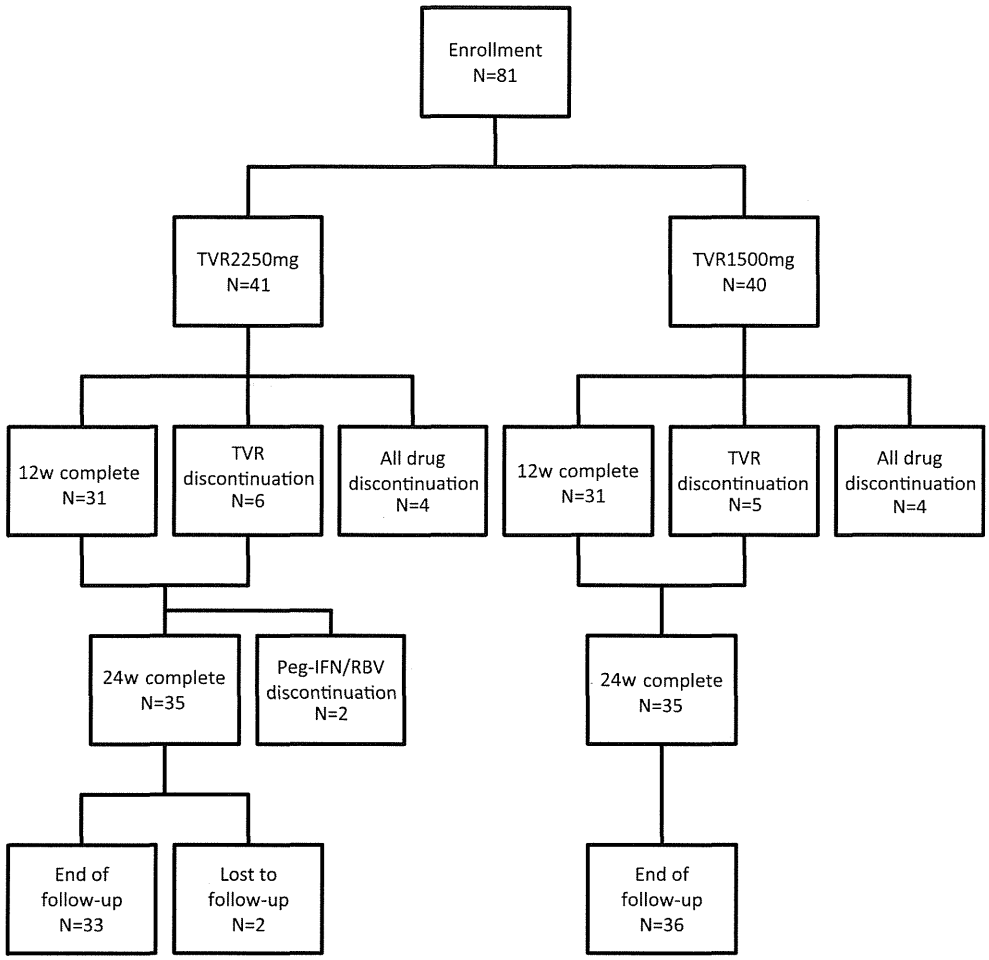

Fig. 1 The patients flow of this study. The patients lost to follow-up were determined as non-SVR

<8.5 g/dl of Hb, affected 39 % of the TVR-2250 patients and 8 % of the TVR-1500 patients. The cumulative occurrence of severe anemia was significantly higher in the TVR-2250 group than in the TVR-1500 group ($p = 0.001$, Fig. 4b). The mean minimum Hb was significantly lower in the TVR-2250 group than in the TVR-1500 group (8.7 ± 1.4 vs. 10.1 ± 1.4 g/dl, $p < 0.001$). As for renal dysfunction, the mean serum creatinine levels were higher (Fig. 5a) and the mean estimated glomerular filtration rates (eGFR) were lower in the TVR-2250 group than in the TVR-1500 group during weeks 1–4 (Fig. 5d). A stratified analysis by age clearly shows that these abnormalities of the serum creatinine levels and eGFR were more marked in older patients (≥60 years old) than younger patients (<60 years old) (Fig. 5b, c, e, f).

