Original Works

Prediction of a Non-virological Response to Pegylated Interferon and Ribavirin Combination Therapy for Genotype 1 Chronic Hepatitis C Based on Amino Acid Substitution in the HCV Core Region and the Early HCV RNA Reduction Rate

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Summary: Background and Aim: I here presented an easy method to predict a non-virological response (NVR) to pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy in chronic hepatitis C patients on the basis of amino acid (aa) substitutions in the hepatitis C virus (HCV) core region and serum HCV RNA reduction rate in early period of therapy.

Method: I enrolled 444 patients with genotype 1 chronic hepatitis C and high viral loads who received PEG-IFN/RBV combination therapy. After the initiation of therapy, aa substitutions in the HCV core region and serum HCV RNA levels were serially quantified.

Results: Analyses using receiver operating characteristic curves demonstrated a strong correlation between the HCV RNA reduction rate and virological response at 2 and 4 weeks of therapy. In patients with an HCV RNA reduction rate $<$0.85 log at 2 weeks and $<$1.36 log at 4 weeks, the NVR rate was 77.3% and 75%, respectively, in cases with a mutant-type HCV core aa 70.

Conclusions: NVR to PEG-IFN/RBV combination therapy can be predicted at a probability of above 75% when HCV core aa 70 is mutated and the HCV RNA reduction rate is $<$0.85 log at 2 weeks and $<$1.36 log at 4 weeks.

Key Words: Chronic hepatitis C, Genotype 1, PEG-IFN/RBV combination therapy, NVR.

Received: August 17, 2012. Accepted: August 23, 2012
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The authors indicated no potential conflict of interest.

Introduction

Infection with hepatitis C virus (HCV) is the leading cause of liver cirrhosis and hepatocellular carcinoma worldwide[1]. Now, a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) is recognized as the standard therapy for chronic hepatitis C[2]. Currently, more than 40% of genotype 1 chronic hepatitis C patients successfully maintain undetectable HCV RNA after completion of the 48-week course of PEG-IFN/RBV combination therapy; this is defined as a sustained virological response (SVR); however, genotype 1 chronic hepatitis C patients with high viral load (serum HCVRNA>100 KIU/ml) show a poor response to IFN-based therapy[3)4)].

PEG-IFN/RBV combination therapy can achieve a higher SVR rate than IFN monotherapy, but the rate remains at approximately 40%. Because both PEG-IFN and RBV have many adverse effects, such as cytopenia, skin rash, gastrointestinal symptoms, depression, fever and fatigue, many patients have to discontinue this therapy irrespective of the various virological responses.

Substitutions of amino acid (aa) 70 and/or 91 in the HCV core region have been reported to be significant predictors of non-SVR in Japan[5]. Monitoring of viral kinetics is also useful for an early prediction of the response to PEG-IFN/RBV combination therapy. As the average age of hepatitis C patients in Japan are getting older and they are likely to suffer from various adverse effects, the identification of those who are unlikely to respond to antiviral therapy in its early stages is important to avoid various adverse effects and reduce the high therapy cost. In addition, the early identification of responders motivates patients to adhere to therapy. In the present study, i examined whether combined examination of aa substitutions in the HCV core region and HCV dynamics in the early stages of therapy can be used as a tool for the early, rapid, and simple prediction of a non-virological response (NVR) or not.

Patients and methods

Patients

I enrolled 444 patients with genotype 1 chronic hepatitis C and high viral loads who received PEG-IFN/RBV combination therapy. All patients were admitted to and followed up at the outpatient clinic of the University Hospital of Kyoto Prefectural University of Medicine or 20 associated hospitals between December 2004 and August 2008. The patients included 236 men and 208 women, with the ages ranging from 19 to 76 years.

