診断と治療のTopics

C型肝炎

Hepatitis C among HIV-infected patients

独立行政法人国立病院機構大阪医療センター消化器科科長 三田 英治
Eiji Mita

Summary

いまや，HIV感染者の死亡原因の第２位が肝疾患関連死である。HIV感染はC型慢性肝疾患の進展を加速させ，逆にHCV感染は抗HIV療法(ART)での肝障害の頻度・程度を悪化させる可能性があるなどHIV感染の病態を修飾する。HCVに対するワクチンがない現状では，まず感染防止，感染した場合は慢性化の阻止，慢性肝炎の場合は早期の治療介入などに重点を置いた対応が求められる。

Key words

- HCV
- インターフェロン治療
- リバビリン
- telaprevir

疫学

C型肝炎ウイルス(hepatitis C virus；HCV)は全世界で約１億3,000万人が感染し，400～500万人がHIVと重複感染している[1]。また，アメリカではHIV感染者の約30％がHCV陽性と報告されている[2)3)]。一方，日本では2004年の厚生労働省の研究班による全国調査でHIV感染者の19.2％がHCV抗体陽性で，このうち約80％がHCV-RNA陽性と報告されている[4]。日本では，HIV・HCV重複感染者の多くが血液製剤による感染が原因である。その他では，男性同性愛者間，異性間性交渉，注射による薬物乱用[5]などが感染経路である。

アメリカの大規模研究(n＝23,441)におけるHIV感染患者の死因調査で，AIDS(31.1％)に次いで肝疾患関連死(14.5％)が多いことが報告されている[6]。そして，HCVが重複感染している場合には死亡に至る相対危険度が6.7倍高値であり，C型肝炎をコントロールすることが重要である。

HCVの急性感染

HIV感染が確認されたとき，必ずHCVおよびB型肝炎ウイルス(hepatitis B virus；HBV)感染の有無は確認されているはずである。HIV感染が診断された時点でHCV感染を認めなくても，経過中にAST/ALT上昇を認めた場合はHCVマーカーを再検索するが，HCV抗体だけではなく，必ずHCV-RNAを測定すべきである。AST/ALTが異常値をとった時点でもHCV抗体が陽性化しないケースがあるため，必ずHCV-RNAまで

調べなければならない。これは，HIV感染の有無にかかわらず実施すべき手順である[7]。また，AST/ALTが正常範囲でも感染のリスク行動が継続されている場合，毎年1回HCV抗体を測定することもHCV感染を早期に把握するうえで有用といえる。

HCVは，いったん感染すると70～90%と高率にキャリア化することが知られており，HIV感染者でも同様のことがいえる。そのため，C型急性肝炎と診断された場合，治療介入を検討することになる。日本ではペグインターフェロン(peginterferon；Peg-IFN)単独治療を選択することが多く(保険適応外)，HIV非感染者ではgenotypeにかかわらず90%近いHCV排除率が得られる。しかし，HIV感染者に対し急性期にインターフェロン(interferon；IFN)導入を図った治療成績の報告は少ない。一般的には，HCV初感染が確認されて6ヵ月経過してもHCV血症が持続する場合に，慢性化と判定してIFN治療を行うことが多い。

一方，HIV・HCV感染が同時にみつかった場合，HCV感染時期を特定する情報は問診以外になく，診断に難渋する。ただ，若年者であった場合，C型肝炎の罹病期間は短いと考えられる。HCVの初感染からの期間が短いほどIFN治療効果は高いため，若年者では積極的にIFN治療を行うことを勧める。

C型慢性肝疾患の疫学

Benhamouらは[8]，HIV感染C型慢性肝炎症例と患者背景をマッチさせたHIV非感染C型慢性肝炎症例の肝線維化の進展速度を比較し，HCV単独感染例に比べHIV重複感染例は進展が速いことを報告している。肝線維化進展速度を年率で表現すると，HIV重複感染例では0.153/年であり，計算上HCV初感染から26年で肝硬変になるのに対して，HCV単独感染例では0.106/年であり，計算上HCV初感染から38年で肝硬変になるという(図1)。

またPineda[9]らは，C型肝硬変症例が非代償期に入ってからの生存期間をHIV感染の有無で検討している。HIV感染群がHIV非感染群に比し，若い(中央値 38歳 vs. 66歳)，男性が多い(86% vs. 58%)，HBs抗原陽性者が多い(24% vs. 4%)など背景因子に違いを認めるものの，平均生存期間がHIV感染群で16ヵ月，HIV非感染群で48ヵ月と，HIV感染が肝硬変の終末期においても病状悪化の一因になっていることが示されている。

C型慢性肝炎に対する抗ウイルス療法

以上のことから，HIV感染C型慢性肝炎に対しては，早期にHCV排除を目指した治療介入が望まれる。治療は，HIV感染の有無にかかわらずガイドラインに沿ったものとなる。日本人のHCVキャリアにおけるgenotypeやウイルス量の分布は，genotype 1型(ほとんどが1b型)が約70%で，高ウイルス量(≧5.0 $\log_{10}$IU/mL)が約50%，低ウイルス量(<5.0 $\log_{10}$IU/mL)が約20%という割合である。一方，残り約30%がgenotype 2型で，高ウイルス量と低ウイルス量は半数ずつという内訳である。つまり，genotype 1型・高ウイルス量症例が日本人のHCVキャリアの約半

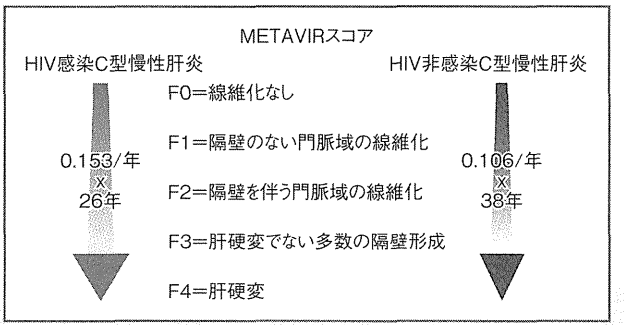

図1．HIV感染の有無とC型慢性肝炎の肝線維化進展速度

数となるが，この集団は現在の標準治療であるPeg-IFN・リバビリン併用療法をもってしても，ウイルス排除率は45～50%に留まる。他方，genotype 1型・低ウイルス量症例およびgenotype 2型症例では，ガイドラインで推奨される治療(表1)を行うことで90%近いウイルス排除率が期待できる。HIVを重複感染しているとウイルス排除率が若干抑えられるが，やはり「genotype 1型かつ高ウイルス量」症例以外であれば，病状の許すかぎり(合併症の有無，本人のモチベーションなどを考慮して)積極的にIFN治療を行うべきと考える。しかし，genotype 1型・高ウイルス量症例に対するPeg-IFN・リバビリン併用療法のウイルス排除率は低値であり[10)-13)](表2)，今後プロテアーゼ阻害薬との3剤併用療法が認可された場合は第一選択となるだろう(表1)。

次に，診療ガイドラインの要点を記載する。まず，初回治療で低ウイルス量症例なら，genotypeにかかわらずIFN単独治療もしくはPeg-IFN単独治療を行う。一方，高ウイルス量症例ならPeg-IFN・リバビリン併用療法を行い，genotype 1型なら48週治療，genotype 2型なら24週治療を行う。Genotype 1型の場合，HCV-RNAの陰性化が12週目以降36週目までなら治療期間を72週に延長する。ただ，現実的には24週目までに陰性化しないとウイルス排除率は低く，24週目の時点で継続治療の必要性を検討するべきである。HIV感染を合併する場合はウイルス排除率が低いため，海外から治療期間の工夫が提言されている[14)](図2)。すなわち，4週目までにHCV-RNAの陰性化が得られなければ，genotype 1型なら72週，genotype 2型なら48週まで治療期間を延長するというものであ

表1．C型慢性肝炎に対する初回治療ガイドライン(2011年)

	genotype 1型	genotype 2型
高ウイルス量 (5.0 log_{10}IU/mL 300fmol/L 1 Meq/mL以上)	・Peg-IFNα-2b＋リバビリン(48～72週間) ・Peg-IFNα-2a＋リバビリン(48～72週間) ※ 精神症状が課題なら ・IFNβ＋リバビリン(48～72週間) ★telaprevir認可後は ・Peg-IFNα-2b＋リバビリン ＋telaprevir(24週間)	・Peg-IFNα-2b＋リバビリン(24週間) ※精神症状が課題なら ・IFNβ＋リバビリン(24週間)
低ウイルス量 (5.0 log_{10}IU/mL 300fmol/L 1 Meq/mL未満)	・IFN(24週間) ・Peg-IFNα-2a(24～48週間)	・IFN(8～24週間) ・Peg-IFNα-2a(24～48週間)

