ORIGINAL ARTICLE

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Treatment Response and Long-Term Outcome of Peginterferon α and Ribavirin Therapy in Korean Patients with Chronic Hepatitis C

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Background/Aims: Peginterferon plus ribavirin remains a standard therapy for patients with chronic hepatitis C (CHC) in Korea. We investigated the efficacy and long-term outcome of peginterferon and ribavirin therapy in Korean patients with CHC, particularly in relation to the stage of liver fibrosis. **Methods:** The incidence of sustained virological response (SVR), hepatic decompensation, hepatocellular carcinoma, and liver-related death was analyzed in 304 patients with CHC; the patients were followed up for a median of 54 months. **Results:** Among patients with HCV genotype 1, the SVR rate was 36.7% (18/49) and 67% (69/103) for patients with and without cirrhosis, respectively (p<0.001). For patients with non-1 HCV genotypes, the SVR rates were 86.0% (37/43) in cirrhotic patients and 86.2% (94/109) in noncirrhotic patients. SVR significantly reduced the risk of liver-related death, hepatic decompensation, and hepatocellular carcinoma, which had hazard ratios of 0.27, 0.16, and 0.22, respectively (all p<0.05). However, despite the SVR rate, patients with advanced fibrosis were still at risk of developing liver-related complications. **Conclusions:** A relatively high SVR rate was achieved by peginterferon plus ribavirin therapy in Korean patients with CHC, which improved their long-term outcomes. However, all CHC patients with advanced hepatic fibrosis should receive close follow-up observations, even after successful antiviral treatment. **(Gut Liver 2016;10:808-817)**

Key Words: Hepatitis C virus clinical trials; Hepatitis C virus treatment; Hepatitis C, clinical; Viral hepatitis

INTRODUCTION

More than 170 million people are estimated to be infected with hepatitis C virus (HCV) worldwide, and its prevalence in Korea is approximately 1.29% in people 40 years of age and older.[1,2] Most cases of HCV infection progress to chronic hepatitis C (CHC), which leads to cirrhosis in 15% to 56% of patients with CHC. Once cirrhosis develops in these patients, hepatocellular carcinoma and death occur, with incidence rates of 1.4% to 4.9% and 2% to 4% per year, respectively.[3] Globally, one-fourth of cirrhosis or hepatocellular carcinoma cases are related to HCV infections.[4]

Previous studies have demonstrated that sustained virological response (SVR) with interferon-based antiviral treatment could improve the prognosis of patients with CHC by reducing hepatic decompensation, hepatocellular carcinoma, and liver-related death.[5-7] However, SVR rates in patients with advanced fibrosis or cirrhosis have been unsatisfactory, with the result being 33% to 51% for patients with HCV genotypes 1/4 and 57% to 61% for patients with HCV genotypes 2/3.[8] Fortunately, however, several combination trials of new oral and direct-acting antiviral agents have reported SVR rates exceeding 90% even in patients with advanced fibrosis who failed to respond to interferon-based treatments, regardless of HCV genotypes.[9,10] However, effective emerging therapies remain out of reach for most patients in the near future due to their high costs, leaving peginterferon plus ribavirin as a standard therapy for CHC in Korea for the time being.

Although some Korean studies have reported relatively higher SVR rates in patients with HCV genotype 1 and non-1 genotypes compared to Western studies,[11,12] the reasons for these improved responses have not been clearly delineated, and the response rate in cirrhotic patients remains uncertain. Some Western studies demonstrated that successful antiviral treatment in patients with CHC halted progression of hepatic fibrosis, but the risk of hepatocellular carcinoma remained even after achieving SVR.[8,13]

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However, this evidence is insufficient to establish concrete surveillance strategies against liver cancer for patients with CHC who achieve SVR with antiviral treatment, since there are few reports regarding long-term posttreatment outcomes in patients with CHC according to liver fibrosis stage before treatment.

Therefore, we have extensively analyzed retrospective clinical practice data regarding treatment response to standard peginterferon and ribavirin combination therapy and long-term posttreatment outcomes in relation to hepatic fibrosis stage in Korean patients with histologically confirmed chronic hepatitis or clinically evident cirrhosis due to HCV infection.

MATERIALS AND METHODS

1. Patients

A total of 376 patients with CHC received peginterferon and ribavirin combination therapy at Korea University Anam Hospitals from February 2003 to February 2014. After excluding 25 patients who were still under treatment at analysis, 17 without pretreatment serum HCV RNA data, and 30 patients lost to follow-up before SVR assessment, 304 patients were included in the final analysis. Eight patients had a past history of curatively treated hepatocellular carcinoma. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board for human investigations of Korea University Anam Hospital (ED15233-09-2015). Informed written consent was waived because of the retrospective nature of this study.