All patients were positive for serum HCV RNA and had elevated serum alanine aminotransferase (ALT) levels for at least 6 months. They were negative for hepatitis B virus surface antigen and human immunodeficiency virus. Patients with coexisting liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, or evidence of alcohol abuse, were excluded from this study. Patients with diabetes mellitus requiring insulin therapy or psychiatric diseases were also excluded. Liver needle biopsy was performed prior to therapy, and histological diagnoses were made according to the classification of Desmet et al.[6]. Informed consent was obtained from all participants, and the study protocol was approved by the ethical committee of the university.

Study protocol

PEG-IFN α-2b (PegIntron; Schering-Plough Corp., Kenilworth, NJ, USA) was administered once a week according to body weight (1.5 μg/kg/week). RBV (Rebetol; Schering-Plough Corp) was orally

administered at a dosage of 1000 mg (body weight, ≥80 kg), 800 mg (body weight, ≥60 kg), or 600 mg (body weight, <60 kg). The dosage of PEG-IFN was decreased when blood examination showed neutrophils of <750/mm^3 and/or platelet counts of <80000/mm^3. The dosage of RBV was decreased by 200 mg/day when the hemoglobin levels decreased by >2 g/dl during the first 2 weeks of therapy and/or when blood examination showed hemoglobin levels of <10 g/dl. The therapy duration was initially defined as 48 weeks, but extension was permitted to up to 72 weeks depending on patient's request. Therapy was discontinued when severe adverse effects appeared or blood examination showed hemoglobin levels of <8.5 g/dl, platelet counts of <50000/mm^3, and/or neutrophils of <500/mm^3. Negativity of serum HCV RNA during therapy was defined as virological responders (VR) and when it was not as NVR.

Measurements

The presence or absence of serum HCV RNA was assessed using a qualitative HCV RNA assay kit (Amplicor HCV v2.0; Roche Diagnostic Systems, Tokyo, Japan) with a lower detection limit of 50 IU/ml. Blood samples were obtained at baseline, 24 h, 2, 4, 12, and 24 weeks after the initiation of combination therapy and 24 weeks after the end of therapy. HCV genotypes were determined in a serological genotyping assay. Genotypes 1 and 2 in this assay correspond to genotypes 1 (1a, 1b) and 2 (2a, 2b), respectively, as proposed by Simmonds et al.[7]. Liver specimens were stained with Perls' Prussian blue to study iron loading and were scored from 0 to 4+ on the basis of the scoring system of MacSween et al.[8]. Steatosis was defined as the presence of fat droplets in >10% of hepatocytes in an adequate number of liver lobules and was scored as absent (0), slight (>0-10%, 1), mild (11-33%, 2), moderate (34-66%, 3), and severe (≥67%, 4)[9].

Serum leptin levels were determined using a commercially available immunoassay kit (Linco Research, St Charles, MO, USA), and adiponectin levels were determined using an ELISA kit (Adiponectin ELISA Kit; Otsuka Pharamaceutical Co., Tokyo, Japan). Serum insulin levels were determined using a RIA kit (Insulin Riabead Ⅱ Kit; Abbot, Tokyo, Japan). The insulin resistance index was calculated as follows: HOMA-IR = IRI × FGP/405. BMI was calculated as weight (in kg) divided by the square of height (in m). Substitutions of aa 70 or 91 in the HCV core region in genotype 1b was determined using the procedure reported by Akuta et al.[10].

Statistical analysis

Statistical analyses were performed using the Statistical Package of Service Solutions (SPSS Inc., Chicago, Ⅱ, USA) software, version 15.0. Data were expressed as medians with interquartile ranges. Groups were compared using the Mann-Whitney U-test, unless otherwise specified in the text. The Kruskal-Wallis test was used for comparison of multiple groups. Frequency analysis was performed using χ^2 and Fisher's exact tests. All tests were two-sided, and P values of <0.05 were considered significant. Receiver operating characteristic (ROC) curves were used to determine the relationship between virological responses (VR) and reductions in HCV RNA.

