peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: Amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol 46:403–410.

Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2007b. Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b. J Med Virol 79:1686–1695.

Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Miyakawa Y, Kumada H. 2007c. Prediction of response to pegylated interferon and ribavirin in hepatitis C by polymorphisms in the viral core protein and very early dynamics of viremia. Intervirology 50:361–368.

Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2007d. Amino acid substitutions in the hepatitis C virus core region are the important predictor of hepatocarcinogenesis. Hepatology 46:1357–1364.

Arase Y, Chayama K, Ikeda K, Tsubota A, Suzuki Y, Saitoh S, Kobayashi M, Suzuki F, Akuta N, Someya T, Kobayashi M, Kumada H. 2001. Randomized controlled clinical trial of lymphoblastoid interferon-alpha for chronic hepatitis C. Hepatol Res 21:55–66.

Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, Hosaka T, Sezaki H, Yatsuji H, Kawamura Y, Kobayashi M, Kumada H. 2007. Interferon-induced prolonged biochemical response reduces hepatocarcinogenesis in hepatitis C virus infection. J Med Virol 79:1485–1490.

Bruno S, Camma C, Di Marco V, Rumi M, Vinci M, Camozzi M, Rebucci C, Di Bona D, Colombo M, Craxi A, Mondelli MU, Pinzello G. 2004. Peginterferon alfa-2b plus ribavirin for naïve patients with genotype 1 chronic hepatitis C: A randomized controlled trial. J Hepatol 41:474–481.

Chayama K, Tsubota A, Arase Y, Saitoh S, Koida I, Ikeda K, Matsumoto T, Kobayashi M, Iwasaki S, Koyama S, Morinaga T, Kumada H. 1993. Genotypic subtyping of hepatitis C virus. J Gastroenterol Hepatol 8:150–156.

Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer Jr. HC, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag JL, Van Thiel DH, Tamburro C, Lefkowitch J, Albrecht J, Meschievitz C, Ortego TJ, Gibas A. 1989. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized, controlled trial. Hepatitis Interventional Group. N Eng J Med 321:1501–1506.

Desmet VJ, Gerber M, Hoofnagle JH, Manna M, Scheuer PJ. 1994. Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 19:1513–1520.

Di Bisceglie AM, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, Goodman Z, Banks SM, Hoofnagle JH. 1989. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized double blood, placebo controlled trial. N Eng J Med 321:1506–1510.

Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, Lok AS, Bonkovsky H, Morgan TR, Dienstag JL, Ghany M, Morishima C, Snow KK. 2007. Prolonged antiviral therapy with peginterferon to prevent complications of advanced liver disease associated with hepatitis C: Results of the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. Hepatology 46:290A.

Donlin MJ, Cannon NA, Yao E, Li J, Wahed A, Taylor MW, Belle SH, Di Bisceglie AM, Aurora R, Tavis JE. 2007. Pretreatment sequence diversity differences in the full-length hepatitis C virus open reading frame correlate with early response to therapy. J Virol 81:8211–8224.

Dusheiko GM. 1998. The natural course of chronic hepatitis C: Implications for clinical practice. J Viral Hepatol 5(Suppl 1):9–12.

El-Shamy A, Sasayama M, Nagano-Fujii M, Sasase N, Imoto S, Kim SR, Hotta H. 2007. Prediction of efficient virological response to pegylated interferon/ribavirin combination therapy by NS5A sequences of hepatitis C virus and anti-NS5A antibodies in pre-treatment sera. Microbiol Immunol 51:471–482.

Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Izumi N, Marumo F, Sato C. 1995. Comparison of full-length sequences of interferon sensitive and resistant hepatitis C virus 1b. J Clin Invest 96:224–230.

Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Ogura Y, Izumi N, Marumo F, Sato C. 1996. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 334:77–81.

Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, Arase Y, Fukuda M, Chayama K, Murashima N, Kumada H. 1998. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: A prospective observation of 2215 patients. J Hepatol 28:930–938.

Jouet P, Roudot-Thoraval F, Dhumeaux D, Metreau JM. 1994. Comparative efficacy of interferon alfa in cirrhotic and noncirrhotic patients with non-A, non-B, C hepatitis. Gastroenterology 106: 686–690.

Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, Shimotono K. 1990. Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis. Proc Natl Acad Sci USA 87:9524–9528.

Kenny-Walsh E. 1999. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 340:1228–1233.

McHutchison JG, Patel K, Schiff ER, Gitlin N, Mur RE, Everson GT, Carithers RL Jr, Davis GL, Marcellin P, Shiffman ML, Harver J, Albercht JK. 2008. Clinical trial: Interferon alfa-2b continuous long-term therapy versus repeated 24-week cycles for retreating chronic hepatitis C. Aliment Pharmacol Ther 27:422–432.

Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hürter D, Nawrocki M, Kruska L, Hensel F, Petry W, Häussinger D. 1998. Progress of chronic hepatitis C: Results of a large, prospective cohort study. Hepatology 28:1687–1695.

Nomura H, Kashiwagi Y, Hirano R, Tanimoto H, Tsutsumi N, Higasgi M, Ishibashi H. 2007. Efficacy of low dose long-term interferon monotherapy in aged patients with chronic hepatitis C genotype 1 and its relation to alpha-fetoprotein: A pilot study. Hepatol Res 37:490–497.

Poynard T, McHutchinson J, Goodman Z, Ling MH, Albrecht J. 2000. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Group. Hepatology 31:211–218.

Original Paper

Intervirology

Intervirology 2008;51:1–6
DOI: 10.1159/000118789

Received: December 5, 2007
Accepted after revision: December 13, 2007
Published online: February 29, 2008

Efficacy in Patients with Dose Reduction in Combination Therapy of Peginterferon and Ribavirin for Chronic Hepatitis C

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Key Words
Chronic hepatitis C · Peginterferon · Ribavirin · Dose reduction

Abstract
Objective: The aim of this study was to elucidate efficacy after dose reduction in combination therapy of peginterferon and ribavirin for chronic hepatitis C. ***Methods:*** Inclusion criteria were hepatitis C virus (HCV) genotype 1b, serum HCV RNA level of ≥100 KIU/ml, dose reduction of peginterferon and/or ribavirin between the first 4 weeks and 20 weeks after the initiation of treatment. 164 patients were enrolled in this retrospective cohort study. Predictive factors for sustained viral response (SVR) after dose reduction were examined. ***Results:*** Out of the 146 patients treated with dose reduction, 57 had SVR. Multivariate analysis showed that SVR occurred when serum HCV RNA at the time of dose reduction was negative ($p < 0.001$) and total ribavirin dose was ≥100% of the anticipated total dose ($p < 0.001$). 57% (55/97) of patients with undetectable serum HCV RNA at the time of dose reduction had SVR. In contrast, only 4% (2/49) of patients with detectable serum HCV RNA at the time of dose reduction had SVR. ***Conclusions:*** On dose reduction of combination therapy for chronic hepatitis C, undetectable serum HCV RNA at the time of dose reduction and attainment of the total ribavirin dose of ≥100% enhance SVR.

Introduction

Combination therapy of peginterferon and ribavirin for hepatitis C virus (HCV) induces sustained virological response (SVR) in 50–60% of cases with genotype 1 and in 80–90% of cases with genotype 2. These SVR rates in patients treated with combination of peginterferon and ribavirin were higher than those treated with interferon (IFN) alone [1–6]. Thus, combination therapy of peginterferon and ribavirin has been recommended as a first choice for chronic hepatitis C. However, combination therapy has been associated with various adverse events, such as psychological disturbances, poor appetite, skin rash, infection, anemia and leukopenia [1, 2, 5, 7]. Dose reduction or even discontinuation of treatment often becomes necessary in combination therapy for chronic hepatitis C. In several studies, the reduction rate due to severe side effects was reported to be about 25–40%.