2. Diagnostic methods

HCV genotyping, HCV RNA quantification, and analysis of IL28B genotypes (rs12979860) were performed using the techniques described in Supplementary Table 1. The histological progression of hepatic fibrosis in liver biopsy specimens was divided into five stages using the Batts-Ludwig system: F0 (no fibrosis), F1 (portal fibrosis), F2 (periportal fibrosis), F3 (septal fibrosis), and F4 (cirrhosis).[14] Cirrhosis was evident in 62 patients based on imaging and clinical findings. Hepatocellular carcinoma was diagnosed by pathology or based on clinical diagnostic criteria from the European Association for the Study of the Liver (EASL).[15] Clinically relevant portal hypertension (CRPH) was defined by the presence of esophagogastric varices or thrombocytopenia ($<10^5/mm^3$) with splenomegaly. Decompensated cirrhosis was defined by the presence of ascites, variceal bleeding, hepatic encephalopathy, and Child-Pugh score ≥7. Well-compensated cirrhosis was defined as the state of compensated cirrhosis corresponding to Child-Pugh score 5.

3. Treatment

We administered 180 μg peginterferon α-2a (Pegasys; Roche Pharma AG, Reinach, Switzerland) weekly regardless of body weight or 1.5 μg/kg peginterferon α-2b (Pegintron; Merck & Co., Kenilworth, NJ, USA) weekly, in combination with 1,000 or 1,200 mg/day ribavirin (body weight ≤75 kg or >75 kg, respectively) for 48 weeks to patients with HCV genotype 1, and 800 mg/day ribavirin regardless of body weight for 24 weeks to patients with non-1 HCV genotypes. Peginterferon α-2a was used in 43.1% (131/304) and peginterferon α-2b in 57% (173/304) of patients. The type of peginterferon to be used was just determined by the judgement of attending physician.

4. Outcomes

Virological responses were defined by EASL guidelines for CHC.[16] All virological responses were determined by intention-to-treat analysis. All patients were evaluated for other virological responses except rapid virological response (RVR). Long-term outcomes were evaluated by the occurrence of hepatic decompensation (defined by ascites, variceal hemorrhage, hepatic encephalopathy, or Child-Pugh score >6), hepatocellular carcinoma, all-cause death, and liver-related death.

5. Statistical methods

Student t-test was used to compare the mean of continuous variables. Chi-square and Fisher exact tests were applied to compare the frequencies of categorical variables. Univariate and multivariate logistic regression analyses were used to identify factors associated with SVR. Univariate and multivariate Cox regression analyses were performed to identify factors associated with long-term outcomes. In both analyses, variables with $p<0.1$ in univariate analysis were included in the stepwise multivariate analysis. Cumulative incidence rates and curves for each event were plotted using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and p-values <0.05 were considered statistically significant in all analyses.

RESULTS

1. Baseline characteristics

A total of 304 patients were followed up for 4 to 118 months (median, 54 months); their baseline characteristics according to HCV genotype and cirrhosis are summarized in Table 1. There were 152 patients each with HCV 1 (six genotype 1a, 141 genotype 1b, and five unclassified) and non-1 genotypes (149 genotype 2 and three genotype 3). Liver cirrhosis was found in 92 patients, of whom 49 and 43 belonged to HCV genotypes 1 and non-1, respectively; 52 (57%) had clinically relevant portal hypertension; 18 (20%) and one (1%) had Child-Pugh score of 6 and 7, respectively; four (4%) showed signs of decompensated cirrhosis, and there were no genotype differences associated with these characteristics.

The incidence of the IL28B (rs12979860) CC genotype was 88% as a whole, and did not vary according to HCV genotypes

Table 1. Baseline Characteristics, Patient Adherence, and Virological Response to Treatment according to the Genotype of HCV and Presence of Liver Cirrhosis