表2．HIV感染C型慢性肝炎に対するPeg-IFN・リバビリン併用療法の治療成績

	APRICOT[10)]	ACTG A5071[11)]	RIBAVIC[12)]	Barcelona[13)]
症例数	868	133	412	95
Peg-IFN	2a	2a	2b	2b
リバビリン	800mg	600～1,000mg	800mg	800～1,200mg
CD4値およびHIV-RNA	「≧200/mm^3」or「100～199/mm^3 でHIV-RNA＜5,000copies/mL」	＞100/mm^3 かつHIV-RNA＜10,000copies/mL	＞200/mm^3	＞250/mm^3 かつHIV-RNA＜10,000copies/mL
ALT	2度は上昇	不問	不問	正常上限の1.5倍以上
genotype 1型の割合	60%	77%	48%	55%
bridging fibrosisを認める慢性肝炎＋肝硬変の割合	12%	11%(肝硬変)	39%	29%
genotype 1型のウイルス排除率	29%	14%	17%	38%

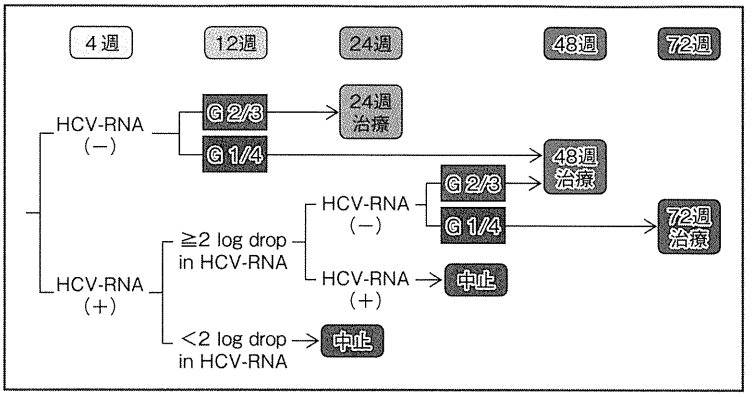

図2．HIV感染C型慢性肝炎に対するIFN治療期間の提言
G：genotype

る。また，血液製剤によってHCV感染を起こした症例も多くgenotype 3型やgenotype 4型症例を経験するが，この提言ではgenotype 3型はgenotype 2型の，genotype 4型はgenotype 1型の治療に準じている。

最近，HCV genotype 1型・高ウイルス量症例に対するPeg-IFN・リバビリン併用療法の反応を規定する因子としてインターロイキン(interleukin；IL)-28Bの一塩基多型(single nucleotide polymorphism；SNP)が報告された[15) 16)]（表3）。すなわち，IL-28BのSNP(保険適応外)がメジャーホモ接合体なら治療の反応性が良好で(厳密にいうと，経過中にリバビリンを減量することによって治療終了後に再燃するケースはあるのだが)，ヘテロ接合体もしくはマイナーホモ接合体なら治療反応性が不良である(図3)。治療反応性が不良と予測される場合は，プロテアーゼ阻害薬との3剤併用療法を行うことを検討すべきであろう。

また，抗HIV療法(antiretroviral therapy；ART)で使う薬物のなかには，リバビリンとの薬物相互作用で注意を要するものがある[17)]。リバビリンはジダノシン(ddI)の細胞内濃度を増大し，膵炎や乳酸アシドーシスを起こすが，同様のことが他の非核酸系逆転写酵素阻害薬(non-nucleoside reverse transcriptase inhibitor；NNRTI)でも観察される。また，ジドブジン(AZT)はリバビリンと併用すると高度の貧血を起こすことがあり，できれば併用を避ける。一方IFNでは，エファビレンツ(EFV)との併用で精神神経症状の増悪をきたすことがあり，できれば併用を避ける。

表3．Genotype 1型に対するPeg-IFN・リバビリン併用療法の治療効果を規定するIL-28BのSNP

SNP	rs8099917[15)]	rs12979860[16)]
メジャーホモ接合体	TT	CC
ヘテロ接合体	TG	TC
マイナーホモ接合体	GG	TT

日本人の頻度としては，メジャーホモ接合体が約4分の3，残りが4分の1の割合である。
rs8099917は真ん中に9が3つ並ぶため，トリプルナインと報告者は名付けている。一方，rs12979860はDuke大学からの報告なので，デュークスニップと学会などで呼ばれることがある。塩基配列TTは，rs8099917ではメジャーホモ接合体，rs12979860ではマイナーホモ接合体と，正反対の意味になるので注意したい。両者は連鎖不均衡を示し，同じことを示していると考えて差し支えない。

しかし，ART薬剤の進化は著しく，現在これらの薬剤は決して必須ではないため対応は可能である。今後もHCVに対する抗ウイルス薬の開発ラッシュが予定されているが，必ずART薬剤との薬理相互作用は検討されているので，情報は提供されると思われる。

C型肝硬変・肝癌に対する治療

C型肝硬変に関しては，包括的治療ガイドラインが示されている。HIV感染者に対して特別なものはなく，このガイドラインを意識した診療に努める。①治癒目的のIFN治療を行うか，②発癌予防および肝癌再発予防でIFN治療を行うか，③IFN治療を行わず(もしく

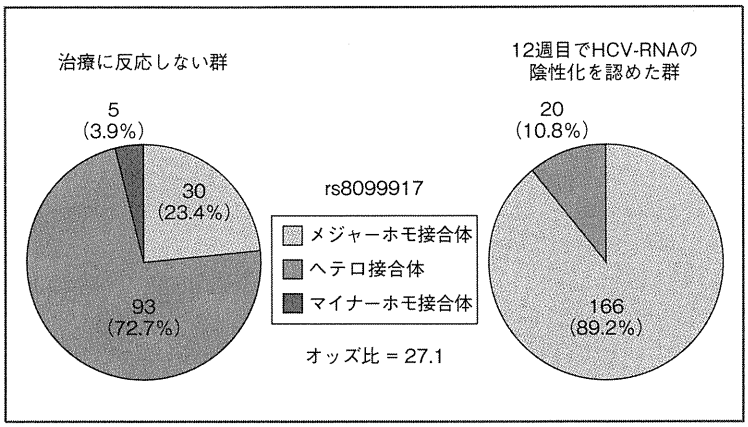

図3．IL-28BのSNP別にみたgenotype 1型に対するPeg-IFN・リバビリン併用療法の治療反応性[15]

は行えず），肝庇護療法を行うかを総合的に判断する。従来，C型肝硬変に対するIFN治療ではリバビリンを併用できなかったが，最近，治癒目的でリバビリンとの併用が保険認可された。C型肝炎のガイドラインは毎年更新されるので，日本肝臓学会のホームページなどを注視していただきたい。IFN治療ができない場合でも根気よく肝庇護療法を行い，肝病変の進展を遅らせることを目指したい。

肝癌も治療のガイドラインが示されている。早期発見には，綿密なサーベイランスが重要で，その必要性を患者に理解してもらうことが基本である。

最後に

HCV・HIV重複感染者の多くが血液製剤を介した感染で，感染期間が長くなるに伴い肝病変が進行している。適切な治療を早急に実施する必要性を感じる。ただ，現在のIFN治療は身体にかかる負担が大きい。経口の抗ウイルス薬でHCV感染を克服できる時代が早く到来することを期待したい。

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Original Article

Impact of ribavirin dose reduction on the efficacy of pegylated interferon plus ribavirin combination therapy for elderly patients infected with genotype 1b and high viral loads

Hiroshi Kohno,[1,4] Hirotaka Kouno,[1,4] Shiomi Aimitsu,[2,4] Yasuyuki Aisaka,[2,4] Mikiya Kitamoto,[3,4] Hiroiku Kawakami[4] and Kazuaki Chayama[4,5]

[1]*Department of Gastroenterology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure,* [2]*Department of Hepatology, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital,* [3]*Department of Gastroenterology, Hiroshima Prefectural Hospital,* [4]*Hiroshima IFN Study Group, and* [5]*Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, Hiroshima, Japan*

Aim: To examine the impact of ribavirin dose reduction on the efficacy of pegylated interferon (PEG IFN) plus ribavirin combination therapy for elderly patients infected with genotype 1b and high viral loads.