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Some authors have reported that adherence to combination therapy enhanced sustained virological eradication in genotype 1 with chronic hepatitis C [8–12]. In the present study, we evaluated the efficacy after dose reduction of combination therapy in Japanese patients. The study design is non-randomized retrospective cohort study.

Materials and Methods

Patients

Eligibility criteria for entry into the study included the following: (1) HCV genotype 1b; (2) serum level of HCV RNA of ≥100 KIU/ml; (3) dose reduction of peginterferon and ribavirin between the first 4 weeks and 20 weeks after the initiation of combination therapy; (4) no corticosteroid, immunosuppressive agents, or antiviral agents used within 6 months; (5) no hepatitis B surface antigens, antinuclear antibodies, or antimitochondrial antibodies detectable in serum, determined by radioimmunoassay, and (6) leukocytes >2,000/mm^3, platelet count >80,000/mm^3, and bilirubin <2.0 mg/ml. We excluded from the study all the patients with the following: (1) a history of alcohol abuse; (2) advanced liver cirrhosis of encephalopathy, bleeding esophageal varices, or ascites. The Institutional Ethics Review Board of our hospital approved our study. The physician in charge explained the purpose and method of this clinical trial, as well as the potential adverse reactions, to each patient, who later gave his/her informed consent for participation.

Combination Therapy of Pegylated-IFN and Ribavirin

For the treatment regimen, the peginterferon (Peg-intron; Schering-Plough Pharmaceutical Co., Osaka, Japan) and ribavirin (Rebetol; Schering-Plough Pharmaceutical Co.) were given based on body weight. At the initiation of combination therapy, patients received peginterferon at a median dose of 1.5 μg/kg (range 1.2–1.6 μg/kg) subcutaneously each week and oral ribavirin at a median dose of 11.9 mg/kg (range 10.0–16.3 mg/kg) daily. The peginterferon dose was adjusted according to body weight (60 μg for ≤40 kg, 80 μg for >40 and ≤60 kg, 100 μg for >60 and ≤80 kg, and 120 μg for >80 and ≤100 kg). The ribavirin dose was adjusted according to body weight (600 mg for ≤60 kg, 800 mg for >60 and ≤80 kg, and 1,000 mg for >80 kg).

The physician in charge reduced the dose of treatment when the blood cell count decreased. Peginterferon was stepwise reduced 20 μg/week if the WBC declined to <1,500/mm^3, leukocyte count to <750/mm^3 or platelet count to <80,000/mm^3. Ribavirin was stepwise reduced 200 mg if the hemoglobin level declined to ≤10 g/dl. The doses of peginterferon and ribavirin could be increased back to starting doses if these adverse events resolved. The amounts of both medications taken by each patient were expressed as a percentage of the anticipated total dose in the 48-week treatment regimen based on body weight. The median duration of treatment was 48 weeks (range 8–96 weeks). A SVR to therapy was defined as clearance of HCV RNA by commercial amplicor HCV qualitative assay (Amplicor HCV, Version 2.0; Roche Diagnostic Systems, Basel, Switzerland) at 6 months after the cessation of combination therapy [13].

Blood samples were obtained just before and 6 months after combination therapy. The samples were stored at –80° until analyzed. Using these blood samples, the HCV RNA level before IFN therapy was analyzed by quantitative PCR assay (Amplicor GT-HCV Monitor Version 2.0; Roche Molecular Systems) [14]. HCV genotype was examined by polymerized chain reaction assay, using a mixture of primers for the six subtypes known to exist in Japan, as reported previously [15]. The start of the follow-up period was defined as the first day of dose reduction in combination therapy. Clinical evaluation and biochemical and hematological tests were performed at 1- to 4-weekly intervals. We evaluated the following: (1) SVR after dose reduction, and (2) predictive factors for SVR after reduction based on combination therapy-related side effects.

Liver Histology before IFN Therapy

Liver biopsy specimens were obtained percutaneously under the observation by laparoscopy using a modified Vim Silverman needle with an internal diameter of 2 mm (Tohoku University style, Kakinuma Factory, Tokyo, Japan), fixed in 10% formalin, and stained with hematoxylin and eosin, Masson's trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. The biopsy specimens were scored according to the system of Desmet et al. [16].

Statistical Analysis

A Cox proportional hazards model was used to analyze the factors contributing to the stop of treatment and dose reduction due to combination therapy: factors examined included age, sex, body mass index, histological findings, HCV load, ALT, hemoglobin, WBC, platelet count, HCV RNA at the time of dose reduction, total ribavirin dose and peginterferon dose. Significance of trends in values was determined with a Cochran-Armitage Trend Test. $p < 0.05$ was considered statistically significant. The SPSS software package (SPSS 11.0 for Windows; SPSS Inc., Chicago, Ill., USA) was used for analyses.

Results

Clinical Characteristics of the Patients

A total of 146 patients were enrolled in the present study. The clinical characteristics of patients before combination therapy are shown in table 1. In 15 patients, a liver biopsy was not available because the patients declined to have a biopsy taken. Reduction time after the initiation of combination therapy was 12.0 ± 12.7 weeks (mean ± SD).

Predictors for SVR after Dose Reduction in Combination Therapy

Out of the 146 patients treated with dose reduction, 57 had SVR. Univariate analysis showed that the following seven factors significantly affected the SVR rate in all the patients: HCV RNA at the time of dose reduction ($p < 0.001$), HCV RNA at week 12 ($p < 0.001$), peginterferon

Table 1. Clinical characteristics before combination therapy of peginterferon and ribavirin in chronic hepatitis C patients (n = 146)

Characteristics	Patients, n or median (range)
Age, years	55 (20–69)
Male/female	81/65
Body weight, kg/height, cm	64.9 (36.7–96.6)/ 163.2 (135.2–185.5)
Body mass index	23.1 (16.6–32.0)
History of interferon therapy (–/+)	79/67
Liver histology (fibrosis, mild/moderate/severe)	61/47/23
HCV load, KIU/ml	1,500 (105–5,000)
AST/ALT, IU/l	55 (20–324)/76 (13–580)
Hemoglobin, g/dl	14.4 (10.4–17.9)
Platelets, $\times 10^4/mm^3$	14.1 (8.4–26.0)
WBC, $\times 10^3/mm^3$	4,200 (2,000–8,800)

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cells.

and/or ribavirin dose ($p < 0.001$), sex ($p < 0.001$), HCV RNA level before treatment ($p = 0.024$), histopathological staging ($p = 0.031$), and HCV RNA at week 24 ($p = 0.042$) (table 2A). The variables were mutually correlated and multivariate Cox regression analysis was performed with the seven statistically significant variables in the model. As shown in table 2B, multivariate analysis showed that SVR occurred when serum HCV RNA at the time of dose reduction after the initiation of combination therapy was negative ($p < 0.001$) and total ribavirin dose was ≥100% ($p < 0.001$).

SVR Rate Based on Adherence of Combination Therapy in Patients with Dose Reduction

The SVR rate based on adherence of combination therapy in patients with dose reduction was evaluated. Patients were divided into two groups based on the negativity or positivity of HCV RNA at the time of dose reduction after the initiation of combination therapy. Table 3A shows the SVR rate based on adherence of combination

Table 2. Predictive factors for SVR after dose reduction, based on combination therapy-related side effects

A Univariate analysis

Factor	Category	Odds ratio	95% CI	p value
HCV RNA at the time of reduction	–/+	1/0.09	0.04–0.21	<0.001
HCV RNA at week 12	–/+	1/0.09	0.04–0.22	<0.001
Total ribavirin dose, %	<100/≥100	1/8.58	3.99–18.47	<0.001
Total peginterferon dose, %	<100/≥100	1/3.37	1.672–7.04	<0.001
Sex	male/female	1/0.20	0.10–0.42	<0.001
HCV RNA, MEq/ml	<1,000/≥1,000	1/0.43	0.21–0.90	0.024
Liver histology, fibrosis	mild/moderate or severe	1/0.46	0.23–0.93	0.031
HCV RNA at week 24	–/+	1/0.12	0.01–0.92	0.042
Hemoglobin, g/dl	<13/≥13	1/2.29	0.87–5.98	0.092
Platelets, $\times 10^4/mm^3$	<10/≥10	1/2.55	0.86–7.61	0.092
WBC, mm^3	<3,000/≥3,000	1/1.14	0.40–1.27	0.062
ALT, IU/l	≥100/<100	1/1.31	0.59–2.93	0.164
Body mass index	<25/≥25	1/1.24	0.59–2.62	0.566
Age, years	<55/≥55	1/1.13	0.35–3.69	0.838

B Multivariate analysis

Factor	Category	Odds ratio	95% CI	p value
HCV RNA at the time of reduction	–/+	1/0.10	0.04–0.28	<0.001
Total ribavirin dose, %	<100/≥100	1/6.90	2.54–19.05	<0.001

ALT = Alanine aminotransferase; WBC = white blood cells.