Discussion

The dose of TVR in triple therapy, a regimen of 750 mg of TVR every 8 h (total 2250 mg/day) was selected all over the world. However, since Western people weigh more than Asian people including Japanese (BMI in phase 3 trials, 26–27 kg/m^2 in Western countries, 22–23 kg/m^2 in Japan) [5–9], the lighter-build Japanese patients may receive an excess of TVR. Therefore, we conducted the first randomized, multicenter study to evaluate the antiviral efficacy and safety after administration of TVR at 750 mg or 500 mg every 8 h with Peg-IFN alfa-2b and RBV.

As for antiviral effect, the HCV RNA reduction for the first 4 weeks of treatment was almost the same in the TVR-2250 group and the TVR-1500 group. Moreover, in stratified analysis for the effect of previous IFN treatment, the SVR rates were almost the same in both TVR groups among the naïve patients and relapsers. The SVR rates in patients with non-response were 100 % (5/5) in the TVR-2250 group and 75 % (6/8) in the TVR-1500 group. In triple therapy with TVR, Peg-IFN and RBV, it has been clearly shown from the phase 3 REALIZE study that the SVR rates were higher in partial-responders than in null-responders [7]. Among the patients with non-response in this study, 4 partial-responders were included in the TVR-

Table 1 Baseline characteristics of patients

Factor	TVR-2250	TVR-1500	*p* value
Number	41	40	
Age (years old)	60.1 ± 8.7	61.0 ± 8.8	0.50
Gender (male/female)	23/18	23/17	1.00
Body weight (kg)	*60.6 ± 11.3*	*60.4 ± 11.2*	*0.98*
BMI (kg/m^2)	*23.0 ± 3.4*	*22.9 ± 3.2*	*0.81*
Past history of IFN: naïve/relapse/non-response	15/20/5	15/17/8	0.63
HCV RNA (median, $\log_{10}$ IU/ml)	6.9	6.8	0.87
Liver histology[a]: activity: A0/1/2/3	0/22/6/0	0/21/4/0	0.73
Liver histology[a]: fibrosis: F0/1/2/3/4	1/12/8/5/2	2/9/9/4/1	0.89
White blood cell (/μl)	4943 ± 1266	4980 ± 1499	0.79
Neutrophils (/μl)	2578 ± 919	2559 ± 1131	0.85
Red blood cell (×10^4/μl)	451 ± 53	447 ± 65	0.65
Hemoglobin (g/dl)	14.5 ± 1.4	14.3 ± 1.2	0.46
Platelets (×10^4/μl)	16.5 ± 4.4	17.3 ± 5.7	0.84
AST (IU/l)	55 ± 68	42 ± 26	0.16
ALT (IU/l)	63 ± 87	50 ± 39	0.15
Serum creatinine (mg/dl)	0.74 ± 0.19	0.72 ± 0.17	0.36
Uric acid (mg/dl)	5.5 ± 1.4	5.5 ± 1.4	0.70
Estimated glomerular filtration rate (ml/min)	75.4 ± 15.8	77.9 ± 14.6	0.36
IL28B SNP (rs8099917): TT/TG/GG	19/4/1	18/6/0	0.49
TVR dose (mg/kg/day)	38.4 ± 7.3	25.7 ± 5.0	<0.001
Peg-IFN dose (μg/kg/week)	1.49 ± 0.12	1.47 ± 0.13	0.44
RBV dose (mg/kg/day)	11.3 ± 1.5	11.5 ± 1.7	0.63

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *IL28B SNP* interleukin 28 B single nucleotide polymorphism, *TVR* telaprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin

[a] METAVIR

2250 group and 3 partial-responders and all of the 4 null-responders were included in the TVR-1500 group; the SVR rates were 100 % (7/7) among all partial-responders and 50 % (2/4) among the null-responders in the TVR-1500 group. Thus, the administration of TVR at 1500 mg/day is considered appropriate for naïve patients and relapsers, although further analysis is needed for the patients with non-response. This is supported by the report that the antiviral effect was almost the same in both groups of TVR at 750 mg every 8 or 12 h with Peg-IFN alfa-2b and RBV Japanese patients with IL28B rs8099917 TT or relapse to previous IFN therapy [15].

