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

B typeⅢインターフェロン

要点

- type Ⅲインターフェロン(IFN)はIFNλ受容体に結合したのち，type Ⅰ IFNと同様にシグナル伝達系を介して抗ウイルス効果を得る．
- type Ⅲ IFNは肝細胞に高発現し，造血細胞などの発現が少ないため，type Ⅰ IFNと比較し，副作用が少なく，安全に治療に用いることができる可能性がある．
- Genotype 1bのC型慢性肝炎患者に対するPEG-IFNλ1治療では全例で抗ウイルス効果を示し，副作用は少なかった．
- Genotype 1のC型慢性肝炎患者におけるPEG-IFNλ1/リバビリンおよびダクラスタビルまたはアスナプレビル併用試験では治療中止となった1例を除き，全例でSVR12を達成した．

はじめに

近年，これまでのtype Ⅰ IFN(α/βなど)やtype Ⅱ IFN(γ)に加えて，type Ⅲ IFNが同定された．type Ⅲ IFNはIFNλ1(IL-29)，IFNλ2/3(IL28A/B)からなる[1,2]．また近年，C型肝炎ウイルスの自然排除やPEG-IFNα/リバビリン併用療法の治療効果を規定する因子に*IL28B*遺伝子近傍の遺伝子多型の関連性が報告された[3]．このためC型慢性肝炎治療においてtype Ⅲ IFNの抗ウイルス効果の重要性や治療応用が注目され，さまざまな研究が報告されている．

Ⅰ type Ⅲ IFNの抗ウイルス作用

ウイルスに感染すると細胞はIFNを産生する．産生されたIFNは自然免疫，獲得免疫にシグナルを伝達し，抗ウイルス効果を発揮する．type Ⅰ IFNが細胞外に分泌されると細胞表面のIFN受容体(IFNAR)に結合し，Jak/STAT経路を活性化する．STAT1，STAT2はJak1，Tyk2などのJak kinaseによってリン酸化され，核内に移行後，IRF9と結合しIFN-stimulated gene factor3(ISGF3)を形成する．ISGF3はMX1，OASなどのIFN誘導遺伝子を活性化し，これらの働きによって宿主細胞は抗ウイルス状態となる．type Ⅲ IFNはtype Ⅰ IFNと異なる受容体に結合することが知られている．IFNλR1，IL-10Rβのヘテロダイマーに結合しシグナルを伝達する．しかし細胞内シグナルはtype Ⅰ IFNを同様であることが報告されている．したがってtype Ⅲ IFNはtype Ⅰ IFNと独立して，同様の抗ウイルス作用を有する[1,2,4](図1)．

Ⅱ type Ⅲ IFNの特徴

type Ⅲ IFNはtype Ⅰ IFNなどと同様に生体防御に重要な役割を果たしているが，HCV，HBVに対するtype Ⅲ IFNの役割は明らかでなかった．しかし近年の研究によってHCVレプリコン細胞にtype Ⅲ IFNを投与するとHCVの複

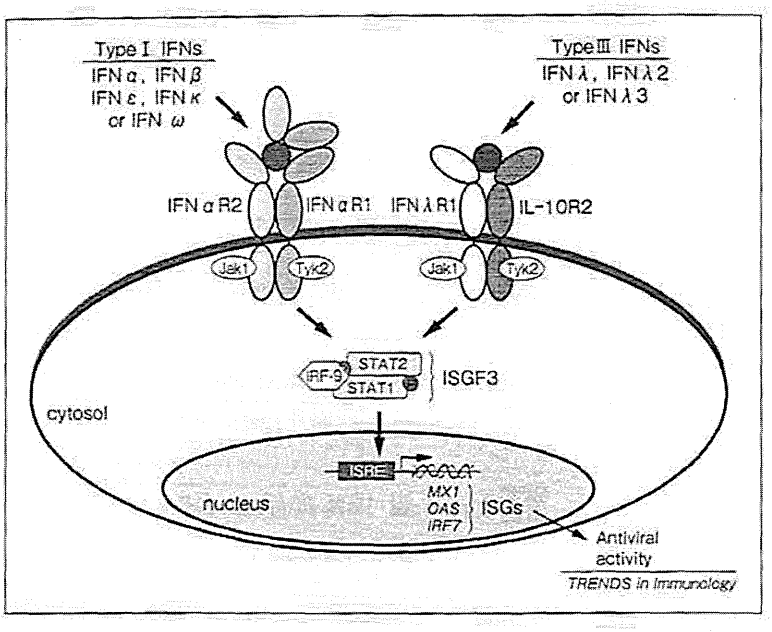


図1 IFN受容体とそのシグナル伝達
(文献4より引用改変)