Table 3. SVR rate based on adherence of combination therapy in patients with **A** negativity and **B** positivity of serum HCV RNA at the time of dose reduction[1]

A

Total peginterferon dose, %	Total ribavirin dose, %				Total
	<60	61–80	81–100	101–130	
<60	25 (1/4)	40 (2/5)	75 (2/4)	none	38 (5/13)
61–80	0 (0/2)	50 (2/4)	60 (6/10)	100 (2/2)	56 (10/18)
81–100	33 (2/6)	36 (5/14)	50 (7/14)	82 (9/11)	52 (23/44)
101–130	none	none	67 (6/9)	79 (11/14)	77 (17/22)
Total	30 (3/10)	39 (9/23)	57 (21/37)	81 (22/27)	57 (55/97)

B

Peginterferon dose, %	Ribavirin dose, %				Total
	<60	61–80	81–100	101–130	
<60	0 (0/4)	0 (0/2)	0 (0/2)	none	0 (0/8)
61–80	0 (0/2)	0 (0/7)	0 (0/1)	0 (0/4)	0 (0/14)
81–100	0 (0/2)	0 (0/7)	0 (0/2)	20 (1/5)	6 (1/16)
101–130	none	none	0 (0/7)	25 (1/4)	9 (1/11)
Total	0 (0/8)	0 (0/16)	0 (0/12)	15 (2/13)	4 (2/49)

[1] $p = 0.08$ for comparison of the 4 peginterferon groups and $p < 0.001$ for comparison of the 4 ribavirin groups (Cochran-Armitage Trend Test).

therapy in patients with negativity of serum HCV RNA at the time of dose reduction. 55 (57%) of 97 patients with undetectable serum HCV RNA at the time of dose reduction had SVR. A stepwise increase in SVR was observed when the dose of ribavirin was increased ($p < 0.001$, Cochran-Armitage Trend Test). SVR was 42.8% (27/63) in patients who had negativity of serum HCV RNA at the time of dose reduction and had adherence of <100% in both peginterferon and ribavirin. Relapse rate after termination of combination therapy was 43% (42/97) in patients with negativity of serum HCV RNA at the time of dose reduction.

Table 3B shows the SVR rate based on adherence of combination therapy in patients with positivity of serum HCV RNA at the time of dose reduction. Only 2 (2%) of 49 patients with positivity of serum HCV RNA at the time of dose reduction had SVR.

Reasons for Dose Reduction

Of 146 patients with dose reduction, 40 had dose reduction of peginterferon only. 53 patients had dose reduction of ribavirin and 53 patients had both reduction of peginterferon and ribavirin. The cause of reduction accounted for the following: anemia 87 (59.6%), leukopenia 39 (26.7%), thrombocytopenia 22 (15.1%) and other reason, such as general fatigue, 46 (31.5%). 55 of 146 patients with dose reduction had two causes for dose reduction.

Discussion

We have described the efficacy in patients with dose reduction after the initiation of combination therapy of peginterferon and ribavirin for chronic hepatitis C. The present study was limited to patients with genotype 1 and HCV load of ≥100 KIU/ml because previous studies have suggested that SVR in patients with genotype 2 or 3 is not adversely affected by dose reduction [5, 6, 17]. Another limitation of the study was that patients were treated for different durations. This heterogeneity makes it slightly difficult to interpret the results of the study.

However, several findings from the present study have direct implications for dose reduction of the combination therapy of chronic hepatitis C in the future. First, unde-

tectable serum HCV RNA at the time of dose reduction and attainment of total ribavirin dose of ≥100% enhanced SVR in patients with dose reduction. For now, the gold standard of treatment for chronic hepatitis C is a 48-week regimen of combination therapy. Many studies have suggested that reducing the ribavirin dose within the first 12–20 weeks of treatment in patients with genotype 1 was associated with a decline in SVR [8, 9, 18]. The present study indicated that the treatment for >48 weeks and the total ribavirin dose of ≥100% enhanced SVR when patients with a dose reduction showed negativity of serum HCV RNA at the time of dose reduction. Second, most patients with detectable HCV RNA at the time of dose reduction did not have SVR regardless of a peginterferon and ribavirin dose of ≥100%. In patients with detectable HCV RNA at the time of dose reduction, prolonged combination therapy could not enhance SVR.

Several predictive factors of SVR to combination therapy in patients without dose reduction have been identified, and these include amino acid (aa) substitutions in HCV CR (double wild-type; arginine at aa 70/leucine at aa 91), low-density lipoprotein cholesterol (≥86 mg/dl), male gender, γ-glutamyl transpeptidase (<109 IU/l), indocyanine green retention test at 15 min (<10%), and ribavirin dose (≥11.0 mg/kg) [19]. The present study indicates that HCV RNA at the time of dose reduction and total ribavirin dose were good indicators for predicting SVR in patients with dose reduction.

Some studies have suggested that SVR is increased when patients receive a higher dose of peginterferon and/or ribavirin according to body weight [1, 20]. However, in the present study, when the patients had detectable HCV RNA at the time of dose reduction, they had a slight chance of achieving a SVR regardless of prolonged combination therapy with a total dose of ≥100%. Thus, the suitable strategies of combination therapy for chronic hepatitis C patients with dose reduction within the first 20 weeks of treatment are as follows: (1) When the patients show undetectable serum HCV RNA at the time of dose reduction, they should be given combination therapy aimed at SVR; they should be treated with combination therapy of peginterferon and total ribavirin dose of ≥100%. (2) When they show a detectable serum HCV RNA at the time of dose reduction, they should not be given combination therapy aimed at SVR.

In conclusion, on dose reduction of combination therapy in patients with genotype 1b and high virus load, undetectable serum HCV RNA at the time of dose reduction and attainment of the total ribavirin dose of ≥100% enhance SVR.

Acknowledgements

The present work was supported in part by grants-in-aid from Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labor and Welfare.

References

1 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.

2 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.

3 Bruno S, Cammà C, Di Marco V, Rumi M, Vinci M, Camozzi M, Rebucci C, Di Bona D, Colombo M, Craxi A, Mondelli MU, Pinzello G: Peginterferon alfa-2b plus ribavirin for naïve patients with genotype 1 chronic hepatitis C: a randomized controlled trial. J Hepatol 2004;41:474–481.

4 Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group: Peginterferon-alpha-2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.

5 Dalgard O, Bjøro K, Hellum KB, Myrvang B, Ritland S, Skaug K, Raknerud N, Bell H: Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology 2004;40:1260–1265.

6 Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A: Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005;352:2609–2617.

7 Iwasaki Y, Ikeda H, Araki Y, Osawa T, Kita K, Ando M, Shimoe T, Takaguchi K, Hashimoto N, Kobatake T, Tomita M, Kawaguchi M, Kobashi H, Sakaguchi K, Shiratori Y: Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. Hepatology 2006;43:54–63.