Methods: A total of 72 patients, over 65 years old, were recruited for this study. Patients were divided into groups receiving either 600–800 mg of ribavirin according to bodyweight (Group 1, $n = 36$) or 400 mg of ribavirin (Group 2, $n = 36$) plus 1.5 μg/kg (range: 1.3–2.0 μg/kg) of PEG IFN-α-2b for 48 weeks.

Results: Total ribavirin doses were administrated at 9.80 ± 2.39 mg/kg per day (3.29 ± 0.80 g/kg) for Group 1 and 5.87 ± 1.82 mg/kg per day (1.97 ± 0.61 g/kg) for Group 2 ($P < 0.001$). According to the total clearance (CL/F) of ribavirin, 34 of 36 patients in Group 1 received over-doses of ribavirin. In contrast, numbers of those receiving equivalent doses of ribavirin were two of 36 patients in Group 1 and 36 of 36 patients in Group 2, respectively ($P < 0.001$). End-of-treatment response (ETR) rates were observed in 23 of 36 patients (63.9%) in the standard ribavirin dose protocol and in 23 of 36 patients (63.9%) in the reduction ribavirin dose protocol (NS). Sustained virological response (SVR) rates were observed in 11 of 36 patients (30.6%) in the standard ribavirin dose protocol, and in 13 of 36 patients (36.1%) in the reduced ribavirin dose protocol (NS).

Conclusion: Reduction of ribavirin doses for elderly patients did not affect the outcome for the 48-week combination therapy.

Key words: elderly patients, pegylated interferon, ribavirin, total clearance

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection is estimated to affect 300 million individuals worldwide[1] including 2 million people in Japan.[2] Chronic HCV infection often progresses into liver cirrhosis including the development of associated complications such as gastroesophageal varices, and hepatocellular carcinoma over the course of 20–50 years.[3,4] Pegylated interferon (PEG IFN) plus ribavirin combination therapy is currently the most effective treatment for HCV infection. Patients infected with HCV genotype 1 and high viral load are known as difficult-to-treat, resulting in a sustained virological response (SVR) of approximately 50%.[5,6] The beneficial effects of antiviral therapy in patients with chronic HCV infection include a reduction in the occurrence of hepatocellular carcinoma or hepatic disease-related mortality obtained via SVR. For the SVR, it is recommended that the patient is kept on more than

Correspondence: Dr Hiroshi Kohno, Department of Gastroenterology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, 1-3 Aoyama-cho, Kure 737-0023, Japan. Email: hkouno@kure-nh.go.jp

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80% of the ribavirin dose, adjusted by the bodyweight (BW) during the combination therapy.[7] SVR rate decreased in a stepwise manner in accordance with the ribavirin dose reduction. Ribavirin might result in severe hematological adverse events when the renal function is impaired, because ribavirin concentrations increase, particularly in red blood cells. Generally, the renal function of elderly patients may naturally decrease with age.[8–10] Thus, it is difficult to obtain an SVR in elderly patients infected with genotype 1b and high viral loads.[11] In Japan, a high frequency of adverse events and high rates of discontinuation of combination therapies have also been observed in elderly patients.[12–15] Some studies have reported poor response to combination therapy in elderly patients, especially female elderly patients.[16–18] It is reported that accumulating combination of refractory factors can account for poor response rate.[18]

Thus, elderly patients with impaired renal function would often have adverse events due to ribavirin. In the present study, we examined the impact of ribavirin dose reduction on the efficacy of combination therapies for elderly patients infected with genotype 1b and high viral loads.

METHODS

Patients

THIS STUDY WAS conducted at three locations: the National Organization Kure Medical Center, Hiroshima Red Cross and Atomic Bomb Survivors Hospital, and Hiroshima Prefectural Hospital. A total of 72 patients, over 65 years old, were recruited for this study. All patients were infected with HCV genotype 1b and had high viral load of more than 5.0 log IU/mL as determined by the HCV COBAS TaqMan HCV test (Roche Diagnostics Tokyo, Tokyo, Japan). The linear dynamic range of this assay was 1.2–7.8 log IU/mL and undetectable samples were defined as negative. All eligible patients were required to satisfy the following criteria: (i) aged over 65 years; (ii) liver biopsy within 3 months of the start of therapy; (iii) diagnosis of chronic active hepatitis by conventional classification; (iv) positive for HCV RNA of genotype 1b in serum within 3 months in titers of more than 5.0 log IU/mL by the HCV COBAS TaqMan HCV test; (v) abnormal serum alanine aminotransferase levels for more than 6 months; (vi) leukocyte count of more than 3000/mm^3, platelets of more than 100 000/mm^3; (vii) serum bilirubin of less than 2.0 mg/dL; (viii) lack of liver cirrhosis, hepatocellular carcinoma, autoimmune hepatitis, alcoholic liver disease and any other chronic liver diseases (positive for serological markers of hepatitis B virus); (ix) lack of psychiatric illnesses, including depression, or conditions affecting the bone marrow, alimentary, cardiovascular or pulmonary systems; and (x) no immunosuppressive or antiviral therapy within 6 months prior to entry.

Treatment protocol

Patients were treated with the combination therapy of PEG IFN-α-2b plus ribavirin. Median dose was 1.5 μg/kg (range: 1.3–2.0 μg/kg) of PEG IFN-α-2b s.c. administrated once a week; oral ribavirin was administrated twice daily for a total dose of 400–800 mg.

The standard ribavirin dose protocol (Group 1) was as follows: 36 patients were treated for 48 weeks with a median dose of 1.5 μg/kg (range: 1.3–2.0 μg/kg) of PEG IFN-α-2b plus 600–800 mg ribavirin for patients whose weight was less or more than 60 kg, respectively.

The reduced ribavirin dose protocol (Group 2) was as follows: 36 patients were treated for 48 weeks with a median dose of 1.5 μg/kg (range: 1.3–2.0 μg/kg) of PEG IFN-α-2b plus 400 mg ribavirin.

All patients at the Kure Medical Center and Hiroshima Prefectural Hospital were enrolled in Group 1 and all patients at the Hiroshima Red Cross and Atomic Bomb Survivors Hospital were enrolled in Group 2.

In order to maintain consistency with current guidelines, patients who were HCV RNA positive by polymerase chain reaction and had abnormal alanine aminotransferase levels at 9 months were removed from the study and considered as non-responders.

This study was approved by the Institutional Review Boards of participating clinical sites prior to study initiation, and the study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Total ribavirin clearance

Total clearance (CL/F) was calculated at the beginning of treatment using the method of Kamar *et al.*[16] as follows: CL/F (L/h) = 32.3 × BW × (1 − 0.0094 × age) × (1 − 0.42 × sex) / serum creatinine (sex = 0 for male, 1 for female). Serum ribavirin concentrations were determined by a validated high-performance liquid chromatography/tandem mass spectrometric assay using ^{13C}-ribavirin as an internal standard.[19,20]

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Virological response to IFN

The virological response to IFN was determined by measuring serum HCV RNA levels via the HCV COBAS TaqMan HCV test every 28 days. SVR was defined as a negative serum HCV RNA during the 6 months following completion of IFN administration. All patients, other than those with SVR, were considered to be non-responders.

Histological analysis

All patients underwent liver needle biopsy under sonographic guidance at some time in the 3 months prior to the start of IFN administration. Baseline liver histology of chronic hepatitis was classified, based on the extent of fibrosis, into five stages (F0 = no fibrosis, F1 = mild fibrosis, F2 = moderate fibrosis, F3 = severe fibrosis, F4 = cirrhosis) and, based on activity, of four grades (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity).[21]

Statistical analysis

Baseline clinical characteristics were compared between treatment groups using Fisher's exact test, or the Mann–Whitney *U*-test. Treatment efficacy was analyzed via Fisher's exact test; $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the patients

THERE WERE NO significant differences observed for the general characteristics of the patients for demographic, biochemical, virological and histological features between the standard ribavirin dose protocol (group 1), and the reduced ribavirin dose protocol (group 2) (Table 1).