製を阻害することが明らかとなった[5,6]. type I IFNに対するIFNARは生体内のさまざまな細胞に存在するため, C型慢性肝炎に対するIFNαを用いた治療では多くの副作用を引き起こす. 一方, type III IFNに対するIFNλ受容体は臓器特異的に存在している. 造血幹細胞にはIFNλ受容体は著しく発現が低下しており, また肝細胞に高発現していることが明らかとなっている[5,7]. このためC型慢性肝炎における抗ウイルス治療において, type III IFNはtype I IFNによる治療と比較し, 特に血液毒性などに対して少ない副作用で, 安全に治療を行うことができる可能性が示唆される. このためtype III IFNのC型慢性肝炎患者に対する治療応用が期待されている.

III C型慢性肝炎患者に対するIFNλによる治療

IFNλによるC型慢性肝炎患者に対する治療は現在臨床試験が進行中であり, いくつかの結果が報告されている. これまでのIFNλによる治療の有効性, 安全性についてまとめた.

1 Genotype 1b患者に対するPEG-IFNλ1のリバビリン併用または非併用の第1b相試験[8]

1) 試験デザイン

この試験はgenotype 1bのC型慢性肝炎患者に対して非盲検下に3つのパートにおいてなされた. パート1はIFNαによる治療での再燃例を対象とし, PEG-IFNλ1単剤を1.5または3.0μg/kg投与した. パート2は同様にIFNαによる治療での再燃例を対象とし, PEG-IFNλ1(0.5~2.25μg/kg)およびリバビリンの併用治療を行った. パート3は治療歴のない患者に対して1.5μg/kgのPEG-IFNλ1およびリバビリンの併用治療を行った. いずれのパートにおいても治療期間は4週間であり, PEG-IFNλ1は毎週または1週おきに投与された(図2).

2) 抗ウイルス効果

PEG-IFNλ1投与量にかかわらず, すべての患者において抗ウイルス効果が得られた. PEG-IFNλ1投与量が1.5μg/kg以上の患者ではリバビリン投与の有無にかかわらず, 96%においてHCV RNA 2 Log以上の低下が得られ, 17%の患者においてHCV RNAが検出感度以下に減少し

図2 Genotype 1b 患者に対する PEG-IFNλ1 のリバビリン併用または非併用の第 1b 相試験の試験デザイン
(文献 8 より引用改変)

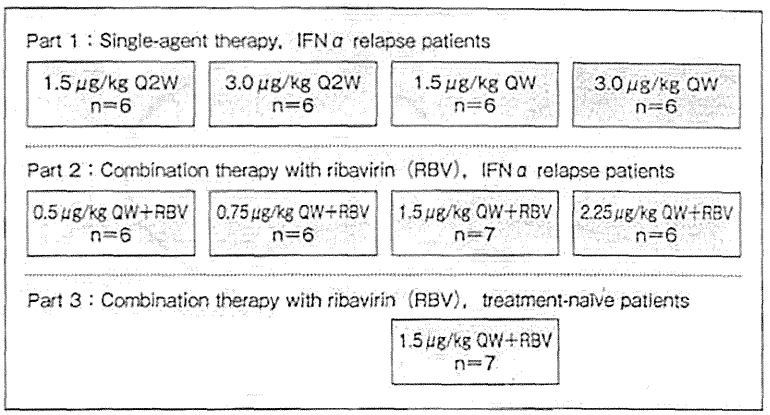
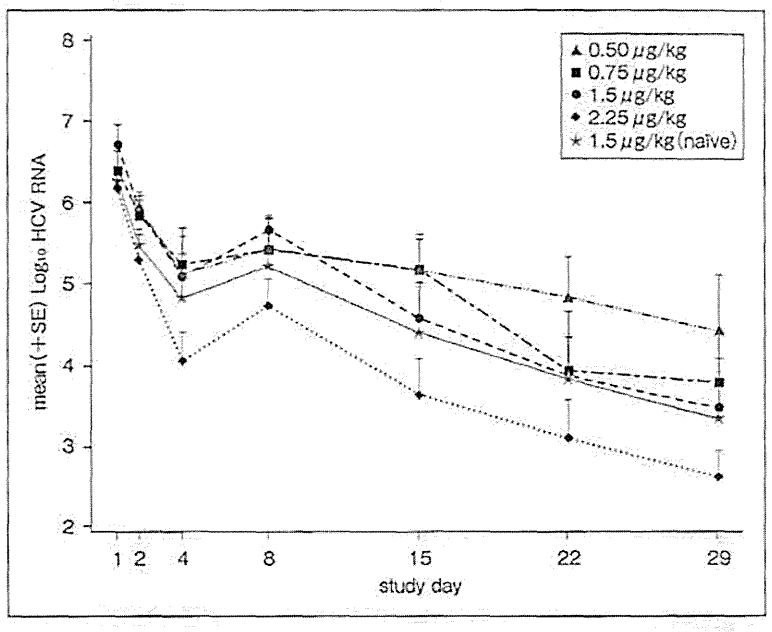