8 McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK; International Hepatitis Interventional Therapy Group: Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061–1069.

9 Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, Lok AS, Morgan TR, Bonkovsky HL, Lee WM, Dienstag JL, Ghany MG, Goodman ZD, Everhart JE; Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial Group: Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology 2004;26:1015–1023.
10 Shiffman ML, Ghany MG, Morgan TR, Wright EC, Everson GT, Lindsay KL, Lok AS, Bonkovsky HL, Di Bisceglie AM, Lee WM, Dienstag JL, Gretch DR: Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. Gastroenterology 2007;132:103–112.
11 Lindahl K, Stahle L, Bruchfeld A, Schvarcz R: High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. Hepatology 2005;41:275–279.
12 Krawitt EL, Gordon SR, Grace ND, Ashikaga T, Ray MA, Palmer M, Yarze JC, Moskowitz S; for the New York New England Study Team. A study of low-dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol 2006;101:1268–1273.
13 Albadalejo J, Alonso R, Antinozzi R, Bogard M, Bourgault AM, Colucci G, Fenner T, Petersen H, Sala E, Vincelette J, Young C: Multicenter evaluation of the Cobas Amplicor HCV assay, an integrated PCR system for rapid detection of hepatitis C virus RNA in the diagnostic laboratory. J Clin Microbiol 1998;36:862–865.
14 Doglio A, Laffont C, Caroli-Bosc FX, Rochet P, Lefebvre J: Second generation of the automated Cobas Amplicor HCV assay improves sensitivity of hepatitis C virus RNA detection and yields results that are more clinically relevant. J Clin Microbiol 1999;37:1567–1569.
15 Dusheiko G, Schmilovitz-Weiss H, Brown D, McOmish F, Yap PL, Sherlock S, McIntyre N, Simmonds P: Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease. Hepatology 1994;19:13–18.
16 Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ: Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–1520.
17 Von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Häussinger D, Herrmann E, Zeuzem S: Peginterferon-alpha-2a (40 kDa) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology 2005;129:522–527.
18 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J: Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003;38:645–652.
19 Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H: Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol 2007;46:403–410.
20 Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, Bourliere M, Renou C, Tran A, Melin P, Hezode C, Chevalier M, Bouvier-Alias M, Chevaliez S, Montestruc F, Lonjon-Domanec I, Pawlotsky JM: Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology 2006;131:1040–1048.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

The Efficacy of Short-Term Interferon-Beta Therapy for Type C Cirrhotic Patients with Genotype 2a and Low Virus Load

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Abstract

Objective The aim of this study was to elucidate the efficacy of short-term interferon (IFN) therapy for type C cirrhotic patients with genotype 2a and low virus load.

Methods The present study was retrospective cohort study. Inclusion criteria were liver cirrhosis, hepatitis C virus (HCV) genotype 2a, the serum HCV RNA level of less than 100 KIU/mL, and IFN period of 6 or 8 weeks. Twenty-five consecutive patients who satisfied the above criteria were treated with IFN-beta daily at the dosage of 6 MU for 6 or 8 weeks. Independent factors that might have influenced sustained virologic response (SVR) were studied using multiple logistic regression analysis.

Results Background of clinical profiles were as follows: median (range) age=64 (53-76) years, male/female=13/12, and median (range) HCV-RNA=31 (8-90) KIU/mL. Out of 25, 14 patients (56.0%) had SVR by the intention-to-treat analysis. The SVR was significantly associated with serum HCV RNA level. Logistic analysis showed that SVR occurred when HCV RNA level was <50 KIU/mL (p=0.047). Based on the difference of the serum HCV RNA level, the SVR rate was 68.4% (13/19) in patients with a serum HCV RNA level of <50 KIU/mL and 16.7% (1/6) in patients with a serum HCV RNA level of ≥50 KIU/mL.

Conclusions The 6 or 8-week IFN-beta therapy is a possible selection of therapy for cirrhotic patients with HCV genotype 2a and a serum HCV RNA level of <50 KIU/mL.

Key words: liver cirrhosis, hepatitis C virus, genotype 2a, low virus load, interferon, sustained viral response

(Inter Med 47: 1085-1090, 2008)
(DOI: 10.2169/internalmedicine.47.0886)

Introduction

Current interferon (IFN) therapy for patients with chronic hepatitis C viral infection has been directed at viral clearance. Recent studies have reported improvement of therapeutic efficacy when IFN is combined with ribavirin (1-8). However, IFN is expensive and has a number of serious side effects. Therefore, if the treatment period would become shorter, it could be preferable.

On the other hand, several predictive factors of sustained viral response (SVR) to IFN have been identified, and these include short duration of disease, young age, absence of liver cirrhosis, genotype 2a, low hepatitis C virus (HCV)-RNA levels, HCV and mutant type of nonstructual5A region (9-15). Patients with liver cirrhosis (LC) have a high development of hepatocellular carcinoma (HCC) and progression to decompensated state. Thus, patients with a cirrhotic state should be treated for protection of progression of LC stage. In particular, LC patients with genotype 2a and low HCV-RNA levels might have the possibility of eradication of HCV RNA with a small dose or a short period of interferon (IFN). However, there is also controversy over how long the IFN therapy should be continued to eradicate HCV RNA in

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Received for publication January 5, 2008; Accepted for publication February 13, 2008
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Table 1. Clinical Characteristics before Short-term Interferon Therapy in Type C Liver Cirrhosis with Genotype 2a and Low Virus Load

Characteristics	(n=25)
Age (years old)*	64 (53-76)
Male/female†	13/12
Period of IFN therapy (6w/8w)†	19/6
Total dose of IFN (MU)*	246 (123-336)
HCV load (KIU/mL)*	31 (8-90)
AST (IU/L)*	83 (39-203)
ALT (IU/L)*	74 (27-412)
Hemoglobin (g/dL)*	12.6 (9.7-16.3)
Platelet(10^4/mm^3)*	11.4 (8.0-17.0)
WBC(10^3/mm^3)*	3.8 (3.0-6.9)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, HCV: hepatitis C virus, IFN: interferon, MU: million unit, WBC: white blood cell count.

*Data are expressed as median (range), †Data are number of patients.

LC patients with genotype 2a and low HCV-RNA.

Thus, in this study, we evaluated the efficacy of short-term interferon (IFN) therapy for type C cirrhotic patients with genotype 2a and a low virus load.

Materials and Methods

Patients

A total of 25 consecutive cirrhotic type C patients treated with IFN-beta for HCV RNA clearance at Toranomon Hospital in Tokyo, Japan between 2002 and 2006 were enrolled in this study. This study was a retrospective cohort study. Enrollment criteria were: repeated alanine aminotransferase (ALT) elevation of greater than the upper normal limits (ALT normal range: 12-50 IU/L) for more than six months; histological evidence of liver cirrhosis at the time of entry into the trial by the use of distinction equation between chronic hepatitis and liver cirrhosis in patients with hepatitis C virus infection (16); positive serum HCV RNA; serum HCV RNA level of less than 100 KIU/mL; genotype 2a. We excluded from the study all the patients: 1) with concurrent hepatitis B virus (HBV); 2) with a history of IFN therapy; 3) Leukocytes <3,000/mm^3, platelets <80,000/mm^3 and bilirubin >1.5 mg/mL before IFN therapy.

Twenty-five patients received IFN at a dose of 6 million units (MU) of natural IFN-beta (Toray Industries or Daiichi Pharmaceutical Co., Tokyo, Japan) daily for 6 or 8 weeks. In general, patients were treated with IFN for 6 weeks and six patients who were treated for 8 weeks were assigned by randomized controlled trial. We regarded sustained virologic response (SVR) to therapy as clearance of HCV RNA by amplicor method (17) for more than 6 months after cessation of therapy. Our study was approved by the institutional ethics review board of our hospital. The physician in charge explained the purpose and method of the clinical trial as well as the potential adverse reactions to each patient, who later gave his/her informed consent for participation.