Results

Clinical backgrounds of the patients

The clinical backgrounds of the 444 chronic hepatitis C patients are presented in Tables 1-A and 1-B. Of the 444 patients, 335 (75.4%) patients showed VR and 109 (24.6%) NVR. Patients with NVR showed significantly advanced hepatic fibrosis (P = 0.036), a higher HCV RNA load (P = 0.025), and a

Table 1(A and B). Clinical backgrounds of the patients

The clinical backgrounds of genotype 1 chronic hepatitis C patients treated with PEG-IFN/RBV combination therapy are compared between virological responders (VR) and non-virological responders (NVR).

Hb: hemoglobin; Plt: platelet; BMI: body mass index

A

	VR	NVR	P
Number of cases	335	109	
Age(years)	55.0[19-76]	57.0[28-73]	0.112
Gender(M/F)	183/152	53/56	0.320
Stage(F0-2/F3-4/N.D.)	202/59/74	60/31/18	0.036
Grade(A0-1/A2-3/N.D.)	95/155/85	26/60/23	0.241
Fatty change(0/1-4/N.D.) 0: none, 1: <10%, 2: 11-33%, 3: 34-66%, 4: 67%<	138/35/162	55/17/37	0.608
Iron loading(0/1-4/N.D.) 0: no iron stain × 400 magnification, 1: recognition × 400 magnification, 2: recongition × 100 magnification, 3: recognition × 25 magnification, 4: recognition × 10magnification	102/72/161	48/27/34	0.481

Clinical backgrouns of the patients with chronic hepatitis C treated with PEG-IFN and RBV combination therapy were compared between virological responders (VR) and non virological responders (NVR).

B

	VR	NVR	P
HCVRNA(KIU/ml)	1500.0 [100-9800]	1785.0 [100-1785]	0.025
Hb(mg/dl)	14.3 [10.4-18.1]	14.2 [9.5-20.2]	0.917
Plt (× 10^4/μL)	16.8 [6-46]	16.2 [7-30]	0.043
Ferritin(ng/ml)	140.0 [5-1094]	158.0 [9-950]	0.087
BMI (kg/m^2)	22.9 [16.0-44.4]	23.5 [18.2-36.5]	0.694
Hyalluronic acid (ng/mL)	60.0 [5-600]	66.0 [4-694]	0.206
Thioredoxin	27.7 [11.1-88.4]	30.3 [10.2-83.4]	0.818
Leptin(ng/ml)	6.2 [0.2-91.6]	6.65 [1.2-26.7]	0.388
Adiponectin(mg/l)	10.1 [1.5-33.3]	10.9 [3.3-25.3]	0.619

Clinical backgrouns of the patients with chronic hepatitis C treated with PEG-IFN and RBV combination therapy were compared between virological responders (VR) and non virological responders (NVR).
Hb: hemoglobin; Plt: pletelet; BMI: body mass index;

lower platelet count (P=0.043) at baseline compared with patients with VR. The SVR rate to therapy was 68.4% (229/335) and 0% (0/109) in VR and NVR patients, respectively.

Assessment of aa substitutions and virological response

Fig. 2 shows the NVR rate in patients classified according to aa substitutions in the HCV core region. The NVR proportion in patients with mutant-type HCV core aa 70 was significantly (P=0.001)

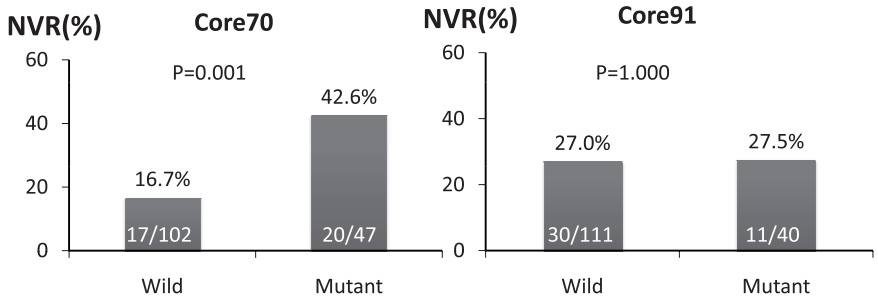

Fig. 1. The relationship between non-virological responders (NVR) and mutations in HCV core amino acid (aa) 70 and/or 91

The NVR rate was examined according to the presence/absence of mutatnt-type HCV core aa 70 and/or 91. The NVR rate was highest (42.6%) in patients with mutant-type HCV core aa.

higher than that in those with wild-type HCV core aa 70. However, the NVR proportion in patients with mutant-type HCV core aa 91 was not significantly different from that in those with wild-type HCV core aa 91 (P=1.000).