図3 IFNλ1 の抗ウイルス効果
(文献 8 より引用改変)



た．未治療症例においても 86％において HCV RNA 2 Log 以上の低下が得られた(図 3，表 1)．

3) 安全性，認容性

インフルエンザ様症状が少なく，リバビリンによる貧血の副作用を除くと血球減少が少ないことから，良好に認容可能であった．多く認められた副作用は全身倦怠感(29％)，嘔気(12％)，筋肉痛(11％)であった．6 例の患者において用量規定毒性を満たす AST，ALT，ビリルビンの上昇を認めたがいずれも PEG-IFNλ の高用量の患者に発現し，休薬や投与中止によって速やかに回復した．好中球数，血小板数は投与前と比べ投与中に優位に低下は認められなかった．またヘモグロビンも PEG-IFNλ 単独投与群では優位な低下は認められなかった．

これら試験より，genotype 1b 患者に対する PEG-IFNλ1 のリバビリン併用または非併用治療は，副作用および血球減少が少ないため認容性が高く，有効な抗ウイルス効果を得られることが証明された．

表1 IFNλ1の抗ウイルス効果のまとめ

	Part 1：treatment relapse, Single-Agent PEG-IFN λ				Part 2：treatment relapse, PEG-IFN λ and RBV				Part 3：treatment-naive, PEG-IFN λ and RBV
	1.5μg/kg Q2W (n=6)	3.0μg/kg Q2W (n=6)	1.5μg/kg QW (n=6)	3.0μg/kg QW (n=6)	0.5μg/kg QW (n=6)	0.75μg/kg QW (n=6)	1.5μg/kg QW (n=6)	2.25μg/kg QW (n=6)	1.5μg/kg QW (n=7)
serum HCV RNA (Log_{10}), mean (range)									
baseline	7.34 (7.08~7.56)	6.47 (6.11~7.17)	6.58 (5.93~7.38)	5.79 (4.21~6.57)	6.17 (5.52~6.60)	6.38 (5.37~7.20)	6.70 (5.89~7.52)	6.18 (5.66~6.92)	6.26 (5.80~6.85)
maxumum decrease from the baseline	2.15 (0.59~5.18)	1.89 (0.98~3.01)	3.60 (2.05~4.95)	3.42 (2.49~4.60)	1.83 (0.49~3.57)	3.00 (0.70~4.66)	3.25 (0.09~5.56)	3.85 (3.20~5.14)	3.27 (1.23~5.45)
virological response, n(%)									
≥2-Log_{10} decrease in HCV RNA	2 (33)	3 (50)	6 (100)	6 (100)	2 (33)	4 (67)	5 (83)	6 (100)	6 (86)
HCV RNA<10000 IU/mL	1 (17)	0	4 (67)	4 (67)	1 (17)	3 (50)	2 (33)	6 (100)	3 (43)
HCV RNA<25 IU/mL	0	0	0	3 (50)	0	1 (17)	0	1 (17)	2 (29)