Regarding safety, the rates of discontinuation of all drugs and the rates of discontinuation of TVR were almost the same in both groups. These discontinuations resulted from adjustment such as drug reduction or interruption of TVR, Peg-IFN and RBV during treatment by a physician in patients in the TVR-2250 group. Indeed, the two-thirds of patients decreased or discontinued TVR and the three-fourths of patients reduced or discontinued Peg-IFN in the TVR-2250 group. However, when adverse effects occurred early in treatment, missing the opportunity to reduce the drug dose might lead to serious adverse effects. Regarding serious adverse effects, the cumulative occurrence of rash more than grade 2 and severe anemia more than grade 3 was significantly lower in the TVR-1500 group. Rash more than grade 2 occurred in 30 % at week 1 and 35 % at week 2 in the TVR-2250 group compared with 8 and 8 % in the TVR-1500 group. Although the differences in occurrence of severe anemia were marked after 6 weeks of treatment, the decreases of Hb from baseline were significantly greater in the TVR-2250 group than in the TVR-1500 group at 4 weeks of treatment. Moreover, two patients developed rash more than grade 3 and discontinued treatment (day 10, day 30), and both of them were in the TVR-

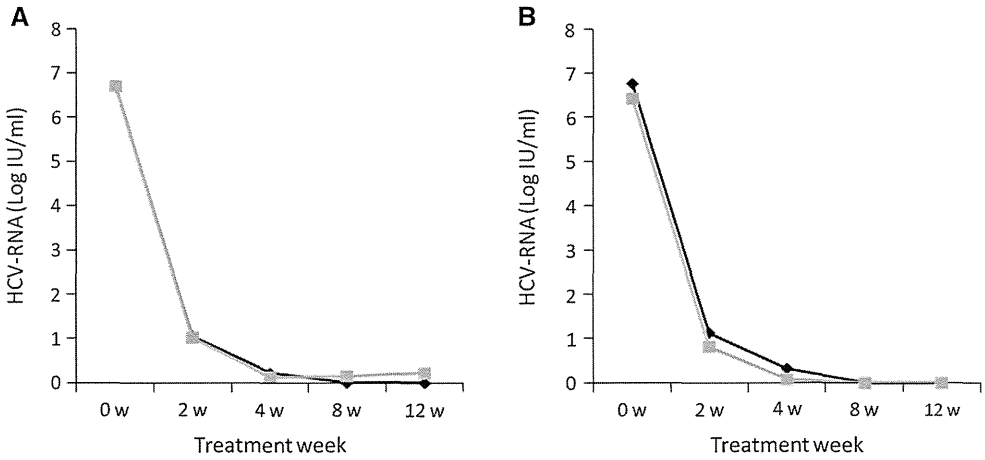

Fig. 2 The mean HCV RNA level. **a** The mean HCV RNA level among all patients. **b** The mean HCV RNA level among naïve patients. *Black line* TVR-2250 group. *Gray line* TVR-1500 group