Blood testing

Blood samples were obtained just before IFN therapy and stored at -80℃. Using these blood samples, HCV-RNA levels before IFN therapy were analyzed by quantitative PCR assay (Amplicor GT-HCV Monitor Version 2.0, Roche Molecular Systems, USA) (18).

On the other hand, serum HCV-RNA at 6 months after the termination of IFN therapy was analyzed by the qualitative PCR assay. The lower detection limit of the qualitative assay is 100 copies/mL. HCV genotype was examined by the PCR assay, using a mixture of primers for the six sub-

Table 2. Predictive Factors for SVR in Short-term Interferon Therapy in Type C Liver Cirrhosis with Genotype 2a and Low Virus Load

Factor	Category	Odds ratio	95% CI	p value*
HCV RNA (KIU/mL)	<50 /≥50	1/0.09	0.01-0.97	.047
AST (IU/L)	≥76 /<76	1/0.46	0.18-1.17	.102
Age (years)	<60/ ≥60	1/0.22	0.04-1.42	.112
Platelet(10^4/mm^3)	<10/≥10	1/3.00	0.57-15.76	.306
WBC(10^3/mm^3)	<4/≥4	1/2.33	0.46-11.81	.367
Sex	Male /Female	1/0.71	0.14-3.58	.682
ALT (IU/L)	<100/≥100	1/0.75	0.13-4.29	.746
Total dose of IFN (IU/L)	<200/≥200	1/1.29	0.23-7.05	.772
Period of IFN therapy (week)	6/ 8	1/1.19	0.20-6.99	.851

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CI: confidence interval, HCV: hepatitis C virus, IFN: interferon, WBC: white blood cell count.

*p value calculated by logistic regression analysis.

types known to exist in Japan, as reported previously (19).

Statistical analysis

Nonparametric procedures were employed for the analysis of background features of the patients with SVR and without SVR, including the Mann-Whitney U test. Independent factors that might have influenced SVR were studied using multiple logistic regression analysis, and the following variables were evaluated as prognostic factors: sex, age, HCV RNA level, liver histology, biochemical factors (AST (aspartate aminotransferase), ALT) before IFN therapy and methods of IFN administration. The SPSS software package (SPSS Inc., Chicago, IL) was used to perform statistical analysis. A p value of <0.05 was considered to indicate a significant difference.

Results

Patients' characteristics

Table 1 shows the characteristics of the 25 patients who had performed IFN therapy. Clinical profiles were as follows: median (range) age=64 (53-76) years, male/female= 13/12, and median (range) HCV-RNA=31 (8-90) KIU/mL. All the patients were categorized as Child-Pugh-Turcotte score class A. Of the 25 patients originally included in this study, in five patients the dose of the IFN therapy was reduced from 6 MU to 3 MU because of general fatigue and thrombocytopenia at the time of 1-3 weeks after the initiation of IFN. Thus, the total dose of IFN was 228.0±79.2 million units (MU). The median (range) leukocyte and platelet count in patients with dose reduction were 3.400 (3.100-4.800)/mm^3 and 95.000 (8.8-11.4)/mm^3, respectively, while those in patients without dose reduction were 4.600 (3.000-6.900)/mm^3 and 120.000 (80.000-120.000)/mm^3. Both leukocyte and platelet count in patients without dose reduction were higher than those in patients with dose reduction (leukocyte; p=0.013, platelet; p=0.011).

Efficacy of treatment

Out of twenty-five patients enrolled on present study, 14 patients (56.0%) had SVR by the intention-to-treat analysis.

Table 3. The Difference of Clinical Backgrounds between Patients with SVR and Those without SVR

	SVR	Non-SVR	p value
Age (years old) † (<60/≥60)	7/7	2/9	0.183
Sex (male/female) †	8/6	5/6	0.647
Period of IFN therapy† (6 week/8 week)	9/5	8/3	0.986
Total dose of IFN (MU) † (<200/≥200)	5/9	5/6	0.698
HCV-load (KIU/mL) *	16 (8-69)	66 (23-98)	0.021
AST (IU/L) *	63 (39-203)	85 (53-141)	0.730
ALT (IU/L) *	75 (27-434)	88 (34-230)	0.557
Hemoglobin (g/dL) *	13.7 (10.1-16.3)	11.7 (9.7-16.1)	0.139
Platelet(10^4/mm^3) *	12.2 (8.7-17.0)	10.0 (8.0-16.0)	0.096
WBC(10^3/mm^3) *	4.0 (3.1-6.9)	3.8 (3.0-5.3)	0.841

ALT: alanine aminotransferase, AST: aspartate aminotransferase, HCV: hepatitis C virus, IFN: interferon, MU: million unit, SVR: sustained virologic response, WBC: white blood cell count.

*Data are expressed as median (range), †Data are number of patients,

‡ p value calculated by the Mann-Whitney U test.

The SVR was significantly associated with serum HCV RNA level. The patients with a HCV RNA level of <50 KIU/mL tend to have high SVR compared to those with higher than that in patients with HCV RNA level of ≥50 KIU/mL (Table 2). Based on the difference of serum HCV RNA level, the SVR rate was 68.4% (13/19) in patients with a serum HCV RNA level of <50 KIU/mL and 16.7% (1/6) in patients with a serum HCV RNA level of ≥50 KIU/mL. Table 3 shows the differences in the clinical background between patients with SVR and those without SVR. The serum level of HCV RNA in patients with SVR was lower than that in patients without SVR.

Adverse events

Within one week after the initiation of treatment, flu-like symptoms appeared in all the patients. The leukocyte count was 4,320±1,370/mm^3 and the platelet count was 119,000± 23,000/mm^3 before the initiation of IFN therapy, whereas the values were 2,670±830/mm^3 and 71,000±17,000/mm^3, respectively, two weeks after the initiation of the therapy. None of the patients withdrew from this treatment due to IFN-related side effects.

Discussion

The present study was limited by non-randomized controlled trial. Another limitation of the study was that the number of the patients was small. However, several findings from the present study have direct implications for the short-term IFN treatment of LC patients with genotype 2a and low virus load.

First, more than 50% of patients cleared HCV RNA. This result indicates that the 6- or 8-week regimen of IFN therapy was preferable to eradicate HCV RNA in LC patients with genotype 2a and low virus load. Second, the patients with HCV RNA level of <50 KIU/mL tend to have high SVR compared to those with higher than that in patients with HCV RNA level of ≥50 KIU/mL. On the treatment

period, the efficacy of the 6-week regimen of IFN therapy was almost the same as that of the 8-week regimen. Moreover, the efficacy of the total dose of IFN of <200 MU was not different from that by the total dose of ≥200 MU. These results indicate that in about two-thirds of LC patients with a genotype 2a and serum HCV RNA level of <50 KIU/mL and low virus load, HCV was eradicated by the 6-week regimen or total dose of IFN of <200 MU.

Regarding the side effects of IFN, no patient withdrew the treatment due to IFN-related side effect. Okanoue et al (20) reported that side effects occurred when the daily IFN dose was increased. In the present study, five patients had to reduce the IFN dose due to IFN side effects. On the IFN therapy for LC patients, the physician in charge should check the clinical findings compared to the patients with chronic hepatitis C.

At present, the combined IFN and ribavirin therapy is a standard therapy for chronic hepatitis C patients with genotype 1b and a high load of HCV-RNA. However, prolonged combination therapy of IFN and ribavirin is associated with various side effects. If the total dose of IFN is decreased and the period of IFN therapy is short, it would be desirable from two points of cost and side effect. Fortunately, in patients with low HCV-RNA levels, HCV RNA tends to be eradicated with a small dose of IFN (21-24). The present study indicates that in patients with a low HCV-RNA, HCV RNA can be eradicated with a small dose of IFN.