（文献8より引用改変）

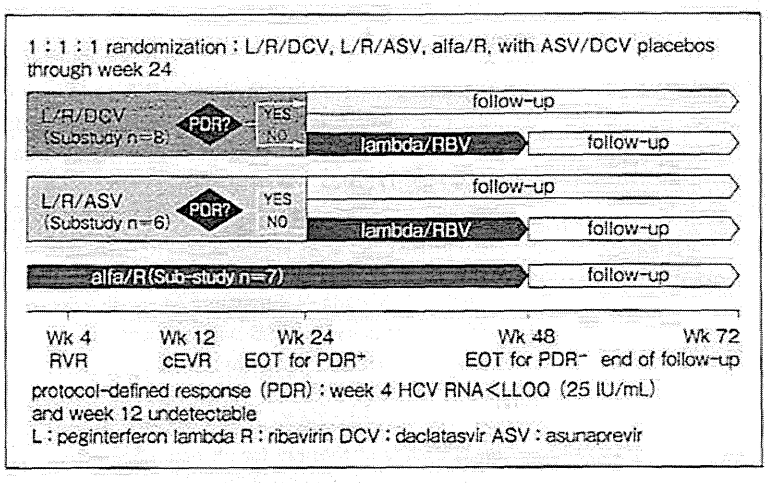


図4 D-LITE Study Design

2 Genotype 1の日本人C型慢性肝炎患者におけるPEG-IFNλ1/リバビリンおよびダクラタスビルまたはアスナプレビル併用の第Ⅱ相試験（D-LITE study）[9]

近年，C型慢性肝炎に対する治療薬としてさまざまなプロテアーゼ阻害薬が開発，臨床応用され，高い有効性が証明されてきている．NS5A阻害薬であるダクラタスビルまたはNS3阻害薬であるアスナプレビルとPEG-IFNλ1/リバビリンの併用臨床試験が行われ，結果が報告されている．

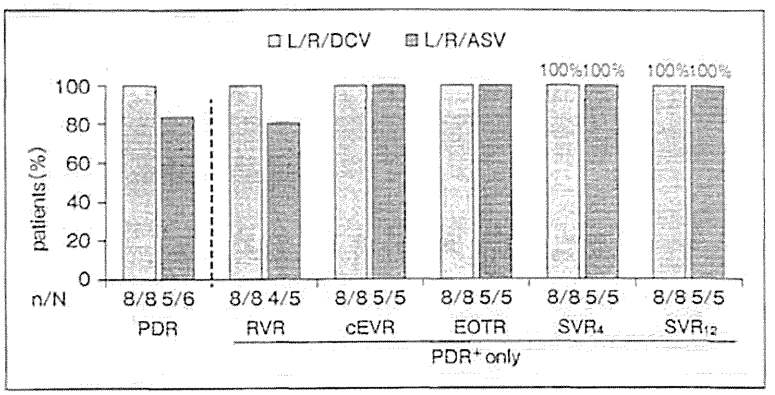
1）試験デザイン

本試験は盲検下ランダム化比較試験である．PEG-IFNλ1/リバビリンおよびダクラタスビルまたはアスナプレビル併用の24週治療またはPEG-IFNα/リバビリンおよびプラセボによる48週治療の3群によって比較された．用量はPEG-IFNλ1/およびPEG-IFNαは180μg，週1回投与，ダクラタスビル60mg1日1回投与，アスナプレビル200mg1日2回投与とした（図4）．

2）抗ウイルス効果

ダクラタスビルまたはアスナプレビル併用症例

図5 D-LITE study 抗ウイルス効果



の93％で治療終了時にウイルス陰性化を得ることが可能であった．アスナプレビル併用群の1例のみが副作用のため3週で治療を中止となり，治療終了時のウイルス陰性化を得られなかったのはこの1例のみであった．治療終了時のウイルス陰性化を得られたすべての症例においてSVR12を達成した（図5）．

3）副作用

ダクラタスビル併用群では重篤な副作用，副作用による治療の中止はなく，アスナプレビル併用群で2例肝機能障害により治療の中止を認めたが，この症例においてもSVR12を達成することができた．肝障害，貧血のほかは重篤な副作用は認められなかった．