Total PEG IFN and ribavirin doses

Table 2 shows total PEG IFN and ribavirin doses in both groups 1 and 2 for patients who completed 48 weeks of the combination treatment. PEG IFN doses were 1.42 ± 0.25μg/kg per week (68.4 ± 11.9 μg/kg) in group 1 and 1.39 ± 0.27μg/kg per week (66.6 ± 12.8 μg/kg) in group 2 (NS). Ribavirin doses were 9.80 ± 2.39 mg/kg per day (3.29 ± 0.80 g/kg) in group 1 and 5.87 ± 1.82 mg/kg per day (1.97 ± 0.61 g/kg) in group 2

Table 1 Baseline characteristics of the patients according to two therapeutic groups

	Standard ribavirin dose protocol ($n = 36$)	Reduced ribavirin dose protocol ($n = 36$)	*P*-value
Mean age (years)	69.3 (65–77)	68.7 (65–75)	NS
Sex (M : F)	16:20	18:18	NS
Bodyweight (kg)	57.4 ± 1.9	58.3 ± 1.7	NS
BMI	23.5 ± 0.7	23.3 ± 0.6	NS
FBS	101.6 ± 19.0	107.1 ± 29.4	NS
HOMA-IR	3.1 ± 0.6	3.3 ± 0.7	NS
SCr	0.72 ± 0.16	0.71 ± 0.12	NS
eGFR (mL/min per 1.73 m^2)	71.8 ± 1.6	74.8 ± 0.6	NS
CL/F	6.20 ± 1.98	6.72 ± 2.11	NS
Basal WBC ($\times 10^3$ mm^3)	4.7 ± 1.2	4.6 ± 1.2	NS
Basal Hb (g/dL)	13.8 ± 1.6	14.0 ± 1.2	NS
Basal ALT (IU/L)	45 ± 24	58 ± 32	NS
Platelet ($\times 10^4$ mm^3)	16.1 ± 4.2	15.4 ± 4.5	NS
Serum HCV RNA (log IU/mL)	6.4 ± 0.4	6.5 ± 0.4	NS
Hyaluronic acid	120.6 ± 135.7	142.1 ± 123.9	NS
Histological findings			
Staging 1/2/3/4	7/11/13/5	8/12/12/4	NS
Grade 1/2/3	15/18/3	14/18/4	NS
History of previous IFN therapies	15	12	NS

Data are mean ± standard deviation.
BMI, body mass index; CL/F, total clearance; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HCV, hepatitis C virus; HOMA-IR, Homeostatic Model of Assessment of Insulin Resistance; IFN, interferon; NS, not significant; SCr, serum creatinine; WBC, white blood cell.

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Table 2 Total ribavirin dose and pegylated interferon (PEG IFN) dose based on bodyweight in two different protocol

	Standard ribavirin dose protocol ($n = 36$)	Reduced ribavirin dose protocol ($n = 36$)	*P*-value
PEG IFN dose/bodyweight (μg /kg)	68.4 ± 11.9	66.6 ± 12.8	NS
(μg/kg/week)	1.42 ± 0.25	1.39 ± 0.27	
Ribavirin dose/bodyweight (g/kg)	3.29 ± 0.80	1.97 ± 0.61	$P < 0.001$
(mg/kg per day)	9.80 ± 2.39	5.87 ± 1.82	
>80% ribavirin doses	15/36	0/36	$P < 0.001$
Ribavirin dose according to CL/F			
Over-dose	34	0	
Equivalent dose	2	36	$P < 0.001$

CL/F, total clearance; NS, not significant.

($P < 0.001$). Numbers of patients administrated over 80% of the dose of ribavirin were 15 of 36 in group 1, and zero of 36 in group 2. Eleven patients maintained the ribavirin dose at start of the therapy in group 1, and 21 patients in group 2. According to the CL/F data, 34 of 36 patients in group 1 received an over-dose of ribavirin. Conversely, two of 36 patients in group 1, and 36 of 36 patients in group 2 received equivalent doses of ribavirin, respectively ($P < 0.001$).

Ribavirin concentration during the therapy of two different therapeutic groups

Figure 1 illustrates the ribavirin concentration of both the standard ribavirin dose (group 1), and the reduced ribavirin dose protocol (group 2) at weeks 2, 4 and 12. At week 2, ribavirin concentrations were 2 021 ± 121 ng/mL in group 1, and 1 449 ± 103 ng/mL in group 2 ($P < 0.001$). At week 4, ribavirin concentrations were 2 283 ± 150 ng/mL in group 1, and 1 776 ± 132 ng/mL in group 2 ($P < 0.001$). At week 12, ribavirin concentrations were 2 217 ± 160 ng/mL in group 1, and 1 861 ± 132 ng/mL in group 2 ($P < 0.001$).

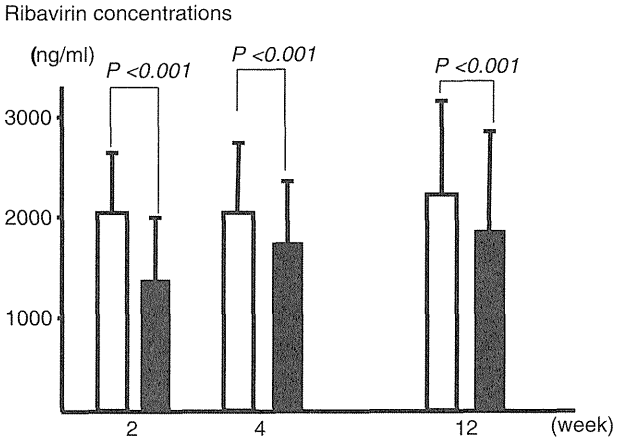

Figure 1 Mean (± standard deviation) of ribavirin concentration in the serum at 4, 8 and 12 weeks from commencing the pegylated interferon-α-2b plus ribavirin therapy. The two treatment groups included the standard ribavirin dose protocol (□, $n = 36$) and reduced ribavirin dose protocol (■, $n = 36$).

In group 1, the serum mean concentration of ribavirin at 4 weeks in patients who experienced reduced ribavirin doses was 2 300 ± 697 ng/mL, and 2 214 ± 1030 ng/mL in patients who did not have reduced ribavirin doses. In group 2, the serum mean concentration of ribavirin at 4 weeks in patients who experienced reduced ribavirin doses was 1697 ± 639 ng/mL, and 1 806 ± 703 ng/mL in patients who did not have reduced ribavirin doses. The ribavirin concentrations in patients who reduced their ribavirin doses did not differ from those who did not reduce ribavirin doses between both therapeutic groups.

Mean hemoglobin (Hb) concentration during the therapy of two different therapeutic groups

Figure 2 illustrates the Hb concentration of both the standard ribavirin dose (group 1) and the reduction ribavirin dose protocol (group 2) at every 4 weeks. Statistically significantly low Hb concentrations in group 1 were observed at weeks 4, 8 and 12 ($P < 0.05$), and at weeks 16, 20, 24, 28, 32 and 36 ($P < 0.01$).

Virological response

Figure 3 illustrates accumulating HCV RNA negative rates during the combination therapy. There were no significant differences in accumulating HCV RNA nega-

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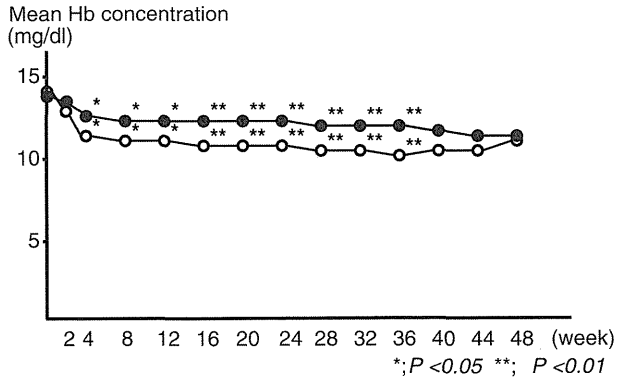

Figure 2 Mean hemoglobin (Hb) concentration at every 4 weeks from the beginning of pegylated interferon-α-2b plus ribavirin therapy. The two treatment groups included the standard ribavirin dose protocol (○, $n = 36$) and reduced ribavirin dose protocol (●, $n = 36$). $^*P < 0.05$; $^{**}P < 0.01$.

tive rates between the standard ribavirin dose (group 1) and the reduced ribavirin dose protocol (group 2).