Conclusion

The present study indicates that the 6 or 8-week of IFN therapy is a possible selection of therapy for liver cirrhotic type C patients with genotype 2a and low virus load.

Acknowledgement

The present work was supported in part by grants-in-aid from Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labour and Welfare.

References

1. McHutchison JG, Poynard T, Pianko S, et al. The impact of interferon plus ribavirin on response to therapy in black patients with chronic hepatitis C. Gastroenterology **119**: 1317-1323, 2000.
2. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med **339**: 1485-1492, 1998.
3. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha 2b plus ribavirin for 48 weeks or 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet **52**: 1426-1432, 1998.
4. Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alpha 2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. Lancet **351**: 83-87, 1998.
5. Schalm SW, Hansen BE, Chemello L, et al. Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. Meta-analysis of individual patient data from European Centers. J Hepatol **26**: 961-966, 1997.
6. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med **343**: 1666-1672, 2000.
7. Lindsay KL, Trepo C, Heintges T, et al. Hepatitis Interventional Therapy Group. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology **34**: 395-403, 2001.
8. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment for chronic hepatitis C: a randomised trial. Lancet **358**: 958-965, 2001.
9. Tsubota A, Chayama K, Ikeda K, et al. Factors predictive of response interferon-alpha therapy in hepatitis C virus infection. Hepatology **19**: 1088-1094, 1994.
10. Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alpha therapy for chronic hepatitis C: A randomized, double blind placebo-controlled trial. N Engl J Med **321**: 1506-1510, 1989.
11. Causse X, Godinot H, Chevallier M, et al. Comparison of 1 or 3 MU of interferon alfa-2b and placebo in patients with chronic non-A non-B hepatitis. Gastroenterology **101**: 497-502, 1991.
12. Chayama K, Saitoh S, Arase Y, et al. Effect of interferon administration on serum hepatitis C virus RNA in patients with chronic hepatitis C. Hepatology **13**: 1040-1043, 1991.
13. Reichard O, Glaumann H, Fryden A, et al. Two-year biochemical, virological and histological follow-up in patients with chronic hepatitis C responding in a sustained fashion to interferon alfa-2b treatment. Hepatology **21**: 918-922, 1995.
14. Shiratori Y, Kato N, Yokosuka O, et al. Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Tokyo-Chiba Hepatitis Research Group. Gastroenterology **113**: 558-566, 1997.
15. Enomoto N, Sakuma I, Asahina Y, et al. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med **334**: 77-811, 996.
16. Ikeda K, Saitoh S, Kobayashi M, et al. Distinction between chronic hepatitis and liver cirrhosis in patients with hepatitis C virus infection. Practical discriminant function using common laboratory data. Hepatol Res **18**: 252-266, 2000.
17. Albadalejo J, Alonso R, Antinozzi R, et al. Multicenter evaluation of the COBAS AMPLICOR HCV assay, an integrated PCR system for rapid detection of hepatitis C virus RNA in the diagnostic laboratory. J Clin Microbiol **36**: 862-865, 1998.
18. Doglio A, Laffont C, Caroli-Bosc FX, Rochet P, Lefebvre J. Second generation of the automated Cobas Amplicor HCV assay improves sensitivity of hepatitis C virus RNA detection and yields results that are more clinically relevant. J Clin Microbiol **37**: 1567-1569, 1999.
19. Dusheiko G, Schmilovitz-Weiss H, Brown D, et al. Hepatitis C virus genotypes; an investigation of type-specific differences in geographic origin and disease. Hepatology **19**: 13-18, 1994.
20. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol **25**: 283-291, 1996.
21. Dalgard O, Mangia A. Short-term therapy for patients with hepatitis C virus genotype 2 or 3 infection. Drugs **66**: 1807-1815, 2006.
22. Tabaru A, Narita R, Hiura M, Abe S, Otsuki M. Efficacy of short-term interferon therapy for patients infected with hepatitis C virus genotype 2a. Am J Gastroenterol **100**: 862-867, 2005.
23. Sato Y, Tokuue H, Kawamura N, et al. Short-term interferon ther-

apy for chronic hepatitis C patients with low viral load. Hepatogastroenterology **51**: 968-972, 2004.

24. Fujiyama S, Chikazawa H, Honda Y, Tomita K. Effective interferon therapy for chronic hepatitis C patients with low viral loads. Hepatogastroenterology **50**: 817-820, 2003.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Suitable Treatment Period in Patients with Virological Response during Combination Therapy of Peginterferon and Ribavirin for Chronic Hepatitis C

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Abstract

Objective The aim of this study was to determine the suitable treatment period in patients who achieve virological response during combination therapy of peginterferon and ribavirin for chronic hepatitis C virus infection.

Methods Inclusion criteria were HCV-genotype 1b, serum HCV RNA level of ≥100 KIU/ml before treatment, and negativity of serum HCV RNA during treatment. The 366 patients were enrolled in this retrospective cohort study. Patients were classified into four groups according to difference of response: rapid-virological response (RVR) at week 4 after the initiation of treatment (n=37), early-virological response (EVR) at week 5-12 (n=161), late-virological response (LVR) at week 13-24 (n=131), and superlate-virological response (SLVR) at week 25-48 (n=37). A non-relapse in patients with undetectable HCV RNA during therapy was defined as clearance of HCV RNA 6 month after the cessation of therapy.

Results Of the 366 patients, 241 had non-relapse and the non-relapse rate in each group was 89% (33/37) in RVR, 79% (127/161) in EVR, 54% (71/131) in LVR, and 27% (10/37) in SLVR. In RVR, 26 of 27 patients with continuance of negative HCV RNA of ≥30 weeks during treatment had non-relapse. In EVR, patients with period of negative HCV RNA of ≥40 weeks had non-relapse rate of 90% (71/79). In LVR and SLVR, all nine patients with continuance of negative HCV RNA of ≥60 weeks had non-relapse.

Conclusion A suitable treatment period of combination therapy for chronic hepatitis C should be determined based on the time of attainment of negative HCV RNA.

Key words: chronic hepatitis C, peginterferon, ribavirin, suitable treatment period

(Inter Med 47: 1301-1307, 2008)
(DOI: 10.2169/internalmedicine.47.0797)

Introduction

Current evidence indicates that combination therapy of peginterferon and ribavirin for hepatitis C virus (HCV) is associated with a higher rate of sustained virological response (SVR) compared with interferon (IFN) alone (1-7). Hence, combination therapy of peginterferon and ribavirin for HCV has been recommended as a first choice for chronic hepatitis C. During combination therapy, the serum level of HCV RNA becomes negative in about 70 to 80% of patients with genotype 1 and a high virus load. However, about 20 to 30% of patients with negativity of HCV-RNA during combination therapy relapse after termination of 48 week treatment. Thus, there is an ongoing need to refine treatment strategies because many patients do not respond or relapse after treatment.

Jensen et al reported that a rapid virological response (RVR), defined as undetectable HCV RNA at week 4 of treatment with peginterferon α-2a plus ribavirin, was the

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single best predictor of SVR in genotype 1 patients treated for either 24 or 48 weeks in a randomized, multinational trial (8). This indicates that patients with RVR should be treated for a short course-regimen. In contrast, it may be necessary to treat patients without RVR using a long course-regimen.

The selection of duration of treatment and optimum doses of combination therapy is an area of active investigation (9-15). When the patients with chronic hepatitis C have an undetectable HCV RNA during combination therapy, it is not clear how long the physician should continue the treatment. Thus, in this present study, we performed a retrospective study to examine the relationship between attainment time of negativity of serum HCV RNA after the initiation of combination therapy and the continuance period of negative HCV RNA in patients with undetectable HCV-RNA during treatment.

