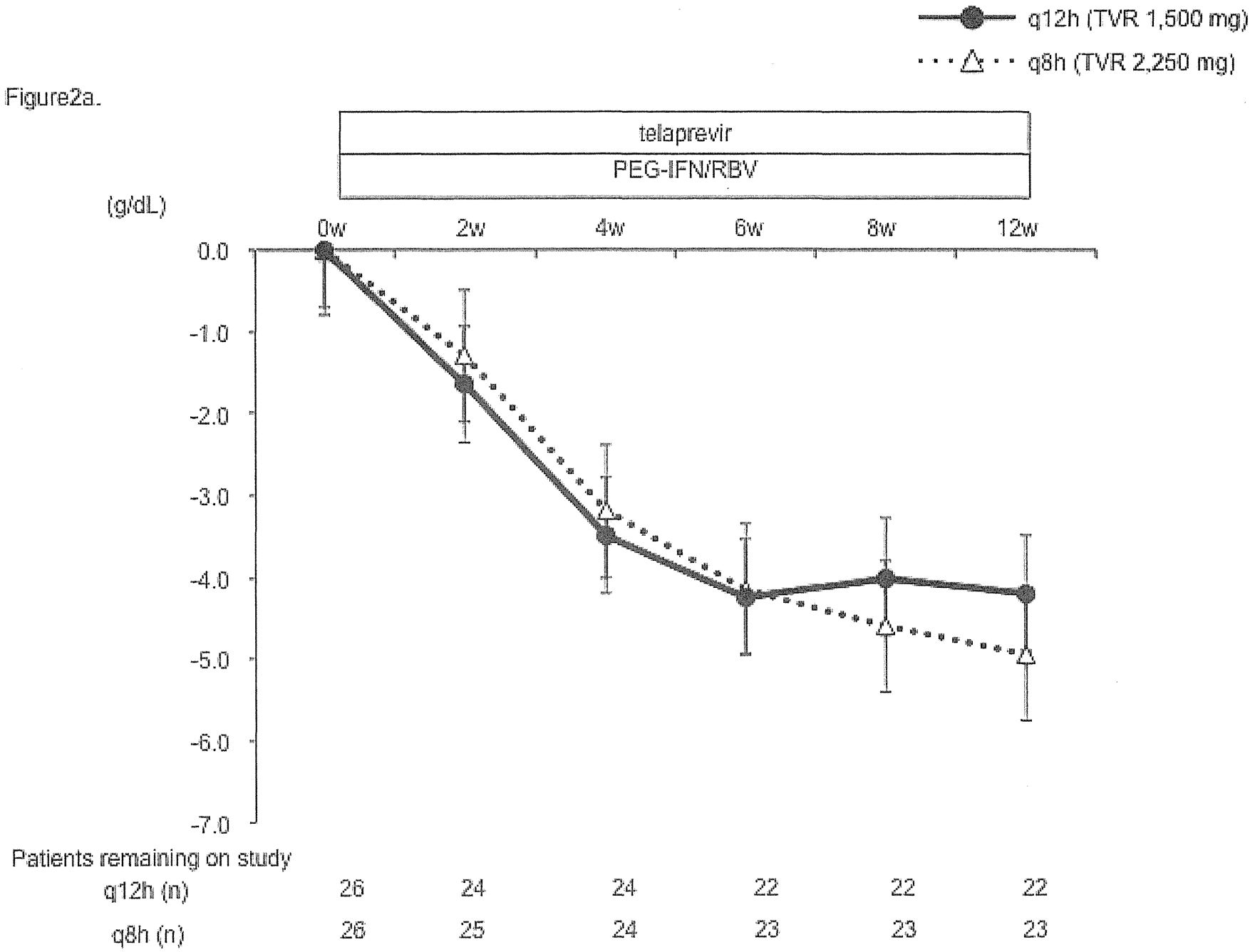
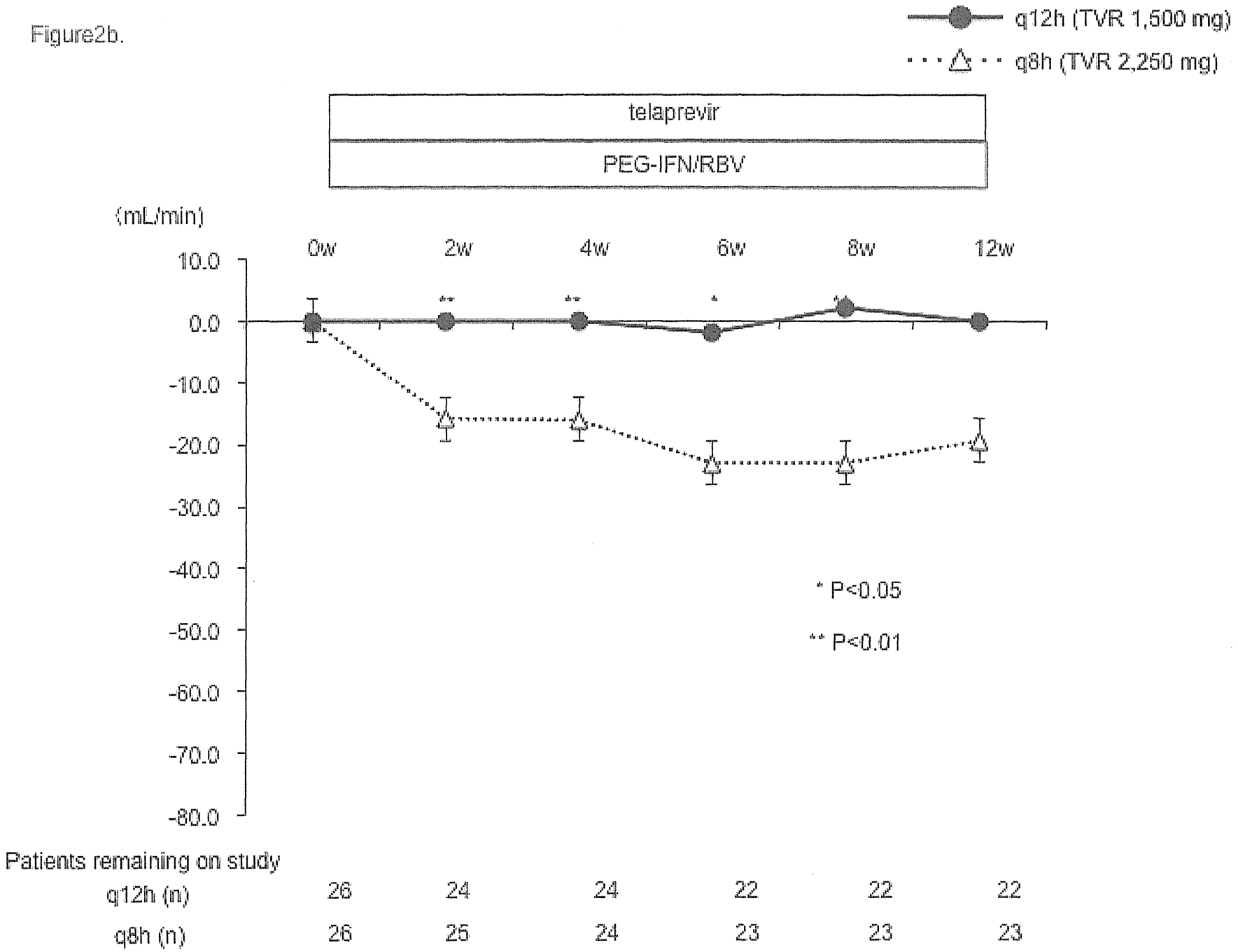