Variable	Genotype 1 (n=152)		Genotype non-1 (n=152)		p-value			
	Non-LC (I) (n=103)	LC (II) (n=49)	Non-LC (III) (n=109)	LC (IV) (n=43)	I vs II	III vs IV	I vs III	II vs IV
Age, yr	56.5±11.3	64.7±10.1	56.3±12.4	61.8±10.6	<0.001*	0.011*	0.888*	0.187*
Male sex	57 (55)	23 (47)	45 (41)	27 (63)	0.332†	0.017†	0.041†	0.128†
IL28B, CC genotype	46/52 (89)	21/25 (84)	39/46 (85)	14/14 (100)	0.720‡	0.184‡	0.592*	0.277‡
Body mass index, kg/m^2	24.6±3.5	23.6±3.2	23.9±3.1	24.4±2.4	0.098*	0.380*	0.161*	0.180*
Hemoglobin, g/dL	14.2±1.5	13.2±1.5	13.7±1.4	13.6±1.3	<0.001*	0.716*	0.010*	0.162*
Platelet, ×10^3/mm^3	189.7±51.5	109.8±44.8	190.6±53.4	108.2±38.8	<0.001*	<0.001*	0.900*	0.861*
AST, IU/L	61.5±42.0	74.4±33.5	59.5±67.1	68.1±22.5	0.062*	0.149*	0.802*	0.889*
ALT, IU/L	80.2±64.5	60.6±34.9	77.8±98.0	75.1±56.6	0.049*	0.864*	0.838*	0.139*
Albumin, g/dL	4.2±0.4	3.9±0.5	4.2±0.4	3.9±0.4	<0.001*	<0.001*	0.786*	0.934*
Bilirubin, mg/dL	0.72±0.3	0.88±0.4	0.61±0.3	0.86±0.4	0.009*	<0.001*	0.006*	0.763*
PT INR	1.02±0.1	1.10±0.1	1.02±0.1	1.13±0.1	<0.001*	<0.001*	0.987*	0.079*
CRPH	0	30 (61)	0	22 (51)	<0.001‡	<0.001‡	NA	0.331†
Decompensation	0	1 (2)	0	3 (7)	NA	NA	NA	0.336‡
Ascites	0	1 (2)	0	3 (7)	NA	NA	NA	0.336‡
Child-Pugh score 5/6/7	100/3/0 (97/3/0)	38/11/0 (78/24/0)	106/3/0 (97/3/0)	35/7/1 (81/16/2)	<0.001‡	0.003‡	1.000†	0.443‡
HCV RNA log IU/mL	6.13±1.0	5.77±1.0	5.28±1.2	4.90±1.0	0.038*	0.073*	<0.001*	<0.001*
HCV genotype Ia/Ib	4/95	2/46						
HCV genotype II/III			106/3	43/0				
Type of peginterferon prescribed					0.519†	0.918†	<0.001†	<0.001†
α-2a	66 (64)	34 (69)	22 (20)	9 (21)				
α-2b	37 (36)	15 (31)	87 (80)	34 (79)				
Adherence to treatment								
Treated for								
<12 wk	16 (16)	8 (16)	4 (4)	4 (9)	0.900†	0.161‡	0.004‡	0.368‡
≤75% of full duration	31 (30)	19 (39)	5 (5)	6 (14)	0.287†	0.045†	<0.001†	0.008†
>75% of full duration								
≤75% of full dosage	15 (15)	11 (22)	24 (22)	18 (42)	0.228†	0.014†	0.161†	0.046†
>75% of full dosage	57 (55)	19 (39)	80 (73)	19 (44)	0.056†	<0.001†	0.006†	0.599†
Premature cessation	34 (33)	21 (43)	8 (7)	7 (16)	0.238†	0.096†	<0.001†	0.006†
Intolerance to drug	17 (50)	11 (52)	5 (63)	5 (72)	0.777‡	0.377‡	<0.001‡	0.064‡
Loss to follow-up	5 (15)	2 (10)	2 (25)	1 (14)				
Economic problem	8 (23)	5 (24)	1 (12)	1 (14)				
No response	4 (12)	3 (14)						
Treatment response								
RVR	42/82 (51)	15/43 (35)	83/92 (90)	30/36 (83)	0.082†	0.138†	<0.001†	<0.001†
EVR	82/103 (80)	37/49 (76)	102/109 (94)	41/43 (97)	0.566†	1.000‡	0.003†	0.009‡
cEVR	77/103 (75)	35/49 (71)	100/109 (92)	38/43 (88)	0.663†	0.540‡	<0.001†	0.070‡
ETR	81/103 (79)	36/49 (74)	103/109 (95)	41/43 (95)	0.479†	1.000‡	<0.001†	0.005‡
SVR	69/103 (67)	18/49 (37)	94/109 (86)	37/43 (86)	<0.001†	1.000†	<0.001†	<0.001†

Date are presented as mean±SD or number (%). CRPH means the presence of esophagogastric varices or thrombocytopenia (<10^5/mm^3) with splenomegaly. Decompensation means the presence of ascites or variceal bleeding and/or Child-Pugh score ≥7. IL28B CC genotype means interleukin-28B rs12979860 CC genotype.