Materials and Methods

Patients

Eligibility criteria for entry into the study included the following: 1) HCV genotype 1b; 2) serum level of HCV RNA of≥100 KIU/ml before treatment; 3) no corticosteroid, immunosuppressive agents, or antiviral agents used within 6 months; 4) no hepatitis B surface antigens (HBsAg), antinuclear antibodies, or antimitochondrial antibodies detectable in serum, determined by radioimmunoassay; 5) leukocytes >2,000/mm^3, platelet count >80,000/mm^3, and bilirubin <2.0 mg/ml; 6) negativity of serum HCV RNA within 48 weeks after initiation of combination therapy; 7) duration of treatment of ≥8 weeks; 8) the initiation time of treatment was from December 2004 to September 2006. We excluded from the study all the patients with the following: 1) a history of alcohol abuse; 2) advanced liver cirrhosis of encephalopathy, bleeding esophageal varices, or ascites. The institutional ethics review board of our hospital approved our study. The physician in charge explained the purpose and method of this clinical trial, as well as the potential adverse reactions, to each patient, who later gave his/her informed consent for treatment. Informed consent was obtained after confirming the negativity of serum HCV RNA during combination therapy. A total of 366 HCV patients were enrolled in this retrospective cohort study at the study hospital.

Patients were classified into four groups according to the response of combination therapy: RVR, defined as undetectable HCV RNA at week 4 after the initiation of combination therapy; early virological response group (EVR), defined as undetectable HCV RNA at week of 5 to 12 of combination therapy; late virological group (LVR), defined as undetectable HCV RNA at week 13 to 24 of combination therapy; and super late virological group (SLVR), defined as undetectable HCV RNA at week 25 to 48 of combination therapy. A non-relapse in patients with undetectable HCV RNA during combination therapy was defined as clearance of HCV RNA by commercial amplicor HCV qualitative assay (Amplicor HCV; Ver.2.0, Roche Diagnostic Systems, Basel, Switzerland) at 6 month after the cessation of combination therapy (16).

Patients were classified into four groups and evaluated according to the difference of clinical and biochemical backgrounds. Next, predictors of no-relapse in patients with undetectable HCV RNA in serum during treatment were assessed by the multiple logistic regression analysis. Finally, the no-relapse rate based on the attainment time of negativity of HCV RNA and continuance of negative HCV RNA during combination therapy was examined.

Combination therapy of peginterferon and ribavirin

For the treatment regimen, the peginterferon (Peg-intron, Schering-Plough Pharmaceutical Co., Osaka, Japan) and ribavirin (Rebetol, Schering-Plough Pharmaceutical Co.) were given at the dose described based on body weight. At the initiation of combination therapy, patients received peginterferon at a median dose of 1.4 μg/kg (range, 1.3-1.8 μg/kg) subcutaneously each week and oral ribavirin at a median dose of 11.9 mg/kg (range, 9.5-15.4 mg/kg) daily. The peginterferon dose was adjusted according to body weight (60 μg for ≤40 kg, 80 μg for >40 kg and ≤60 kg, 100 μg for >60 kg and ≤80 kg, 120 μg for >80 kg and ≤100 kg, and 150 μg for >100 kg). The ribavirin dose was adjusted according to body weight (600 mg for ≤60 kg, 800 mg for >60 kg and ≤80 kg, and 1,000 mg for >80 kg).

A total of 202 patients were treated with 48 week regimen and 113 patients were given combination therapy for > 48 week regimen. Treatment for the remaining 51 patients was discontinued because of treatment-related side effects within 48 weeks after the initiation of combination therapy. On the duration of treatment, 126 patients were given combination therapy based on regimen of clinical trial, 142 patients were treated for 48 weeks of within health insurance, and 98 patients were decided by physician's judgement.

Blood samples were obtained just before and 6 months after combination therapy. The samples were stored at -80℃ until analysis. Using these blood samples, the HCV-RNA level before IFN therapy was analyzed by quantitative PCR assay (Amplicor GT-HCV Monitor Version 2.0, Roche Molecular Systems) (17). HCV-genotype was examined by polymerized chain reaction assay, using a mixture of primers for the six subtypes known to exist in Japan, as reported previously (18). Serum alanine aminotransferase (ALT), aspartic aminotransferase (AST) concentrations, and HCV RNA were measured at least once per month during therapy. Negativity of serum HCV RNA was defined as clearance of serum HCV RNA by commercial amplicor HCV qualitative assay.

Follow-up protocol

The start of follow-up period was defined as the first day that showed negative HCV RNA after the initiation of com-

bination therapy. Clinical evaluation and biochemical and hematological tests were performed at 4 weekly intervals.

Liver Histology before IFN therapy

Liver biopsy specimens were obtained percutaneously under observation by laparoscopy using a modified Vim Silverman needle with an internal diameter of 2 mm Tohoku University style, Kakinuma Factory, Tokyo), fixed in 10% formalin, and stained with hematoxylin and eosin, Masson's trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. The biopsy specimens were scored according to the system of Desmet et al (19). Baseline liver histology of chronic hepatitis prior to IFN therapy was classified according to the extent of fibrosis, into four stages: mild (F1), periportal expansion; moderate (F2), portoportal septa; severe (F3), portocentral linkage or bridging fibrosis; liver cirrhosis (F4). Patients with F1 or F2 were considered as non severe fibrosis. Patients with F3 or F4 were considered as severe fibrosis. In 47 patients, a liver biopsy was not available, because the patients declined to have a biopsy taken.

Statistical analysis

Clinical and biochemical backgrounds before combination therapy among groups based on efficacy of treatment were analyzed using Krusukall Wallis test. We used multivariate analysis (multiple logistic regression analysis) to establish which factors contributed to the non-relapse after combination therapy. Results for each variable were transformed into categorical data consisting of two simple original numbers for multivariate analysis. $p<0.05$ was considered statistically significant. The variables that we use for multivariate analysis were age, sex, liver histology, body mass index (BMI), HCV-RNA load, continuance period of negative HCV RNA, attainment timing of negative HCV RNA, AST, ALT, hemoglobin, white blood cell, and platelet count. Significance of trends in values was determined with Cochran-Armitage trend test. A $p<0.05$ was considered statistically significant. The SPSS software package (SPSS 11.0 for windows; SPSS Inc., Chicago, IL, USA)was used for analyses.

Results

Clinical characteristics of the patients

A total of 366 patients were enrolled in the present study. Patients were classified into four groups according to the difference of response: RVR (n=37), EVR (n=161), LVR (n=131), and SLVR (n=37). The clinical and laboratory characteristics of the patients at baseline are shown in Table 1. There was a significant difference in the serum level of HCV RNA before treatment among the four groups classified based on the difference of response.

Predictors of non-relapse in patients

Of the 366 patients originally included in this study, 241 had non-relapse and the non-relapse rates in each group were 89% (33/37)in RVR, 79% (127/161) in EVR, 54% (71/122) in LVR, and 27% (10/37) in SLVR. Next, predictors for non-relapse were assessed in the total 366 patients. Univariate analysis showed that the following ten factors significantly affected non-relapse as shown in Table 2A. Multivariate analysis indicated that non-relapse occurred when serum HCV RNA at week 12 was negative (p=0.003) and continuance of negative HCV RNA during treatment was $\leq$30 weeks (p=0.017) (Table 2B).

Non-relapse based on the attainment time of negativity of serum HCV RNA and continuance period of negative HCV RNA

The non-relapse rate based on the attainment time of negativity of serum HCV RNA and continuance of negative HCV RNA during combination therapy are shown in Table 3. In RVR group, 26 of 27 patients with continuance of negative HCV RNA of $\leq$30 weeks during treatment had non-relapse. In EVR group, patients with period of negative HCV RNA of $\leq$40 weeks during treatment had SVR rate of 90% (71/79). In LVR and SLVR group, all nine patients with continuance of negative HCV RNA of$\leq$60 weeks during treatment had non-relapse.