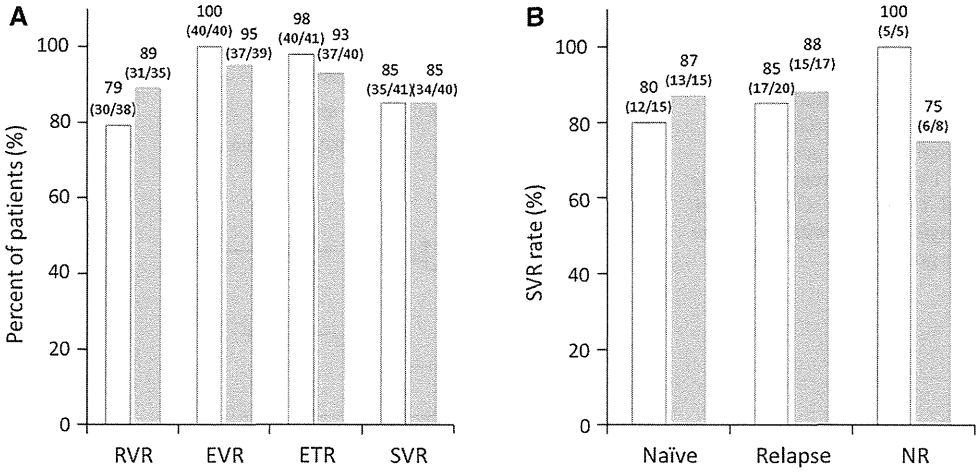

Fig. 3 The longitudinal HCV RNA negative rate and SVR rate. **a** The RVR, cEVR, ETR and SVR rates among all patients. **b** The SVR rates according to IFN history. *White bar* TVR-2250 group. *Gray bar* TVR-1500 group

Table 2 Dose reduction and discontinuation of TVR, Peg-IFN and RBV

	TVR		Peg-IFN		RBV	
	TVR 2250	TVR 1500	TVR 2250	TVR 1500	TVR 2250	TVR 1500
Completed treatment without dose reduction (%)	13 (32)	27* (68)	10 (24)	19** (48)	3 (7)	5 (13)
Completed treatment with dose reduction or temporally discontinuation (%)	18 (44)	4 (9)	25 (61)	17 (42)	32 (78)	31 (78)
Discontinuation (%)	10 (24)	9 (23)	6 (15)	4 (10)	6 (15)	4 (10)
Total dose (median)	162.8 g	125.3 g†	1840 μg	1850 μg	64 g	73 g

TVR telaprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin

* $p = 0.001$, TVR, Completed treatment without dose reduction, TVR-2250 group vs. TVR-1500 group

** $p = 0.03$, Peg-IFN, Completed treatment without dose reduction, TVR-2250 group vs. TVR-1500 group

† $p \leq 0.001$, TVR-2250 group vs. TVR-1500 group

2250 group. As for renal dysfunction, the serum creatinine levels were significantly lower and the eGFRs were significantly higher in the TVR-1500 group than the TVR-2250 group at the early treatment phase (weeks 1–4) (at week 4: serum creatinine, 0.80 ± 0.16 vs. 0.97 ± 0.26 mg/dl; eGFR, 69.3 ± 13.1 vs. 55.8 ± 13.2 ml/min). The tendencies were apparent among the older patients with inherently poor renal function. It was reported that C_{trough} tended to be higher in the 750-mg dose group than in the 500-mg dose group after treatment week 1 from phase 1 study in Japan comparing the two groups of TVR at 500 or 750 mg every 8 h with Peg-IFN alfa-2b and RBV (day 14, 2.64 ± 0.56 vs. 1.91 ± 0.72 μg/ml, day 85, 2.68 ± 0.36 vs. 2.11 ± 0.82 μg/ml) [13]. When TVR was given at 2250 mg/day, the high concentration of TVR at early treatment phase was thought to cause the adverse effects at early treatment phase. Thus, avoidance of such serious adverse effects at the early treatment phase by the reduced administration of TVR at 1500 mg/day can lead to an improved SVR rate among older patients with high risk of HCC and low tolerance for antiviral treatment.

We examined the efficacy and safety according to median of total dose of each drugs in both the TVR-2250 mg group and the TVR-1500 mg group (Supplemental table). Roughly, the SVR rates were higher in the higher total-dose group of each drug than in the lower total-dose group of each drug. On the other hand, the discontinuation rates of all drugs and the discontinuation rates of TVR were higher in the lower total-dose group of each drug than in the higher total-dose group of each drug. These results were thought to reflect that the lower total-dose group included many patients who could not attain SVR because of incompletion of the entire schedule of treatment.