Table 3 shows the end-of-treatment response (ETR) and SVR rates. ETR rates were observed in 23 of 36 patients (63.9%) in the standard ribavirin dose protocol (group 1) and in 23 of 36 patients (63.9%) in the reduced ribavirin dose protocol (group 2) (NS). SVR rates were observed in 11 of 36 patients (30.6%) in the standard ribavirin dose protocol (group 1) and in 13 of 36 patients (36.1%) in the reduced ribavirin dose protocol (group 2) (NS).

In relation to ribavirin dose reduction during the treatment, ETR and SVR rates were examined in each group. In group 1, ETR rates were observed in 12 of 15 patients (80.0%) in the patients who were administrated over 80% of ribavirin and in 11 of 21 patients (52.4%) in the patients who were administrated less than 80% (NS). SVR rates were observed in six of 15

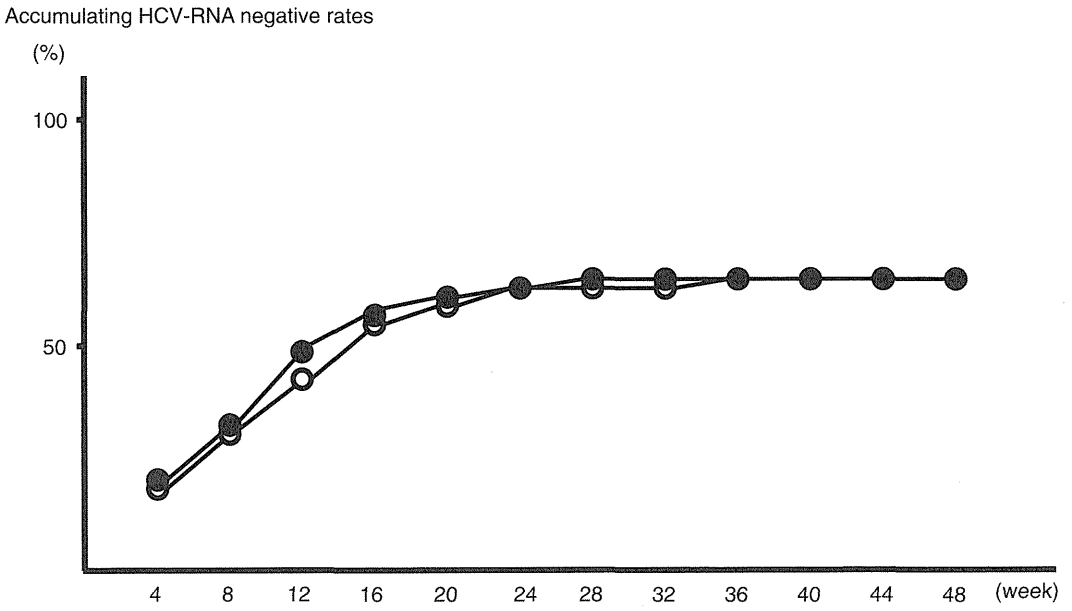

Figure 3 Accumulating hepatitis C virus (HCV) RNA negative rates of the two different protocols of pegylated interferon-α-2b plus ribavirin therapy at every 4 weeks. (○) Standard ribavirin dose ($n = 36$); (●) reduced ribavirin dose ($n = 36$).

Table 3 Virological response rate to two different antiviral protocols

	Standard ribavirin dose protocol ($n = 36$)	Reduced ribavirin dose protocol ($n = 36$)	*P*-value
End-of-treatment virological response rate	63.9% (23/36)	63.9% (23/36)	NS
Sustained virological response rate	30.6% (11/36)	36.1% (13/36)	NS

NS, not significant.

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Table 4 Number of discontinued patients due to adverse events

	Standard ribavirin dose protocol ($n = 36$)	Reduced ribavirin dose protocol ($n = 36$)	*P*-value
Depression	2	1	
Anemia	1	0	
Fatigue	1	3	
Dyspnea	1	0	
Ocular fundus bleeding	1	0	
Rheumatoid arthritis	0	1	
Appetite loss	0	1	
Total	6/36 (16.7%)	6/36 (16.7%)	NS

NS, not significant.

patients (40.0%) in the patients who were administrated over 80% and in five of 21 patients (23.8%) in the patients who were administrated less than 80% (NS). The patients who were administrated over 80% of the dose of ribavirin showed relatively good SVR rates of 40%; however, patients who could maintain that dose did not gain a majority. In group 1, ETR rates were observed in eight of 11 patients (72.7%) who maintained the ribavirin dose at the start of therapy and in 15 of 25 patients (60.0%) in the patients whose dose was reduced. SVR rates were observed in four of 11 patients (36.4%) who maintained the ribavirin dose at the start of therapy and in seven of 25 patients (28.0%) whose dose was reduced. In group 2, ETR rates were observed in 13 of 21 patients (61.9%) who maintained the ribavirin dose at the start of therapy and in 10 of 15 patients (66.7%) whose dose was reduced. SVR rates were observed in eight of 21 patients (38.1%) who maintained the ribavirin dose at the start of therapy and in five of 15 patients (33.3%) whose dose was reduced. There were no significant differences in relation to ribavirin dose reduction during the treatment in each therapeutic group.

Adverse events causing discontinuation of treatment

Table 4 summarizes the adverse events resulting in the discontinuation of treatment in both groups. In group 1, six patients discontinued therapy due to adverse events (two depression, one anemia, one fatigue, one dyspnea and one ocular fundus bleeding). In group 2, six patients discontinued therapy due to adverse events (one depression, three fatigue, one rheumatoid arthritis and one appetite loss). Discontinuation rates during combination therapy were six of 36 (16.7%) in group 1 and six of 36 (16.7%) in group 2 (NS). During the combination therapy, two patients from group 1 and one patient from group 2 developed hepatocellular carcinoma and discontinued combination therapy.

DISCUSSION

RECENTLY, PEG IFN plus ribavirin combination therapy has become regarded as the current standard of care for patients infected with HCV genotype 1 and a high viral load. It is known worldwide that these patients should be maintained on more than 80% of their PEG IFN and ribavirin dosage.[7] In particular, SVR rate decreases in a stepwise manner in accordance with the ribavirin dose reduction. In the present study, patients who were maintained on more than 80% of ribavirin were approximately 40% among the standard group, and not prevalent among the modified group. However, the rate of SVR in the standard group was not so good, and similar to that observed for the modified group. These results may indicate that high doses of ribavirin do not lead to SVR in elderly patients. The results and statements of the present study are in conflict with the well-known consensus. However, the rule of 80% ribavirin is derived from previous studies that had not included elderly patients.[7] Recently, combination therapy for elderly patients older than 65 years has been documented in Japan. In these reports, the SVR rate in elderly patients infected with HCV genotype 1 and high viral load was less than 40%, similar to our data.[15,22] A high frequency of adverse events and high rates of discontinuation of combination therapies have also been observed in elderly patients.[12–15] For achieving SVR in patients infected with HCV genotype 1 and high viral load, prolonged negative HCV RNA status of at least 12 months would be important.[23,24] Indeed, the extended treatment improves SVR rates in patients

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infected with HCV genotype 1 with late virological response to PEG IFN with ribavirin.[24,25] However, it is unlikely that continuation of a full dose of ribavirin based on BW would be tolerable for elderly patients older than 65 years, especially in extended treatment.

The rate of discontinuation was similar between the standard dose group and reduced dose group. Ribavirin treatment can result in severe hematological adverse events when the renal function is impaired, because ribavirin concentrations increase, particularly in red blood cells. Generally, the renal function of elderly patients may naturally decrease with age.[16–18] Thus, elderly patients often demonstrated higher ribavirin concentrations when they were administrated a standard dose based on BW. Indeed, the serum levels of ribavirin were significantly lower in the reduced dose group at 3 months after the start of combination therapy, and some patients in the standard dose group had higher serum levels of ribavirin. However, the serum levels among both therapeutic groups were obviously lower than suitable concentrations of ribavirin for eliminating HCV.[26] In the present study, two-thirds of group 1 patients required reduction of ribavirin, while one-third of group 2 patients required dose reduction, even if they were started on a dose of 400 mg. Moreover, the ribavirin concentrations in patients who discontinued ribavirin did not differ in those in continued therapy, between both therapeutic groups. These results would demonstrate that ribavirin could be harmful for elderly patients even if the serum levels of ribavirin were less than the suitable concentrations for SVR. The suitable concentrations for the elderly patients would show an individual variation, and thus the levels of ribavirin would not necessarily regulate dose reduction and discontinuation in the elderly.