Assessment of viral kinetics according to aa substitutions

HCV RNA was quantified at 24 h, 2, 4, and 12 weeks after the initiation of combination therapy. The decrease in HCV RNA in log10 at each point was calculated, and viral kinetics was compared on the basis of aa substitutions. Fig. 3-A shows the HCV kinetics of patients with wild-type and mutant-type aa 70 in the HCV core region during combination therapy. The serum HCV RNA reduction rate in patients with wild-type versus (vs) mutant-type HCV core aa 70 at 24 h, 2, 4, and 12 weeks were 1.2 vs 1.1 (P=0.069), 1.5 vs 0.7 (P<0.001), 2.0 vs 1.6 (P<0.001), and 2.4 vs 1.6 (P<0.001), respectively. The HCV RNA reduction rate in patients with wild-type HCV core aa 70 was significantly higher than that in those with mutant-type HCV core aa 70 after 2, 4, and 12 weeks of combination therapy.

Fig. 3-B shows the HCV kinetics of patients with wild-type and mutant-type HCV core aa 91 during combination therapy. The serum HCV RNA reduction rate in patients with wild-type vs mutant-typeHCV core aa at 24 h, 2, 4, and 12 weeks were 1.2 vs 0.8 (P=0.049), 1.3 vs 1.1 (P=0.066), 1.7 vs 1.7 (P=0.256), and 2.0 vs 2.1 (P=0.270), respectively. These results show that the HCV RNA reduction rate in patients with wild-type HCV core aa 91 was significantly higher at 24 h than that in patients with mutant-type HCV core aa 91, but was not significant differences in the later period of therapy.

The sensitivity and specificity of viral reduction rate at 24 h, 2, 4, and 12 weeks for predicting NVR was analyzed by plotting ROC curves (Fig. 4 and Table 2). The area under the curve after 2 and 4 weeks of therapy was larger than that after 24 h and 12 weeks (0.858 and 0.874 vs 0.799 and 0.800, respectively). We therefore used the viral decrease at 2 and 4 weeks of therapy to predict NVR. At 2 weeks of therapy, the threshold for predicting NVR was 0.85 log; at this threshold, sensitivity was 85.0% and specificity was 78.3%. At 4 weeks of therapy, the threshold for predicting NVR was 1.36 log; at this threshold, sensitivity was 89.0% and specificity was 80.0%. Thus, the decrease in HCV RNA after 2 and 4 weeks of therapy correlated well with NVR.

Assessment of aa substitutions and viral kinetics as predictors of NVR

Finally, i examined the association between viral kinetics and HCV core aa 70 mutation. The NVR