At present, triple therapy is available as simeprevir (SMV) (a second-generation PI), Peg-IFN and RBV [16–18]. The SVR rate among the naïve patients and relapsers was almost 90 %, and the adverse effects profile was generally similar across the SMV and placebo control groups of Peg-IFN and RBV with the exception of mild reversible hyperbilirubinemia, without serum aminotransferase abnormalities. Therefore, triple therapy with SMV,

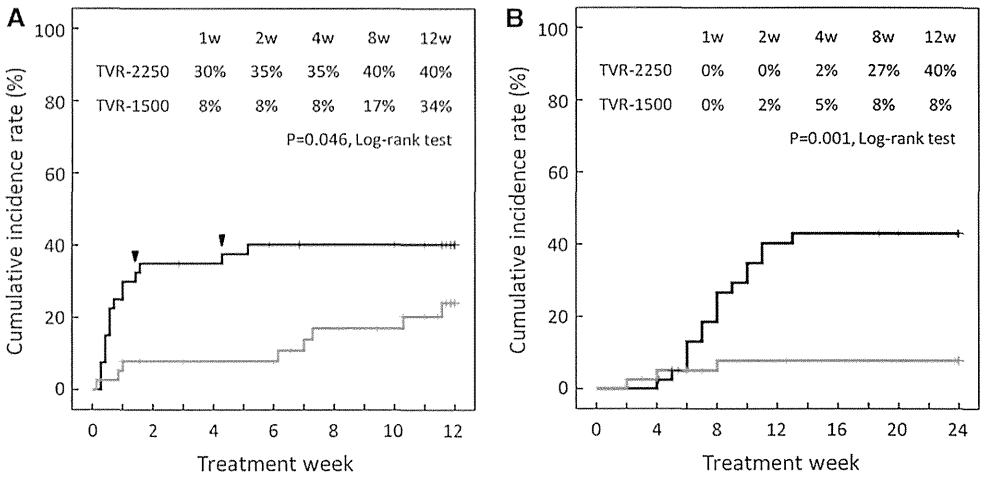

Fig. 4 Cumulative occurrence of rash more than moderate and severe anemia. **a** Rash more than moderate (Grade 2). **b** Severe anemia (Grade 3, hemoglobin <8.5 g/dl). *Black line* TVR-2250 group. *Gray line* TVR-1500 group. *Closed down triangle* patients with rash more than grade 3

Peg-IFN and RBV is recommended as first-line therapy for the naïve patients and relapsers. However, the SVR rate was insufficient at 34 % among the patients with non-response in Japan [9] and at 38–59 % among the patients with null-response in Europe [18]. Triple therapy with 1500 mg/day of TVR, Peg-IFN and RBV for the patents with non-response may allow for more treatment options, although the patients with non-response were too small to conclude the relationship between TVR dose and SVR rate in this study. Indeed, the treatment guideline from the Japanese Society of Hepatology recommends triple therapy with 1500 mg/day of TVR as well as triple therapy with SMV as a therapeutic option for the patients with non-response. Further analysis using a larger-cohort is needed to clarify the effect of 1500 mg/day of TVR in the patients with non-response.

The limitations of this study are described below. In order to prove non-inferiority of 1500 mg of TVR compared to 2250 mg of TVR for SVR, 123 patients in both group (total 246 patients) were required (expected SVR rate, 70 % in 2250 mg of TVR, 75 % in 1500 mg of TVR, $\alpha = 0.025$, $\Delta = 0.10$, power = 0.8). In the present study, we reported the preliminary results of the antiviral effect and the adverse effect among the TVR-2250 group and the TVR-1500 group. The non-inferiority of 1500 mg of TVR compared to 2250 mg of TVR for SVR could not be revealed because the number of cases enrolled in this study was too small. Second, in this randomized study, the naïve, relapse and non-response to previous treatment patients were divided into two groups without bias. However, among non-responders, the distribution of patients with null-response was to some extent idiosyncratic. Patients with null-response were too small in number to examine the antiviral efficacy of 1500 mg/day of TVR. A larger-cohort study should be conducted to clarify this. Third, a genetic polymorphism near the IL28B gene has been reported to be associated with SVR in triple therapy with TVR, Peg-IFN and RBV [19]. In this study, although the IL28B genotype was examined in approximately 60 % of patients, we could not obtain patients' consent for examination of IL28 SNP, which is information about the human genome in the remaining 40 % of patients. However, we tried to examine more closely the relationship between the IL28B genotype and the SVR rates in the cases in whom the IL28B genotype was obtained. According to IL28B single nucleotide polymorphism, the SVR rate was 95 % (18/19) in the TVR-2250 group and 83 % (15/18) in the TVR-1500 group among the patients with rs8099917 TT ($p = 0.34$). The patients with rs8099917 non-TT had small counts (5 cases with 80 % of SVR in the TVR-2250 group and 6 cases with 100 % of SVR in TVR-1500 group). As for the SVR rates according to the previous IFN treatment response and IL28B genotype, there were no significant difference between the TVR-2250 mg group and the TVR-1500 mg group among the same category of previous IFN treatment response and IL28B genotype (SVR rates of TVR-2250 mg group and TVR-1500 mg group, naïve patients with TT, 100 % (7/7) vs, 83 % (5/6), $p = 0.46$, naïve patients with non-TT, no patients vs. 100 % (2.2); relapser with TT, 89 % (8/9) vs, 88 % (8/9), $p = 1.00$, relapser with non-TT, 67 % (2/3) vs. 100 % (3/3), $p = 1.00$; NR patients with TT, 100 % (3/3) vs. 67 % (2/3), $p = 1.00$, NR patients with non-TT, 100 % (1/1) vs. 100 % (1/1), $p = 1.00$). Further analysis using a larger-cohort is needed to clarify the effect of IL28B status on the TVR-1500 group. Fourth, the concentration of TVR should be measured in order to examine the antiviral effect more closely. However, the concentrations of TVR measured, because the patients' serum, was not preserved in this study. This problem is also subject of future investigation.