この試験より，PEG-IFNλ1/リバビリンに加えてプロテアーゼ阻害剤薬であるダクラタスビルまたはアスナプレビルを併用することできわめて高い抗ウイルス効果を得ることが可能であった．ダクラタスビル併用による治療はより認容性も高く，さらなる大規模な試験が望まれる．

まとめ

IFNλによる治療は従来のIFNα，βと同様に抗ウイルス効果を示し，その受容体の分布からより副作用の少ない治療が可能となると考えられる．また現在さまざまな開発が進んでいるプロテアーゼ阻害薬との併用にとってきわめて高い治療効果と安全性をもつ治療となる可能性がある．

（玉城信治・泉　並木）

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The prospective randomized study on telaprevir at 1500 or 2250 mg with pegylated interferon plus ribavirin in Japanese patients with HCV genotype 1

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Abstract
Background Triple therapy with telaprevir (TVR), pegylated interferon and ribavirin has improved antiviral efficacy in patients with chronic hepatitis C (CH-C). However, the severe adverse effects caused by TVR are important to resolve. In this prospective, randomized, multicenter, open-label study, the antiviral efficacy and safety in the reduced administration of TVR were examined.
Methods A total of 81 CH-C Japanese patients with HCV genotype 1 were randomized into two regimens of TVR 2250 mg (TVR-2250) or 1500 mg (TVR-1500) and treated with triple therapy for 24 weeks.
Results The mean HCV RNA at start, 2 and 4 weeks of treatment were 6.69 ± 0.70, 1.05 ± 0.74, 0.22 ± 0.48 $\log_{10}$ IU/ml in the TVR-2250 group and 6.70 ± 0.62, 1.02 ± 0.62, 0.13 ± 0.41 $\log_{10}$ IU/ml in the TVR-1500 group. The SVR rates were 85 % in both groups (35/41 and 34/40, respectively). There were no patients with viral breakthrough in either group. As for adverse effects, rash more than moderate and severe anemia with <8.5 g/dl of hemoglobin were higher in the TVR-2250 group than in the TVR-1500 group ($p = 0.046$, $p < 0.001$, respectively). The increase in serum creatinine levels and decrease in estimated glomerular filtration rates were higher in the TVR-2250 group than in the TVR-1500 group.
Conclusions The lower dose of TVR (1500 mg/day) can result in similar SVR rates and lower treatment-related adverse effects compared to the higher dose of TVR

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(2250 mg/day) in triple therapy (UMIN: 000007313, 000007330).

Keywords Chronic hepatitis C · Telaprevir · Pegylated interferon plus ribavirin · Dose reduction

Abbreviations

HCV	Hepatitis C virus
IFN	Interferon
Peg-IFN	Pegylated interferon
RBV	Ribavirin
PI	Protease inhibitor
TVR	Telaprevir
SVR	Sustained virologic response
EOT	End of treatment
HCC	Hepatocellular carcinoma
CH-C	Chronic hepatitis C
Hb	Hemoglobin
WBC	White blood cell
RVR	Rapid virologic response
c-EVR	Complete early virologic response
ETR	End of treatment response
SMV	Simeprevir

Introduction

Antiviral therapy for patients with chronic hepatitis C virus (HCV) genotype 1 infection has changed from interferon (IFN) monotherapy to dual therapy with pegylated IFN (Peg-IFN) and ribavirin (RBV) and then to triple therapy with protease inhibitor (PI), Peg-IFN and RBV [1]. The clinical trials of triple therapy with telaprevir (TVR), which is a first-generation PI, Peg-IFN and RBV have reported that addition of TVR leads to a substantial improvement in sustained virologic response (SVR), defined as an undetectable HCV RNA at 24 weeks after the end of treatment (EOT), compared to Peg-IFN and RBV among naïve patients and re-treatment patients [2–9]. However, severe adverse effects caused by TVR, such as severe anemia, rash and gastrointestinal disorder, were also reported [2, 3, 8, 9]. Generally, older patients and patients with advanced liver fibrosis have greater risk of hepatocellular carcinoma (HCC) and, therefore, should be treated with antiviral therapy as early as possible in order to eliminate HCV. However, adverse effects caused by TVR in those patients may lead to serious complications, such as death [10].