Management of anemia during combination therapy can result in treatment continuation and favorable results. Many trials using erythropoietic agents[27] and vitamin E and C[28,29] which can prevent ribavirin-induced hemolytic anemia have been reported. However, those efforts decreased dose reduction for ribavirin and discontinuation without improved efficacy. Patients in the "2-by-2" positive group (Hb decline >2 g/dL during 2 weeks) and the group with lower CL/F were significantly more likely to discontinue ribavirin due to severe anemia. To decrease the risk of hemolytic anemia, the early reduction of ribavirin due to the "2-by-2" rule can help prevent progression to severe anemia, rather than employing the standard dose reduction according to the manufacture's information.[30] In our opinion, elderly patients who are treated with ribavirin at the 400 mg dose at the start of treatment would decrease their chances of presenting severe anemia. In deed, two-thirds of group 2 patients did not require further dose reduction. The ribavirin dose of 400 mg, used in the current study, almost corresponds to a CL/F adjustment, which has been used as a marker of progressing anemia that necessitates discontinuance of the treatment. In the standard group, almost all patients were regarded as "over-dosing" according to the CL/F assessment, while all patients were of the equivalent dose in the modified group.

Recently, a genome-wide association study demonstrated that inosine triphosphatase (*ITPA*) deficiency protects against ribavirin-induced hemolytic anemia and two functional variants cause *ITPA* deficiency. *ITPA* gene variants protected against anemia in patients treated for chronic hepatitis C. The major alleles of the *ITPA* gene rs1127354 were also strongly associated with ribavirin dose reduction.[31–34] With regard to ribavirin, we should consider not only CL/F but the *ITPA* single nucleotide polymorphisms (SNP). However, *ITPA* SNP assessment would not be available in most general hospitals. The prevalence of the major alleles of the *ITPA* gene strongly associated with anemia under ribavirin-combined treatment is approximately 75%. Thus, we should treat elderly patients appropriately who are more likely to experience declines in Hb levels.

Various factors such as viral factors and host factors have been reported to be associated with poor response to IFN-based treatment. With respect to HCV genotype 1 and a high viral load, interferon sensitivity determining region (ISDR),[35] core mutation 70/91,[16,36–38] *IL-28B*,[38–40] liver fibrosis, insulin tolerance and elderly patients, especially female patients, have been useful predictors as patients who are difficult to treat. Among those mentioned, more important factors such as ISDR, core mutation 70/91, and *IL-28B* cannot be included in the present study. The difference of prevalence in those background factors would regulate the rate of SVR. It is likely that the SVR rate by combination therapy in elderly patients over 65 years old was obviously lower than in younger patients. In the present study, female elderly patients also showed a low SVR rate. As mentioned above, we could not include *ITPA* SNP associated with ribavirin-induced anemia. It is likely that Japanese elderly patients often have ribavirin-associated problems.

In the near future, triple therapy, including inhibiting protease in NS3/NS4 of the HCV polyprotein, will be available.[41] Among triple therapies, telaprevir is currently available orally, and may cause a rapid and

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marked decline in serum HCV RNA levels.[42–44] Triple-combination therapies with PEG IFN, ribavirin and telaprevir are expected to gain an excellent efficacy in treatment-resistant patients infected with HCV genotype 1 and a high viral load. Of note, the addition of telaprevir to the combination of PEG IFN and ribavirin has been associated with an increase in the rate of treatment discontinuation, predominantly due to the adverse events of rash and anemia.[42–44] A decrease in Hb levels was also found to be more common in patients receiving telaprevir-based regimens. The decline in telaprevir-treated patients was 0.5–1.0 dL greater than non-telaprevir-treated patients. In one Japanese report, the treatment was withdrawn in one-third of Japanese patients, mainly due to anemia with Hb levels of less than 8.5 g/dL.[44] However, ribavirin will most likely be required in combination with other specific HCV inhibitors and PEG IFN to achieve the high rates of SVR. Thus, the current experience modifying only ribavirin should contribute to the outcome of a lower discontinuation rate in the elderly patients.

In conclusion, reduction of ribavirin doses for elderly patients did not affect the outcome for the 48-week combination therapy. In our opinion, the elderly patients should be treated by combination therapy with ribavirin at the 400 mg dose at the start of treatment, because elderly patients tend to experience progressing anemia during PEG IFN with ribavirin.

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＜原　著＞

前インターフェロン非治癒の1b高ウイルス量C型慢性肝炎に対する二重濾過血漿交換併用ペグインターフェロン・リバビリン療法（第2報）

平嶋　昇[1)*]　岩瀬　弘明[2)]　都築　智之[2)]　神谷　麻子[2)]
横井　美咲[2)]　斎藤　雅之[2)]　玉置　大[2)]　龍華　庸光[2)]
日比野佑介[2)]　島田　昌明[2)]　後藤　秀実[3)]

要旨：以前インターフェロン治療（IFN）を行ったがSustained viral response（SVR）が得られなかったGenotype 1b・高ウイルス量のC型慢性肝炎12例（男性6例，女性6例，平均年齢60.3才）に対しDouble Filtration Plasmapheresis（DFPP）とペグインターフェロン・リバビリン（PEG IFN・Rib）療法を併用して治療を行った．前治療はIFN単独治療無効（Non responder；NR）3例，IFNα2b・Rib併用療法NR 2例，PEG IFNα2b・Rib併用療法再燃（Relapse；Rel）2例とNR 5例である．DFPPによるHCV RNAの減量は平均1.8（0.1-4.8）Log IU/mlであった．interferon sensitivity determing region（ISDR）とHCV coreアミノ酸（amino acid；aa）の変異はDFPP効果に影響を与えなかった．前治療IFN単独例が前治療Rib併用例よりもDFPPの効果が有意に高かった（$p<0.05$）．前治療IFN単独3例は全例（100%）SVRを獲得した．前治療IFNα2b・Rib併用2例はHCV RNAの陰性化は得られなかった．前治療PEG IFNα2b・Rib併用でRel 2例はSVRを獲得したが，NR 5例はSVRになった例は認められなかった．前治療PEG IFNα2b・Rib-Rel 2例はPEG IFNα2b・Rib投与期間およびAdherenceが前回と同等だったにも関わらずHCV RNA陰性化時期が早まり，DFPPを併用した効果と考えられた．最終的にSVRを獲得したのは12例中5例（41.7%），前治療Rib併用9例中2例（22.2%）であった．SVR率はISDR変異≧2個以上例で2/2（100%），ISDR変異0または1かつcore aa70か91一方が変異例で2/6（33.3%），ISDR0または1かつcore aa2個とも変異例で1/4（25.0%）の順に低下した．以前IFNを行ったがSVRが得られなかったGenotype 1b・高ウイルス量の難治性C型慢性肝炎に対し，DFPP併用PEG IFN・Rib療法を再治療として行う場合は前治療IFN単独NR症例やPEG IFN・Rib併用Rel症例に於いてはSVRが期待できると考えられた．

索引用語：　C型慢性肝炎　　二重濾過血漿交換
ペグインターフェロン・リバビリン療法　　ウイルス変異

緒　言

ペグインターフェロン・リバビリン（PEG IFN・Rib）療法により，Genotype 1b・高ウイルス量の難治性C型慢性肝炎の著効率は改善したが約50%は未だにC型肝炎ウイルス（HCV）の駆除が得られない[1)~3)]．この治療抵抗例にはウイルス側因子であるinterferon sensitivity determing region（ISDR）[4)]やHCV coreアミノ酸（amino acid；aa）変異[5)]，宿主側因子であるIL28B[6)]，治療側因子[7)~9)]などが複雑に関与することが判明している．診療を行う場合にはResponse-guided therapy[10)]が提唱され，治療開始後のHCV動態をみて治療期間を決

1）独立行政法人国立病院機構東名古屋病院消化器科
2）独立行政法人国立病院機構名古屋医療センター消化器科
3）名古屋大学消化器内科
*Corresponding author: hirasima@toumei.hosp.go.jp
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定することが重要である．開始後早期にHCV陰性化が得られること，特にHCV RNA量が早期に2 LogIU/m*l*以上低下することが目安の一つになっている[9]．一方，2008年4月からGenotype1b・高ウイルス量のC型慢性肝炎に対し二重濾過血漿交換[11]（Double Filtration Plasmapheresis；DFPP）が保険適応になった．DFPPでHCVの機械的除去を行って早期にHCV低下後にPEG IFN・Ribを組み合わせることにより，Genotype 1b・高ウイルス量の難治性C型慢性肝炎の治癒率が改善されることが期待されている．今回我々は，以前インターフェロン治療（IFN）を行ったがSustained viral response（SVR）が得られなかった難治症例に対しDFPPとPEG IFN・Ribを併用して治療を行ったので第一報[12]に引き続いて最終結果を報告する．本研究の目的はDFPP併用PEG IFN・Ribの安全性の確認とHCV減量効果の検討である．