HCV, hepatitis C virus; LC, liver cirrhosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT INR, prothrombin time international normalized ratio; CRPH, clinically relevant portal hypertension; RVR; rapid virological response; EVR, early virological response; cEVR, complete EVR; ETR, end of treatment response; SVR, sustained virological response.

*Student t-test; †Chi-square test; ‡Fisher exact test.

or the presence of cirrhosis. Baseline serum HCV RNA level was significantly higher in patients with HCV genotype 1 than that in those with non-1 genotypes (all p<0.001) among both cirrhotic and noncirrhotic patients; among patients with identical HCV genotypes, those with cirrhosis showed significantly lower or a tendency towards lower serum HCV RNA levels at baseline than those without cirrhosis (p=0.038 for genotype 1 and p=0.073 for genotype non-1).

Peginterferon α-2a was more often administered to patients with HCV genotype 1 (66%) and peginterferon α-2b in patients with non-1 genotypes (80%) (both p<0.001), but no preference was observed between patients with and without cirrhosis (Table 1).

2. Adherence to treatment

Treatment was prematurely discontinued in 43% (34/103) and 33% (21/49) of HCV genotype 1 patients with and without cirrhosis, respectively, compared to 16% (7/43) and 7% (8/109) of among patients with identical HCV genotypes, those with cirrhosis showed significantly lower or a tendency towards non-1 genotype patients with and without cirrhosis. Drug discontinu-