Discussion

We have described the incidence of non-relapse and treatment period to enhance the non-relapse rate in patients with undetectable HCV RNA during combination therapy of peginterferon and ribavirin for chronic hepatitis C. In the present study, 241 (66%) of 366 patients with undetectable HCV RNA during combination therapy of peginterferon and ribavirin for chronic hepatitis C showed non-relapse. One-third of patients with undetectable HCV RNA during combination therapy showed relapse. On the other hand, 128 with detectable HCV RNA during combination therapy showed detectable HCV RNA after the termination of combination therapy. The present study was limited to patients with genotype 1 and HCV-load of $\geq$100 KIU/ml. Other limitation is that the present study was not a randomized controlled study; the treatment period was varied.

However, several findings from the present study have direct implications for the combination therapy of chronic hepatitis C in the future. First, non-relapse in patients with undetectable HCV RNA during treatment was associated with attainment time of negativity of serum HCV RNA and continuance of negative HCV RNA. Early undetectable HCV RNA and prolonged negativity of serum HCV RNA enhanced the non-relapse rate. Earlier studies have reported higher SVR rates in patients with undetectable HCV RNA at week 4 than in those with detectable HCV RNA (8, 20, 21). The present results coincided closely with these earlier results.

Second, in RVR group, patients with continuance of nega-

Table 1. Clinical Backgrounds before Combination Therapy of Peginterferon and Ribavirin in Chronic Hepatitis C Patients

	Total	Response				
		RVR	EVR	LVR	SLVR	p
Patients, n	366	37	161	131	37	
Sex, male (%)†	252 (69%)	28 (76%)	119 (74%)	82 (63%)	23 (62%)	.118
Age (yrs)‡	51.6±10.4	51.1±7.0	51.5±10.4	52.0±10.2	52.3±11.7	.399
Weight (kg)‡	64.9±11.1	65.1±10.2	64.7±10.4	65.1±11.1	65.2±10.4	.917
BMI‡	23.5±2.9	23.3±2.8	23.3±2.8	24.1±2.9	24.0±3.2	.248
HCV RNA(KIU/ml)§	1400 (100->5000)	430 (100-1200)	1100 (110->5000)	1750 (130->5000)	1900 (300->5000)	<.001
AST (IU/L)‡	66±43	59±62	64±43	66±41	70±52	.419
ALT (IU/L)‡	94±66	84±52	98±76	91±59	92±65	.321
WBC(10^3/mm^3)‡	4.9±2.9	5.0±2.5	5.1±3.7	4.8±2.2	4.6±1.4	.432
Hb (g/dl)‡	14.7±1.5	14.7±1.6	14.8±1.7	14.7±1.3	14.8±1.3	.887
Platelet(10^4/mm^3)‡	17.7±8.9	17.8±4.6	18.6±9.2	17.1±7.9	17.9±8.5	.616
Fibrosis staging* F1/F2/F3/F4	151/92/56/8	14/7/2/1	76/41/21/3	45/32/27/4	16/12/6/0	.142
Peginterferon/weight (μg/kg)‡	1.4±0.3	1.4±0.3	1.4±0.3	1.3±0.3	1.4±0.3	.916
Ribavirin/weight (mg/kg)‡	11.8±1.4	11.8±1.6	11.7±1.4	11.8±1.4	11.8±1.5	.895

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EVR, early virological response; Hb, hemoglobin; HCV, hepatitis C virus; LVR, late virological response; RVR, rapid virological response; SLVR, super late virological response; WBC, white blood cell;
Normal reference ranges 6-50 IU/L for ALT, 11-38 IU/L for AST,

*Data are number of patients

†Data expressed as number of patients (percentage)

‡Data expressed as mean±standard deviation

§Data expressed as median (range)

tive HCV RNA of ≥30 week during treatment had non-relapse of >90%. Next in EVR group, patients with continuance of negative HCV RNA of ≥40 weeks during treatment had non-relapse of >85%.

Third, in LVR group, patients with continuance of negative HCV RNA of ≥60 weeks during treatment had a high non-relapse rate. The fact that all 9 patients in LVR or SLVR group showed non-relapse after continuance of negative HCV RNA of ≥60 week during treatment is important and impressive. This indicates that patients with delayed undetectable HCV RNA should be treated to continue the negativity of serum HCV RNA for a prolonged period to achieve non-relapse. As described above, for 85% of non-relapse, the desirable duration of negativity of serum HCV-RNA may be 30 weeks in RVR, 40 weeks in EVR and 60 weeks in LVR.

It is desirable to expose patients with chronic hepatitis C to the shortest duration of treatment possible to reduce the likelihood of adverse events and minimize costs. Long-term treatment can be associated with serious side effects and is costly (22). The treatment of combination therapy is expensive; a 24-week treatment course costs approximately 20,000 US $. Regarding the side effects of treatment, previously unreported side effects were not observed in patients treated for more than one year. However, prolonged combination therapy may cause the serious side effects. Accordingly, careful selection of patients for long-term combination therapy is important.

Conclusions

The results of this study underscore the importance of changing the duration of treatment based on the difference of attainment time of negativity of serum HCV RNA in combination therapy for chronic hepatitis C. To attain a non-relapse rate of >85% in patients with undetectable HCV RNA, continuance of negative HCV RNA during treatment are desirable was 30 weeks in RVR group, 40 weeks in

Table 2. Univariate and Multivariate Analyses Identifying Predictors of Non-Relapse Patients with Genotype 1

Table 2A. Univariate Analyses Identifying Predictors of Non-relapse

Factor	Category	Odds ratio	95% Confidence interval	p value
HCV RNA week 12*	-/+	1/0.29	0.18-0.47	< .001
HCV RNA week 24*	-/+	1/0.19	0.09-0.39	< .001
Continuance period of negative HCV RNA (week)	<30/ ≥30	1/4.03	2.34-6.93	<.001
Continuance period of negative HCV RNA (week)	<40/ ≥40	1/3.38	2.06-5.55	<.001
Age (years)	<50/≥50	1/0.44	0.27-0.72	.001
Continuance period of negative HCV RNA (week)	<50/≥50	1/2.67	1.26-5.65	.010
Continuance period of negative HCV RNA (week)	<60/≥60	1/6.66	1.56-28.46	.011
HCV RNA week 4†	-/+	1/0.24	0.07-0.82	.022
Liver fibrosis	F1,F2/ F3,F4	1/0.56	0.33-0.96	.036
HCV-RNA(KIU/mL)	<1000/≥1000	1/0.62	0.38-1.01	.086
ALT (IU/L)	≤50 / >50	1/1.53	0.42-2.56	.101
Hb (g/dL)	<14/ ≥14	1/1.64	0.99-2.70	.107
Platelet ($x10^4/mm^3$)	<15 / ≥15	1/1.42	0.89-2.26	.147
Sex	Male / Female	1/0.75	0.47-1.21	.244
WBC ($x10^3/mm^3$)	<4 / ≥4	1/1.29	0.78-2.12	.325
BMI	<25 / ≥25	1/0.79	0.47-1.31	.351
AST (IU/L)	≤38 />38	1/1.08	0.64-1.83	.952

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Hb, hemoglobin; HCV, hepatitis C virus; SVR, sustained virological response; WBC, white blood cell;

†HCV RNA at week 12, 24 after the initiation of treatment

Table 2B. Multivariate Analyses Identifying Predictors of Non-Relapse

Factor	Category	Odds ratio	95% Confidence interval	p value
HCV RNA week 12*	- / +	1/0.42	0.24-0.74	.003
Continuance period of negative HCV RNA during treatment (week)	<30 / ≥30	1/2.27	1.16-4.47	.017

HCV=hepatitis C virus,

*HCV RNA at week 12 after the initiation of treatment,

EVR, and 60 weeks in LVR.

Acknowledgement

The present work was supported in part by grants-in-aid from

厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業

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第2分冊

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平成21(2009)年3月

厚生労働科学研究費補助金
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(H18-肝炎-一般-005)

平成１８－２０年度　総括・分担研究報告書
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平成２１（２００９）年3月