対象と方法

対象は2008年8月から2009年12月までに名古屋医療センターでDFPPを導入し，名古屋医療センターおよび東名古屋病院でPEG IFN・Rib療法を行った，以前IFNを行ったがSVRが得られなかったGenotype 1b・高ウイルス量C型慢性肝炎患者12例である．本研究は実施計画書を作成して名古屋医療センターの倫理委員会の許可を得てprospectiveに実施した．ウイルス変異は治療開始前にISDR変異数とHCV core領域のaa70およびaa91変異を測定した．HCV core抗原値はCLEIA法で測定し，初回DFPP前後，4週間後，12週間後に測定した．HCV RNAはReal time PCR法で測定し，初回DFPP前，最終5回目DFPP終了直後，4週間，8週目以降は4週間毎測定し治療の効果判定を行った．ブラッドアクセスは，右内頸静脈または大腿静脈よりガンブロ株式会社Gam Cathカテーテル Nを留置して実施した．DFPPは，一次膜に旭化成クラレメディカル社プラズマフローOP，二次膜にカスケードフローEC-50Wを使用し血漿処理50mL/kgを目標とした．DFPPは第1週目に3回，2週目に2回行った．初回DFPP直後にPEG IFNαを注射しRib内服を開始，4回目DFPP直後に2回目注射を行った．PEG IFNの種類はα2aを希望する2例にはα2aを他の10例にはα2bを選択した．有意差検定はWelch検定で行いp＜0.05を有意とした．

成　　績

1．背景因子

DFPP＋PEG IFN・Rib療法を行った12例の背景因子をTable 1に示す．平均年齢60.3（37-74）才，男性6例　女性6例，BMI平均23.8（18.7-29.4）kg/m^2，前治療はIFN単独治療無効（Non responder；NR）3例，IFNα2b・Rib併用療法NR 2例，PEG IFNα2b・Rib併用療法再燃（Relapse；Rel）2例とNR 5例である．前治療がRib併用療法であった症例4～12のIFNのAdherenceは平均85.3（63-100）%，Ribは平均87.2（73.2-100）%であった．HCV RNAは平均6.5（5.4-7.7）Log IU/m*l*であった．肝生検は同意の得られた9例に施行しF1が1例，F2が2例，F3が6例であった．ISDR変異数は0が8例・1が2例・3が1例，5が1例であった．Core aa70変異なし（wild）かつaa91 wildが4例，aa70変異あり（mutant）かつaa91 wildが2例，aa70 wildかつaa91 mutantが2例，aa70 mutantかつaa91 mutant（core double mutant；CDM）が4例であった．ASTは平均61.5（36-108）IU/L，ALTは平均70.9（36-148）IU/L，血小板は平均13.7（10.6-23.0）×10^4/μL，Fibrinogenは平均227.1（182-324）mg/dLであった．

2．DFPPの結果

DFPPは12例全てにおいて5回ずつ施行できた．DFPPの穿刺手技や血漿交換に伴う異常症状や合併症は認められなかった．Fibrinogenが100 mg/dL以下に低下しDFPPを中止した症例は認めなかった．

DFPPによるViral dynamicsを検討した（Table 2, A）．

①DFPP 1回効率：初回DFPP前後でのHCV core抗原値の変化

HCV core抗原値は初回DFPP前（Table 2, b）平均8189（26-31900）fmol/L，初回DFPP後（c）6233（＜20-23200）fmol/Lであった．DFPP 1回効率（b-c/b）は平均25.9（6.4-50.1）%であった．

②全DFPP効率：初回DFPP前と5回目DFPP後でのHCV RNA量の変化

HCV RNAは初回DFPP前（Table 2, a）平均6.5（5.4-7.7）Log IU/m*l*，5回目DFPP後（d）は4.6（1.7-6.6）Log IU/m*l*であった．全DFPP効率（a-d）は平均1.8（0.1-4.8）Log IU/m*l*であった．

3．PEG IFN・Ribの治療経過（Table 2, B）

Case2, 6ではPEG IFNα2a 180 μgにて，それ以外10例はPEG IFNα2bを体重に応じて治療開始した．Adherenceは平均85.1（61.2-100）%であった．Ribは体重に

Table 1 Background characteristics of patients treated by DFPP+PEG IFN・Rib

Case	Age (years)	Sex	Weight (kg)	BMI (kg/m²)	Previous IFN	Adherence IFN (%)	Adherence Rib (%)	Outcome	Liver biopsy	HCV RNA (LogIU/ml)	Viral mutation ISDR	aa70	aa91	AST (IU/L)	ALT (IU/L)	PLT (×10⁴/μL)	Fibrinogen (mg/dL)
1	69	F	45	18.7	IFNα2b 24w			NR	F3A2	6.0	3	W	M	93	36	10.6	188
2	37	F	80	29.4	IFNα2b 24w			NR	F1A2	6.5	0	M	W	53	73	23.0	202
3	61	F	60	26.7	IFNα2b 24w			NR	F2A2	7.7	1	M	M	108	148	14.8	182
4	66	M	55	22.9	IFNα2b・Rib 24w	90	73.2	NR	NT	6.4	1	W	W	42	57	11.9	284
5	63	M	66	24.0	IFNα2b・Rib 24w	100	100	NR	F3A2	6.5	0	M	M	68	117	14.0	182
6	52	F	51	23.9	PEG IFNα2b・Rib 48w	100	86	NR	F3A2	6.3	0	M	M	51	45	14.2	324
7	70	F	61	24.1	PEG IFNα2b・Rib 46w	100	100	Rel	F3A2	6.0	0	W	W	56	62	14.6	191
8	57	M	69	26.5	PEG IFNα2b・Rib 72w	78	89	NR	F3A2	7.3	0	M	W	36	47	15.8	263
9	60	F	51	20.9	PEG IFNα2b・Rib 48w	63	69	NR	F2A2	6.0	0	W	M	50	62	10.1	280
10	74	M	62	22.3	PEG IFNα2b・Rib 34w	63	100	NR	NT	7.4	0	W	W	50	62	13.7	228
11	59	M	62	22.0	PEG IFNα2b・Rib 48w	78	68	NR	NT	6.6	0	M	M	68	77	10.0	197
12	56	M	67	23.7	PEG IFNα2b・Rib 48w	96	100	Rel	F3A3	5.4	5	W	W	63	65	11.7	204
Average:	60.3		60.7	23.8		85.3	87.2			6.5				61.5	70.9	13.7	227.1

IFN: interferon, BMI: body mass index, ISDR: interferon sensitivity determing region, aa: amino acid, n: natural, Rib: ribavirin, w: weeks, NR: non responder, PEG: peglated, Rel: relapse, NT: not tested, W: wild, M: mutant

応じて治療開始し，Adherence は平均 82.2(62.0-100)％であった．Rapid viral response（RVR）および Early viral response（EVR）となった Case2，3，7，12 で 48 週間治療を行った．Late viral response（LVR）となった Case1 では同意が得られず 50 週で治療を終了したが，Case9 では 72 週間治療を継続した．NR と判断した Case 5，6，8，11 では各々 16 週間，24 週間，48 週間，24 週間で治療を中止した．Case4 は Hb 5.9 g/dl まで低下したため 4 週間で，Case10 は血小板 6.2×10^4/μL まで低下したため 8 週間で治療を中止した（Drop out；DO）．

4. PEG IFN・Rib 中の Viral dynamics（Table 2, C）

Case1 の 4 週と 12 週，Case8，9 の 12 週において HCV RNA が陽性にも関わらず HCV core 抗原は感度以下＜20 fmol/L を示した．Case2，3，7，12 では HCV RNA 陰性の時期と HCV core 抗原は感度以下の時期は 4 週と 12 週で一致した．

RVR の Case2 と 12 は SVR を獲得した．EVR の Case 3 と 7 は SVR を獲得した．LVR の Case1 は SVR を獲得したが，Case9 は Rel となった．