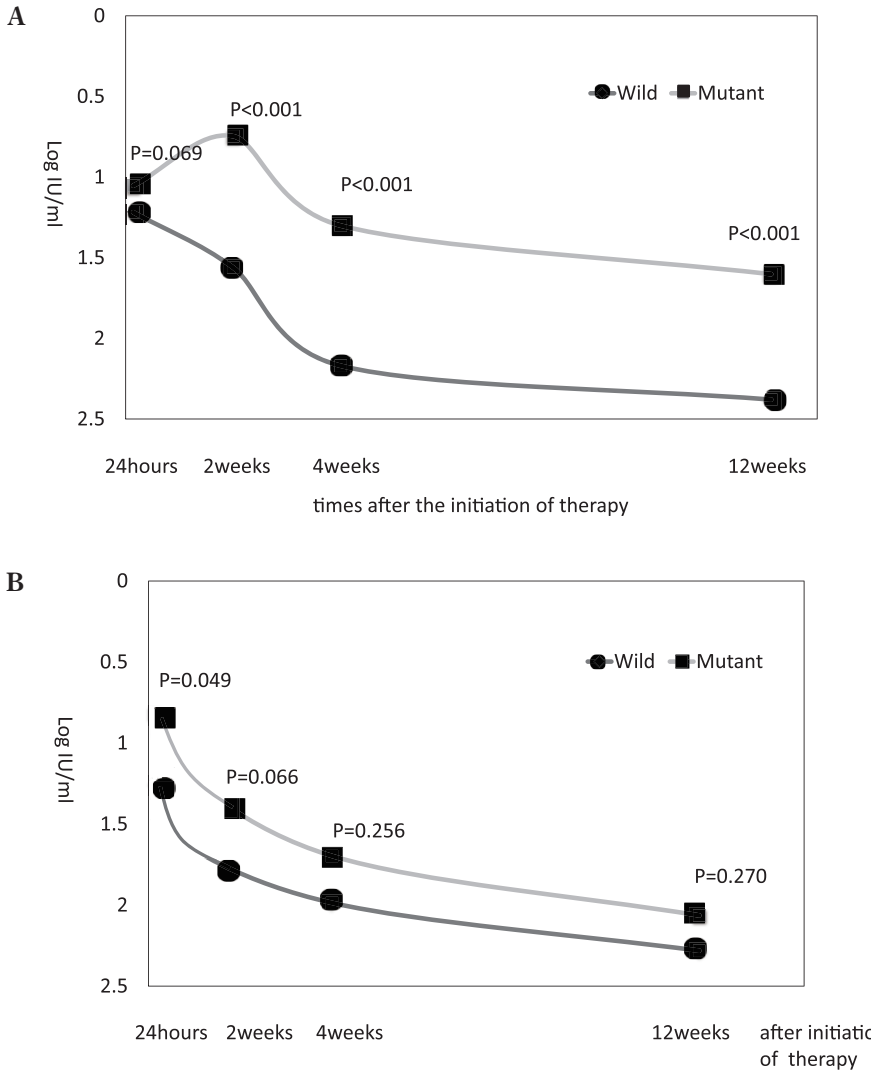

Fig. 2.(A and B). The reduction rate in serum HCV RNA during the early period of therapy
Thereduction ratein serum HCV RNA was examined and expressed as HCV RNA log 24 h/log 0 h, HCV RNA log 2 weeks/log 0 h, HCV RNA log 4 weeks/ log 0 h, and HCV RNA log 12 weeks/log 0 h.

rate was 77.3% in patients with mutant-type HCV core aa 70 and an HCV RNA reduction rate of $<$0.85 log at 2 weeks, and 75% in those with mutant-type HCV core aa 70 and an HCV RNA reduction rate of $<$1.36 log at 4 weeks (Fig. 4).

In patients with genotype 1 chronic hepatitis C and high viral loads, HCV core aa 70 is mutated and the HCV RNA reduction rate is $<$0.85 log at 2weeks and $<$1.36 log at 4 weeks can predicted NVR to PEG-IFN/RIV combination therapy at probability above 75%.