A phase 1b, placebo-controlled, double-blinded study conducted in Europe evaluated the antiviral activity, pharmacokinetics and safety of TVR [11]. That study examined the antiviral activity of TVR for 14 days at 450 or 750 mg every 8 h or 1250 mg every 12 h. The highest trough plasma drug concentrations, and the greatest HCV RNA reduction were measured in the 750-mg-dose group. The most frequent adverse effects were headache, diarrhea, fatigue, nausea and dry skin, and there were no severe adverse effects and no dosing interruptions. As a result, the regimen of 750 mg of TVR every 8 h (total 2250 mg/day) was selected. Subsequently, a phase 2 study for triple therapy with TVR, Peg-IFN and RBV was conducted in Europe and the United States [2–4]. However, a dose-finding study of TVR in triple therapy was not conducted in these phase 2 studies. The dose of TVR in triple therapy was determined based on the TVR monotherapy study. On the other hand, in Japan, the phase 1, open-label, two-arm study of TVR at 500 or 750 mg every 8 h with Peg-IFN alfa-2b and RBV was conducted using 20 chronic hepatitis C (CH-C) patients [12, 13]. The pharmacokinetic parameters such as the area under the plasma concentration time curve from 0 to 8 h (AUC_{0-8h}), the maximum plasma concentration (C_{max}) and the trough plasma concentration (C_{trough}) of TVR were higher in the 750-mg dose group than in the 500-mg dose group, and there was no difference in adverse effect between these two groups. As a result, a regimen of 750 mg of TVR every 8 h (total 2250 mg/day) was selected, although HCV RNA reduction was similar in both groups.

In the phase 3 study of triple therapy with TVR, Peg-IFN and RBV, similar SVR rates were observed in clinical trials in Europe, the United States and Japan (naive 69–75 vs. 73 %, treatment-relapse, 83–88 vs. 88 %) [5–9]. Whereas the rate of discontinuation of all drugs and the rate of discontinuation of TVR were 7–10 % and 7–12 % in Europe and the United States, those rates were higher at 17 % and 19 % in Japan. As for the severe adverse effects, rash and anemia were more frequent in Japan compared to Europe and the United States (rash 12 % vs. <1 %; anemia 11 % vs. 2 %). More adverse effects with triple therapy in Japanese patients may result from excessive doses of TVR because the dosage of TVR is constant, and Japanese people tend to weigh less than Western people. Alternatively, Asian people including Japanese can cause severe adverse effects compared to Western people. Therefore, the triple therapy with reduced TVR, Peg-IFN and RBV has the potential to improve safety of Japanese patients with CH-C.

In this multicenter, randomized study, we examined the antiviral efficacy and safety in triple therapy after administration of two TVR dosages: 1500 and 2250 mg/day.

Patients and methods

Patients

The current study was a prospective, randomized, multicenter, open-label study conducted by Osaka University

Hospital and other institutions participating in the Osaka Liver Forum. A total of 81 CH-C patients were enrolled in this study between December 2011 and December 2012.

Eligible patients were 20 years of age and older, had chronic HCV genotype 1 infection with a viral load of more than 10^5 IU/ml, did not have co-infection with hepatitis B or anti-human immunodeficiency virus and had an absolute neutrophil count of 1500/mm^3 or more, a platelet count of 10×10^4/mm^3 or more, and a hemoglobin (Hb) level of 12 g/dl or more. The patients were accepted regardless of history of IFN treatment. The patients were excluded if they had decompensated cirrhosis, HCC or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), an experience with splenectomy or partial spleen embolization, chronic renal failure, depression or immunodeficiency. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki amended in 2002 and was approved by the ethics commission of Osaka University Hospital and independent or institutional review boards of all study centers (UMIN000007313, 000007330). All patients provided written informed consent before participating in the study.