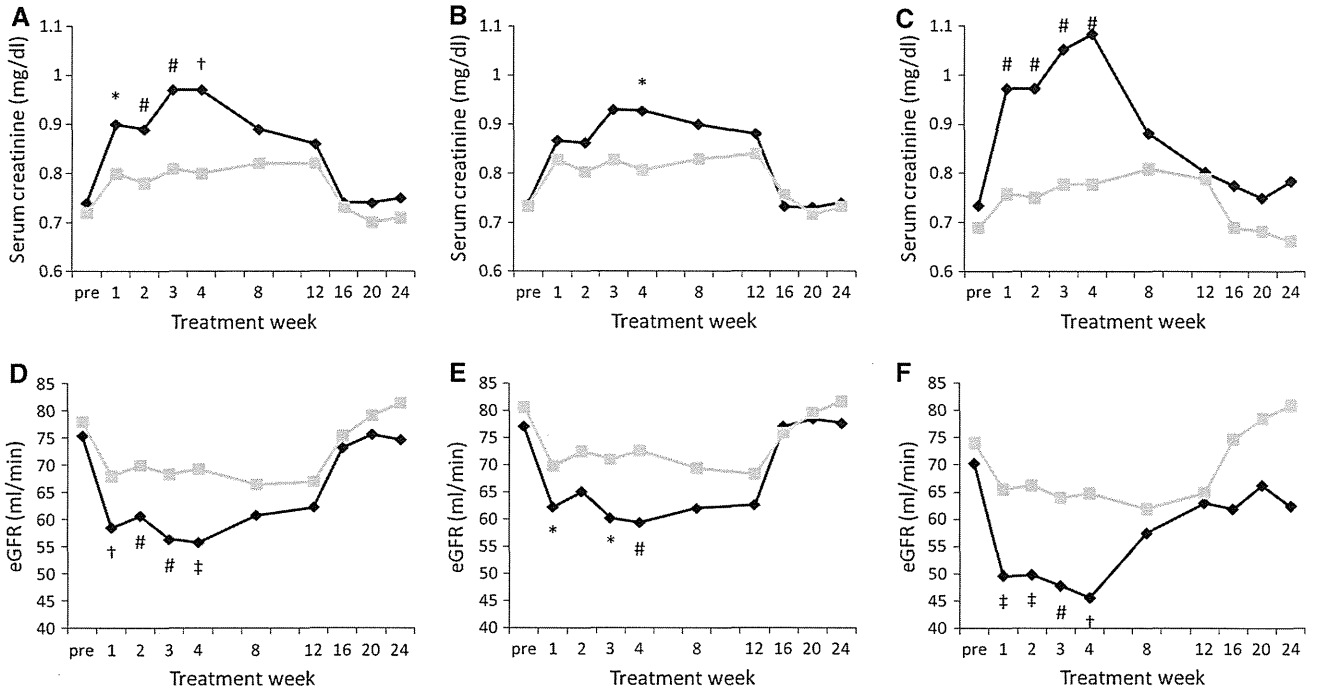

Fig. 5 The mean serum creatinine level and estimated glomerular filtration rates during the treatment. **a–c** The mean serum creatinine level during the treatment. **d–f** The mean estimated glomerular filtration rates during the treatment. **a**, **d** All patients. **b**, **e** Patients <60 years old **c**, **f** Patients ≥60 years old *Black line* TVR-2250 group. *Gray line* TVR-1500 group. $^{*}p < 0.05$, $^{\#}p < 0.01$, $^{\#}p = 0.001$, $^{\ddagger}p < 0.001$; TVR-2250 group vs. TVR-1500 group

In conclusion, the administration of a lower dose of TVR (1500 mg/day) can result in similar efficacy and fewer treatment-related adverse effects compared to the higher dose of TVR (2250 mg/day) in triple therapy with TVR, Peg-IFN and RBV.

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HEPATOLOGY PRACTICE VOL.3

C型肝炎の診療を極める

基本から最前線まで

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常任編集
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C型肝炎の現在と未来がわかる!

文光堂

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Ⅳ．C型肝炎を理解するための最前線研究のトピックス

付録

9 データマイニングによる予後・治療反応予測