q12h (TVR 1,500 mg)
q8h (TVR 2,250 mg)
telaprevir
PEG-IFN/RBV
(g/dL)
0w
2w
4w
6w
8w
12w
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
Patients remaining on study
q12h (n) 26 24 24 22 22 22
q8h (n) 26 25 24 23 23 23

Figure2b.


q12h (TVR 1,500 mg)
q8h (TVR 2,250 mg)
telaprevir
PEG-IFN/RBV
(mL/min)
0w
2w
4w
6w
8w
12w
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-80.0
* P<0.05
** P<0.01
Patients remaining on study
q12h (n) 26 24 24 22 22 22
q8h (n) 26 25 24 23 23 23

Supplementary Figures

Supplementary Figure 1. Study design. Administration of drugs, randomization, and time points when PK study was performed are noted.

Supplementary Figure 2. Enrolment and outcomes. Patients who completed the 24 weeks therapy were classified as having completed treatment.

Supplementary Figure 3. Cumulative rate of undetectable HCV RNA in serum during treatment. Statistical analysis was performed on differences between 1,500mg and 2,250mg patients at 2 and 4 weeks from the start of the therapy and at the end of the observation period (SVR_{12}).

Supplementary Table 1. Comparison between IFNL3 (rs8099917) and IFNL4 (ss469415590) genotypes

	rs8099917				
ss469415590		TT	TG	GG	total
	TT/TT	50	0	0	50
	TT/ΔG	1	1	0	2
	ΔG/ΔG	0	0	0	0
	total	51	1	0	52

■discrepancy

	rs12979860				
ss469415590		CC	CT	TT	total
	TT/TT	50	0	0	50
	TT/ΔG	0	2	0	2
	ΔG/ΔG	0	0	0	0
	total	50	2	0	52

Supplementary Table 2. SVR rates stratified by response to previous therapy, age , gender and platelet count

	750mg q8h group (n=26)	750mg q12h group (n=26)	P-value
Previous IFN therapy −n/N (%)			
naïve	13/14 (92.9%)	9/11 (81.8%)	0.56
relapse	8/9(88.9%)	11/11 (100%)	0.45
non-response	3/3 (100%)	4/4 (100%)	1.00
Age −n/N (%)			
≤59	11/11 (100%)	11/11 (100%)	1.00
≥60	13/15 (86.7%)	13/15 (86.7%)	1.00
Gender −n/N (%)			
Male	16/17 (94.1%)	18/18 (100%)	0.49
Female	8/9(88.9%)	6/8(75%)	0.58
Platelet −n/N (%)			
10≤	21/23 (91.3%)	23/25 (92%)	1.00
>10	3/3 (100%)	1/1 (100%)	1.00

Supplementary Table 3. Adverse events leading to discontinuation of all treatment or TVR only.

(a)

All treatment discontinuation	750mg q8h group(n=26)	750mg q12h group (n=26)	P-value
anemia	2(7.7)	0(0)	0.49
renal damage (creatinine increase)	1(3.8)	0(0)	1.00
anemia or renal damage	3(11.5)	0(0)	0.10
skin rash	0(0)	1(3.8)	1.00
syncope	0(0)	1(3.8)	1.00
anorexia	0(0)	2(7.7)	0.49
total	3(11.5)	4(15.4)	0.17

(b)

TVR discontinuation	750mg q8h group (n=26)	750mg q12h group (n=26)	P-value

anemia	2(7.7)	0(0)	0.49
renal damage (creatinine increase)	4(15.4)	0(0)	0.11
anemia or renal damage	6(23.0)	0(0)	0.02
skin rash	0(0)	1(3.8)	1.00
syncope	0(0)	1(3.8)	1.00
pneumonia	1(3.8)	0(0)	1.00
anorexia	4(15.4)	4(15.4)	1.00
total	11(42.3)	6(23.1)	0.14