Study design

This study was a randomized, open-label trial. Patients were stratified according to gender and age (<60 vs. ≥60 years old) and were randomly assigned to one of two groups. The TVR-1500 group received 1500 mg/day of TVR (TELAVIC; Mitsubishi Tanabe Pharma, Osaka, Japan), Peg-IFN alfa-2b (PEGINTRON; MSD, Tokyo, Japan) and RBV (REBETOL; MSD) for 12 weeks, followed by Peg-IFN alfa-2b and RBV for 12 more weeks. The TVR-2250 group received 2250 mg/day of TVR, Peg-IFN alfa-2b and ribavirin for 12 weeks, followed by Peg-IFN alfa-2b and RBV for 12 more weeks. The randomization was performed at a 1:1 ratio between the two groups.

TVR was administered orally at a dose of 500 or 750 mg every 8 h after food. Peg-IFN alfa-2b was administered subcutaneously once a week at a dose of 60–150 μg/kg based on body weight (body weight 35–45 kg, 60 μg; 46–60 kg, 80 μg; 61–75 kg, 100 μg; 76–90 kg, 120 μg; 91–120 kg, 150 μg), and RBV was administered orally twice a day at a total dose of 600 to 1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg), according to a standard treatment protocol for Japanese patients. In principle, the patients were treated with TVR, Peg-IFN and RBV for 12 weeks, followed by Peg-IFN and RBV for 12 weeks. If patients had detectable HCV RNA at 12 weeks or any time during weeks 13 through 20, they were not permitted to complete the remainder of the assigned duration of therapy.

Dose modification

Dose modification followed the manufacturers' drug information. The initial dose of RBV was reduced by 200 mg per day when the Hb level was <13 g/dl at baseline. The dose of Peg-IFN alfa-2b was reduced to 50 % of the assigned dose if the white blood cell (WBC) count declined to <1500/mm^3, the neutrophil count to <750/mm^3, or the platelet count to $<8 \times 10^4$/mm^3. RBV was also reduced from 1000 to 600 mg, from 800 to 600 mg, or from 600 to 400 mg if the Hb level decreased to <12 g/dl, and the dose was reduced by an additional 200 mg per day when the Hb level was <10 g/dl. The dose of RBV was also reduced by 200 mg per day if the Hb level dropped more than 1 g/dl within a week, and this level was <13 g/dl. TVR, Peg-IFN alfa-2b and RBV were withdrawn or interrupted if the WBC count declined to <1000/mm^3, the neutrophil count to <500/mm^3, the platelet count to $<5 \times 10^4$/mm^3, or the Hb level to <8.5 g/dl. TVR was reduced from 2250 to 1500 mg, from 1500 to 750 mg according to adverse effects of TVR, such as rash, anemia, intestinal disorder and increase of serum creatinine levels by physician's decision. The use of erythropoietin was not allowed for elevating the Hb level. In the case of drug interruption with TVR or Peg-IFN and RBV, if peripheral blood finding or adverse effects subsided, resumption of treatment was allowed.

Histological evaluation

Pre-treatment liver biopsies were conducted within 6 months of the start of the combination therapy. Histopathological interpretation of the specimens was performed by experienced liver pathologists who had no clinical, biochemical or virological information. The histological appearances, activity and fibrosis were evaluated according to the METAVIR histological score [14].

Virologic assessment and definition of viral response

Serum HCV RNA levels were quantified with the COBAS Taqman HCV test, version 2.0 (detection range 1.2–7.8 log IU/ml; Roche Diagnostics, Branchburg, NJ). Serum HCV RNA level was assessed before treatment, at weeks 2, 4, 8, 12, 16, 20 and 24 during treatment and 24 weeks after the therapy. A rapid virologic response (RVR) was defined as undetectable serum HCV RNA at week 4, a complete early

virologic response (c-EVR) as undetectable serum HCV RNA at week 12 and an EOT response (ETR) as undetectable serum HCV RNA at EOT. An SVR was defined as an undetectable serum HCV-RNA level at 24 weeks after the EOT. Relapse was defined as an undetectable serum HCV RNA level at the EOT but a detectable amount after the EOT. Non-response was defined as a detectable HCV RNA level during therapy. Breakthrough was defined as quantifiable HCV RNA after undetectable HCV RNA during therapy.

Safety assessment

Chemical and hematologic assessments and a safety assessment were performed every week during the first 12 weeks of treatment and every 4 weeks from week 12 to week 24 of treatment. At each visit, data on adverse effects were collected and physical examinations were performed, if clinically indicated.