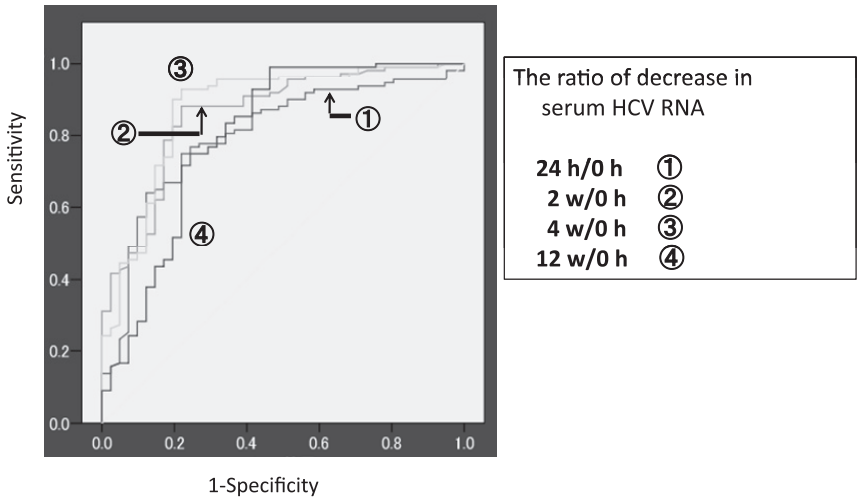

Fig. 3. Receiver operating characteristic (ROC) curve analysis
ROC curve analysis was performed to clarify the relationship between non-virological responders (NVR) and the decrease in serum HCV RNA at each time point.

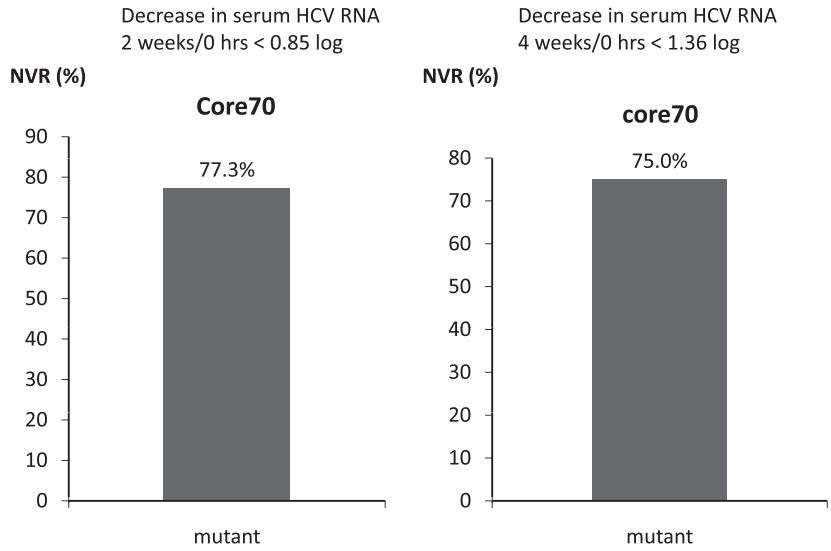

Fig. 4. The rate of non-virological responders (NVR) in the criteria
The NVR ratewas examined in patients with decreases in serum HCV RNA log 2 weeks/log 0 h and log 4 weeks/log 0 h.

Table 2. Area under the curve (AUC) values in receiver operating characteristic (ROC) curve analysis
The AUC values in ROC curve analysis (Fig. 4) are presented for each time point.

	AUC	95% C.I	P
The ratio of decrease in serum HCV RNA (24 h/0 h)	0.799	0.720-0.879	<0.001
The ratio of decrease in serum HCV RNA (2w/0 h)	0.858	0.791-0.926	<0.001
The ratio of decrease in serum HCV RNA (4w/0 h)	0.874	0.805-0.943	<0.001
The ratio of decrease in serum HCV RNA (12w/0 h)	0.800	0.709-0.891	<0.001

The AUC values in the ROC curve analysis (Fig 4) were presented at each time point.

Discussion

Currently, various host factors, such as adipokines, insulin resistance, body mass index (BMI), alcohol abuse, and hepatocyte steatosis, have been reported to be the predictors of SVR after PEG-IFN/RBV combination therapy[11-15]. In this study, I aimed to determine the factors that can predict NVR in the early stage of PEG-IFN/RBV combination therapy. As shown in Tables 1-A and 1-B, NVR showed a more advanced stage of fibrosis, a higherHCV RNA load, and a higher platelet count at baseline. Moreover, these patients presented a higher frequencyof mutant-type HCV core aa 70. Thus, reduction rate of HCV- RNA on 2 and 4 weeks after the start of PEG-IFN/RBV combination therapy correlated well with NVR.