要点

- データマイニングとはデータを網羅的に解析する技術であり，なかでも決定木解析は医師の臨床的思考形態に類似したフローチャート形式の予測モデルを作成する解析法である．
- 予測モデルのフローチャートに個々の症例のデータを当てはめるだけで，簡単に臨床で活用できる．
- 年齢，血小板数，アルブミン値，AST値の組み合わせで，5年以内の発癌率が20.9%の高リスク症例と0%の低リスク症例を判別できる．
- AFP値と血小板数の組み合わせで，3年以内の発癌率が7.2%の高リスク症例と1%未満の低リスク症例を判別できる．
- 年齢，AFP値，血小板数，γ-GTP値，性別の組み合わせで，ペグインターフェロン・リバビリンの2剤併用療法でSVRが得られる確率が77%の症例と22%の難治症例を判別できる．
- 宿主遺伝子*IL28B*とウイルス遺伝子ISDRを加えることで，SVRの予測精度は向上し，SVRが得られる確率が90%の症例と7%の難治症例を判別できる．
- 年齢と総リバビリン投与量の組み合わせで，治療終了後のHCV RNA再燃リスクを評価できる．目標とすべきリバビリン投与量は体重当たり3.0g以上である．
- 72週間の延長治療のメリットがある症例は，46.5~58.5歳以上，コレステロール値211.5mg/dL未満の女性である．

はじめに

C型肝炎ウイルス（hepatitis C virus：HCV）に対する標準治療法は，直接HCV阻害薬（DAA）の登場により，DAA・ペグインターフェロン・リバビリンの3剤併用療法あるいは経口薬のみのDAA併用療法に移行していく．その先陣を切って保険収載されたテラプレビル・ペグインターフェロン・リバビリンの3剤併用療法は，すでに広く使用されており，高い有効性が報告されている．その一方で，貧血，重篤な皮疹，腎障害などの副作用もあり，線維化進行例や高齢者では同3剤併用療法が施行できない症例もあり，依然としてインターフェロン・リバビリンの2剤併用療法は治療の選択肢の一つである．

難治性のgenotype 1型，高ウイルス量における2剤併用療法のウイルス学的著効（sustained virological response：SVR）率は約50%であり，高齢者や女性ではSVR率が低い[1,2]．しかしながら60歳以上の高齢女性でもSVRとなる症例は20~30%存在し，また逆に若年男性でも非SVRとなる症例が約30~40%存在するため，治療効果と関連するウイルス因子[3,4]，宿主因子[5~7]と臨床データを組み合わせてSVRが高率に期待できる症例を治療開始前に同定する工夫が必要である．