Statistical analysis

Baseline continuous variables were expressed as the mean ± standard deviation or median and categorical variables as frequencies. The virologic response was evaluated in intention-to-treat set. Differences between the two groups were assessed by a Chi Square test or a Mann–Whitney U test and a t test. The cumulative incidence of adverse effects was assessed with the Kaplan–Meier method and a log-rank test. A p value < 0.05 was considered significant. Statistical analysis was conducted with SPSS version 19.0 J (IBM, Armonk, NY, USA).

Results

Patients

Eight-one Japanese patients underwent randomization and received treatment (Fig. 1). The baseline characteristics of the patients were similar between the two treatment groups except for the TVR dose (Table 1). The mean TVR dose per body weight was significantly higher in the TVR-2250 group than in the TVR-1500 group. Among the patients with non-response, 4 patients were partial-responder with ≥ 2 $\log_{10}$ IU/ml of HCV RNA decrease in previous Peg-IFN and RBV and no patients were null-responder with <2 $\log_{10}$ IU/ml of HCV RNA decrease in previous Peg-IFN and RBV in the TVR-2250 group (one patient was unknown). There were 3 partial-responders and 4 null-responders were in the TVR-1500 group (one patient was unknown).

Virologic response

The mean HCV RNA at start, 2 and 4 weeks of treatment were 6.69 ± 0.70, 1.05 ± 0.74 and 0.22 ± 0.48 $\log_{10}$ IU/ml, respectively, in the TVR-2250 group and 6.70 ± 0.62, 1.02 ± 0.62 and 0.13 ± 0.41 $\log_{10}$ IU/ml, respectively, in the TVR-1500 group, and there was no significant difference (Fig. 2a). As for naïve patients, similar decreases in HCV RNA were attained in both groups (Fig. 2b). There was no significant difference in RVR, cEVR, ETR and SVR rates in both groups (Fig. 3a). According to history of IFN treatment, there was no significant difference in SVR rates in both groups (Fig. 3b). Two patients with non-SVR in the TVR-1500 group were null-responders in previous Peg-IFN and RBV.

Drug reduction and discontinuation

All three drugs were discontinued until 12 weeks in 4 patients (10 %) in both groups. TVR was discontinued in 10 patients (24 %) of the TVR-2250 group and in 9 patients (23 %) of the TVR-1500 group. The main reasons for discontinuation of TVR were anemia, rash, gastrointestinal disorder, general fatigue, hyperbilirubinemia and renal dysfunction. Table 2 shows the proportion of patients with dose reduction and discontinuation due to adverse effects. Although the discontinuation rates of TVR were similar in both groups, the number of patients without dose reduction or discontinuation of TVR was larger in the TVR-1500 group than in the TVR-2250 group (68 vs. 32 %, $p = 0.001$). RBV was reduced at 93 % in the TVR-2250 group and 88 % in the TVR-1500 group, and the number of patients without dose reduction or discontinuation of TVR was low in both groups (7, 13 %, respectively). On the other hand, the number of patients without dose reduction or discontinuation of Peg-IFN was larger in the TVR-1500 group than in the TVR-2250 group (24 vs. 48 %, $p = 0.03$).

Adverse effects

Rash was common in the TVR-2250 group (68 %: grade 1, 28 %; grade 2, 35 %; grade 3, 5 %) and in the TVR-1500 group (58 %: grade 1, 36 %; grade 2, 22 %; grade 3, 0 %). The cumulative occurrence of rash more than moderate was significantly higher in the TVR-2250 group than in the TVR-1500 group ($p = 0.046$, Fig. 4a). Anemia, defined as a decline of more than 3 g/dl of Hb, occurred in 98 % of the TVR-2250 patients and 85 % of the TVR-1500 patients. The decreases of Hb from baseline were significantly greater in the TVR-2250 group than in the TVR-1500 group at 4 and 8 weeks of treatment (4 weeks, 3.4 ± 1.1 vs. 2.8 ± 1.3 g/dl, $p = 0.03$; 8 weeks, 4.5 ± 1.4 vs. 3.4 ± 1.3 g/dl, $p = 0.001$). Severe anemia, defined as