I then combined the results of mutant-type HCV core aa 70 and the HCV RNA reduction rate at 2 and 4 weeks of therapy. The NVR rate in patients with mutant type HCV core aa 70 and HCV RNA reduction rate of $>$0.85 log at 2 week were 77.3% and with mutant-type HCV core aa 70 and HCV RNA reduction rate of $>$1.36 log at 4 week were 75%.

Thus, my criteria may be used easily by general practitioners to estimate the probability of NVR to PEG-IFN/RBV combination therapy within 1 month of initiation of therapy for genotype 1 chronic hepatitis C patients who received PEG-IFN/RBV combination therapy. Although the examination of aa substitutions in the HCV genome is not covered by public health insurance in Japan, these substitutions can be measured easily by PCR[16].

In PEG-IFN/RBV combination therapy of chronic hepatitis C, the interval between the start of therapy and disappearance of serum HCV RNA is considered to be a reliable marker for the prediction of outcome[17], and response-guided therapy is recommended. However, in clinical practice, most patients prefer to know the probability of NVR before or immediately after the initiation of therapy. In this regard, my criteria with an HCV RNA reduction rate of $<$0.85 log at 2 weeks and $<$1.36 log at 4 weeks and mutant-type HCV core aa 70 can strongly predict NVR with a probability of above 75% within 2 weeks or a month after the initiation of therapy. We advocate that our criteria is useful for a wide range of physicians as simple and easy predictor.

Recently, a strong association was reported between interleukin 28B (IL28B) gene polymorphism

and the response to PEG-IFN/RBV combination therapy in genotype 1 chronic hepatitis C patients[18-20], but it is difficult to advocate a criterion comprising these factors for use by a wide range of Japanese general practitioners because it requires host genome analysis.

Evaluation of hepatic fibrosis by liver biopsy contributes to the prediction of NVR (Table 1-A). However, because liver biopsy is not required by the Japanese public health insurance for the prescription of PEG-IFN/RBV combination therapy, many patients refuse to undergo liver biopsy but are willing to be treated with the combination therapy. In this regard, my criteria provides useful information regarding efficacy of the combination therapy without liver biopsy in its early stages.

A reduction rate of <0.85 log at 2 weeks and/or <1.36 log at 4 weeks with mutant-type HCV core aa 70 were the criteria used. This criteria is useful to predict NVR in PEG-IFN/RBV combination therapy for genotype 1 chronic hepatitis C patients. Recently, studies on response-guided therapy recommended prolonged therapy for up to 72 weeks for patients with late virological response[21-24].

Acknowledgment

The author expresses special thanks to Yoshito Itoh, Associate Professor of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine and Toshikazu Yoshikawa, President of Kyoto Prefectural University of Medicine, for their contributions to this study.

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〈和文抄録〉

Core70，ISDR のアミノ酸変異と治療早期ウイルス減少率からみた 1 型 C 型肝炎患者に対する PEG-IFN/RBV 療法の NVR 予測の検討

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C 型慢性肝炎に対するペグインターフェロン・リバビリン（PEG-IFN/RBV）併用療法は最も強力な治療法であるが，費用が高くつく．従って，効果が望めない症例の治療早期の効果予測は臨床上有用と考えられる．本研究では，C 型慢性肝炎で PEG-IFN/RBV 併用療法を受けた 444 例を対象に治療中に HCV RNA が消失した症例を virological responder （VR），HCV RNA が消失しなかった症例を non virological responder（NVR）として治療早期の HCV RNA 減少率と治療効果に関係するとされる HCV core の 70 番目のアミノ酸変異の有無を組み合わせて治療早期の NVR 規定因子を検討した．HCV core の 70 番目のアミノ酸が変異型の場合，2 週間後の HCV RNA の減少率が 0.85 log 未満であれば NVR 率は 77.3％，4 週間後の HCV RNA の減少率が 1.36 log 未満であれば NVR 率は 75.0％であり，臨床応用に有用と考えられた．

キーワード：C 型慢性肝炎，1 型，ペグインターフェロン・リバビリン併用療法，NVR.