DO の Case4 と 10 では HCV RNA の陰性化は得られなかった．

5. 最終治療結果（Table 2, D）

前治療 IFN 単独で NR だった Case1-3 の 3 例は 3 例全例（100％）SVR を獲得した．前治療 IFNα2b・Rib 併用療法で NR だった Case4，5 の 2 例は HCV RNA の陰性化は得られなかった．前治療 PEG IFNα2b・Rib 併用療法で Rel だった Case7 と 12 では SVR を獲得したが，NR だった 5 例は Case9 で LVR となったものの最終的には Rel となり，SVR を獲得した例は認められなかった．最終的に SVR を獲得したのは対象全 12 例中 5 例（41.7％），前治療 Rib 併用療法 9 例中 2 例（22.2％）であった．

6. HCV 遺伝子変異と治療効果（Table 3）

① ISDR 変異数と core 変異別 DFPP の効果（⊿ HCV RNA）

ISDR 変異 2 個以上 2 例では DFPP 前後で HCV RNA は平均－1.5 Log IU/ml の低下，ISDR0 または 1 かつ CDM でない 6 例では平均－2.3 Log IU/ml の低下，ISDR0 または 1 かつ CDM4 例では平均－1.4 Log IU/ml の低下であった．

② ISDR 変異数と Core 変異別最終治療結果

SVR 率は ISDR≧2 では 2/2（100％），ISDR 0 または 1 では 3/10（30.0％）であった．Core の変異を組み合

Table 2 Viral dynamics treated with DFPP and PEG IFN・Rib therapy

Case	Viral dynamics by DFPP (A)						PEG IFN・Rib therapy (B)					Duration of treatment (weeks)
	Before treatment		After 1st DFPP		After 5th DFPP		PEG IFN			Rib		
	HCV RNA a (logIU/ml)	Core antigen b (fmol/L)	Core antigen c (fmol/L)	⊿ b-c/b (%)	HCV RNA d (LogIU/ml)	⊿ a-d (LogIU/ml)	Kind	Initial dose (μg)	Adherence (%)	Initial dose (mg)	Adherence (%)	
1	6.0	4760	3660	23.1	5.4	0.6	α2b	80	99.1	600	98.3	50
2	6.5	4300	3430	20.2	1.7	4.8	α2a	180	95.8	800	100	48
3	7.7	20200	15400	23.8	4.9	2.8	α2b	100	100	600	72.3	48
4	6.4	5290	4360	17.6	4.3	2.1	α2b	100	67.0	600	68.0	4
5	6.5	2510	1510	39.8	4.8	1.7	α2b	100	100	800	100	16
6	6.3	4510	3380	25.1	6.2	0.1	α2a	180	100	600	82.1	24
7	6.0	26	<20	23.1	4.3	1.7	α2b	100	100	600	100	48
8	7.3	20800	16600	20.2	4.7	2.6	α2b	100	68.8	800	89.2	48
9	6.0	1020	668	34.5	4.5	1.5	α2b	80	61.2	600	64.3	72
10	7.4	31900	23200	27.3	6.6	0.8	α2b	80	67.0	600	68.0	8
11	6.6	2490	2330	6.4	5.5	1.1	α2b	100	62.0	800	62.0	24
12	5.4	465	232	50.1	3.1	2.3	α2b	100	100	800	82.6	48
Average:	6.5	8189	6233	25.9	4.6	1.8±1.2			85.1		82.2	

Case	Viral dynamics during PEG IFN・Rib (C)										The initial point of HCV RNA-negative (weeks)	Virological response	(D) Final outcome of treatment	Reason of discontinuance of treatment
	Core antigen (fmol/L)			HCV RNA (LogIU/ml)										
	Before	4W	12W	Before	4W	8W	12W	24W	48W	72W				
1	4760	<20	<20	6.0	3.8	1.6	1.2	0	0		21	LVR	SVR	
2	4300	<20	<20	6.5	0	0	0	0	0		4	RVR	SVR	
3	20200	113	<20	7.7	2.0	0	0	0	0		7	EVR	SVR	
4	5290	4360		6.4	3.3	3.7	6.0	4.9	6.4		—		DO	Anemia
5	2510	1670	2340	6.5	5.1	5.1	4.8	5.8			—		NR	
6	4510	2490	3560	6.3	6.2	6.5	6.2	6.4			—		NR	
7	26	<20*	<20	6.0	0*	0	0	0	0		5 [12]	EVR	SVR	
8	20800	8980	<20	7.3	4.6	3.2	2.3	2.5	3.2		—		NR	
9	1020	468	<20	6.0	4.0	4.0	1.2	0	0	1.2	24	LVR	Rel	
10	31900	12300	30100	7.4	6.6	6.0	6.4				—		DO	Thrombocytopenia
11	2490	2110	1980	6.6	6.4	5.5	4.7	5.6	7.2		—		NR	
12	465	<20	<20	5.4	0	0	0	0	0		4 [8]	RVR	SVR	

*data of 5W　　SVR: 5/12 (41.7%)

[ ] previous treatment (relapse case)

Table 3 Viral mutation and outcome of treatment

Viral mutation		⊿HCV RNA (LogIU/m*l*) by DFPP	Final outcome	n	SVR %
ISDR mutation≧2	n＝2	1.5±1.2	SVR	2	100
ISDR mutation 0 or 1 without CDM	n＝6	2.3±1.4	SVR Rel NR DO	2 1 1 2	33.3
ISDR mutation 0 or 1 with CDM	n＝4	1.4±1.1	SVR NR	1 3	25

ISDR: interferon sensitivity determing region, CDM: core double mutant
RVR: rapid viral response, EVR: early viral response, LVR: late viral response

Table 4 Previous IFN therpy and outcome of treatment

Pevious IFN		⊿HCV RNA (LogIU/m*l*) by DFPP	Final outcome	n	SVR %
IFN monotherapy	n＝3	2.7±2.1*	SVR	3	100
IFNα2b・Rib	n＝2	1.9±0.3**	NR DO	1 1	0
PEG IFNα2b・Rib	n＝7	1.4±0.8***	SVR Rel NR DO	2 1 3 1	28.6

The viral load reduction rate of NRs to a previous IFN monotherapy was significantly higher than that of the patients who previously received Rib combination therapy. (*and**, *and***; $p<0.05$)
ISDR: interferon sensitivity determing region, CDM: core double mutant
RVR: rapid viral response, EVR: early viral response, LVR: late viral response

わせるとSVR率はISDR 0または1かつCDM以外で2/6(33.3%), ISDR 0または1かつCDMで1/4(25.0%)であった.

7. 前IFN別の治療効果（Table 4）

①前IFN別DFPPの効果（⊿HCV RNA）

IFN単独3例のDFPP前後でのHCV RNAは平均−2.7 Log IU/m*l*の低下, IFNα2b・Rib 2例では平均−1.9 Log IU/m*l*の低下, PEG IFNα2b・Rib 7例では平均−1.4 Log IU/m*l*の低下であった. DFPP前後の⊿HCV RNAはIFN単独例とIFNα2b・Rib例およびPEG IFNα2b・Rib例の間に有意差を認めた（$p<0.05$）.

②前IFN別最終治療結果

SVR率はIFN単独例で3/3（100%）, IFNα2a・Rib例で0/2（0%）, PEG IFNα2b・Rib例で2/7（28.6%）であった.

考　案

PEG IFN・Ribの登場により, Genotype 1b・高ウイルス量の難治性C型慢性肝炎の著効率は改善したが約50%は未だにC型肝炎ウイルス（HCV）の駆除が得られない治療抵抗例である[1)~3)]. 治療抵抗因子が様々提唱される中で, 一般臨床では治療開始後のHCV動態をみて治療期間を決定するResponse-guided therapy[10)]が提唱され, HCV RNA量が早期に2 Log IU/m*l*以上低下することが効果判定の目安の一つになっている[9)]. 従って, 治療早期に強制的にでも二重濾過血漿交換（DFPP）でHCV RNA量を減少させた上でPEG IFN・Ribを併用すれば, Genotype 1b・高ウイルス量の難治性C型慢性肝炎の著効率は改善する可能性がある. 特に, 一度IFNを行った症例では再治療を行う場合は前回よりも効果向上が望まれる. そこで今回我々は, 以前IFNを行ったがSVRが得られなかったGenotype 1b・高ウイルス量の難治性症例に対し再治療の一環としてDFPPとPEG