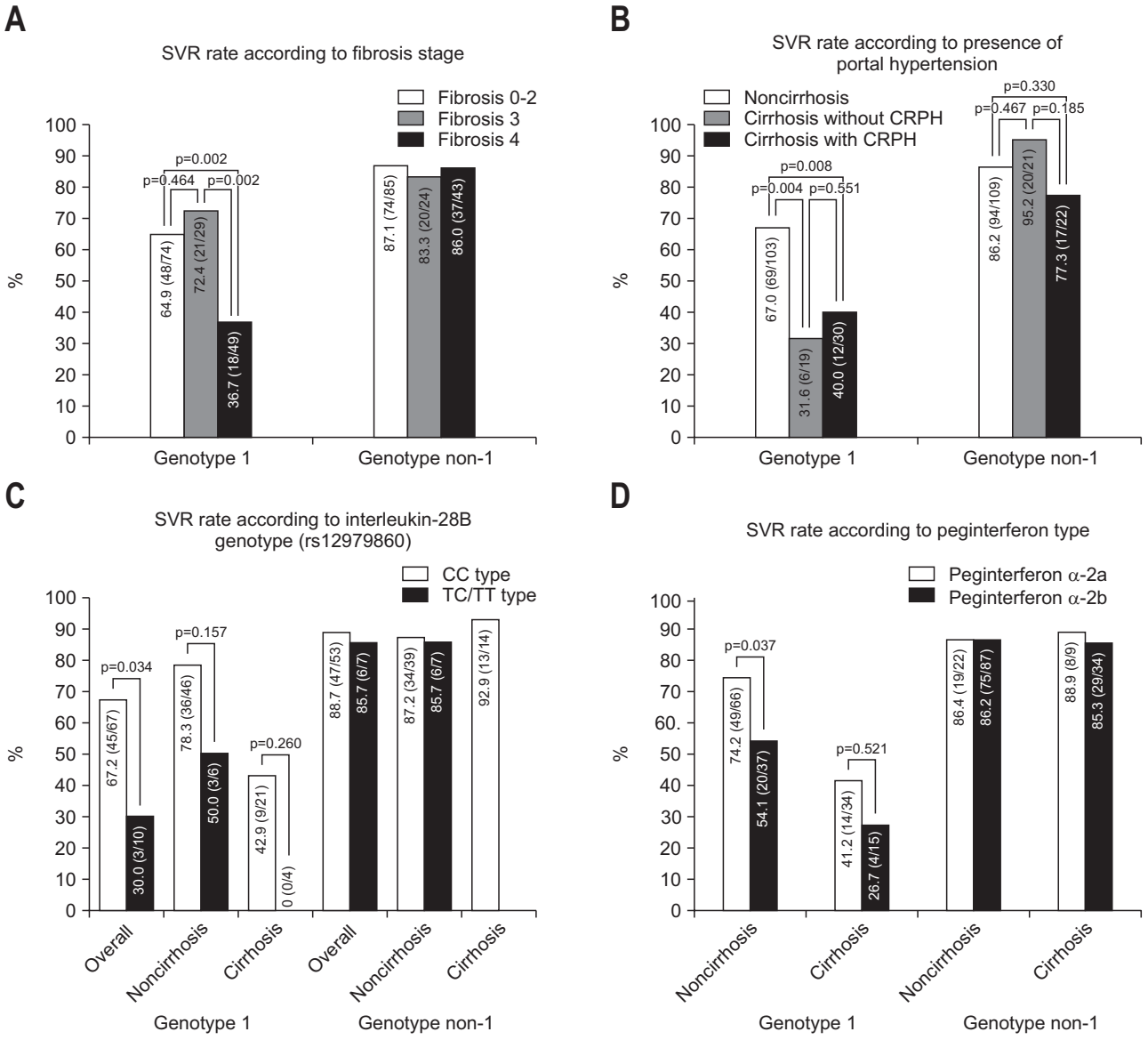

Fig. 1. Sustained virological response (SVR) rates according to the genotype of hepatitis C virus (HCV), stage of hepatic fibrosis, presence of portal hypertension, genotype of IL-28B, and type of peginterferon. (A) For patients with HCV genotype 1, the SVR rate was significantly lower in patients with cirrhosis than in patients with bridging or less advanced fibrosis. (B) The presence of clinically relevant portal hypertension (CRPH) was not significantly associated with the SVR rate in patients with cirrhosis. (C) For patients with HCV genotype 1, the SVR rate was significantly higher in patients with the CC genotype of interleukin-28B (IL-28B) rs12979860 than in those with the TC/TT genotype. (D) In noncirrhotic patients with the HCV genotype 1, peginterferon α-2a resulted in a significantly higher SVR rate than peginterferon α-2b. However, the SVR rates in patients with non-HCV genotype 1 did not differ according to the stage of hepatic fibrosis, presence of portal hypertension, genotype of IL-28B, or type of peginterferon.

ation occurred more frequently in patients with HCV genotype 1 than patients with non-1 genotypes among patients with and without cirrhosis (all p<0.01). The proportion of patients who received drugs of more than 75% of scheduled dosage was lower in patients with cirrhosis than those without cirrhosis for both HCV genotype 1 (38% vs 55%, p=0.056) and non-1 (44% vs 73%, p<0.001). The most common cause of discontinuation was severe adverse drug effects (54%, 38/70) (Table 1, Supplementary Table 2).

3. Virological response

Achievement of virological response to standard peginterferon and ribavirin combination therapy is shown in Table 1. Among patients with HCV genotype 1, SVR was achieved in 36.7% (18/49) and 67% (69/103) of patients with and without cirrhosis (p<0.001), respectively. In comparison, among patients with non-1 HCV genotypes, SVR rates were 86.0% (37/43) in cirrhotic patients and 86.2% (94/109) in noncirrhotic patients. The SVR achievement rate did not differ significantly between the F0-2 and F3 groups containing patients with HCV genotype 1; similarly, the rate did not differ significantly among the F0-2, F3, and F4 (cirrhosis) groups consisting of patients with HCV non-1 genotypes (Fig. 1A). In addition, among patients with cirrhosis, the SVR rate did not differ significantly between those with and without portal hypertension, regardless of HCV genotype (Fig. 1B).

4. Factors associated with SVR

Multivariate logistic regressions analyses confirmed that well-known baseline factors were independently associated with SVR, including serum HCV RNA levels and other variables such as the presence of cirrhosis in patients with HCV genotype 1 and age in patients with HCV non-1 genotypes (Table 2). Along with these baseline predictors, SVR was independently and positively correlated with RVR achievement and treatment adherence, including actual drug dosage in patients with HCV genotype 1 and actual duration of drug exposure in patients with non-1 genotypes (Table 2). In fact, the SVR rate in genotype 1 patients with and without cirrhosis who received >75% of the planned dosage reached 58% and 88%, respectively, which further increased to 83.3% and 93% with the additional presence of RVR. Among patients with non-1 genotypes, SVR rates exceeded 90% in both cirrhosis and noncirrhosis patients with drug exposures for >75% of expected duration, and reached 97.6% in those under 65 years of age with serum HCV RNA levels ≤5 $\log_{10}$ IU/mL (Supplementary Tables 3 and 4).

Furthermore, among patients with HCV genotype 1, the IL-28B CC genotype was associated with significantly higher SVR rates after adjusting for baseline predictors (p=0.019 vs TC/TT genotypes) (Fig. 1C), while peginterferon α-2b was linked with a significantly lower SVR rate (p=0.007 vs peginterferon α-2a) (Table 2, Fig. 1D).

5. All-cause and liver-related deaths

Among the 304 patients, there were 19 deaths during the follow-up period (median, 54 months) after treatment initiation, including 12 liver-related deaths. Detailed causes of death were as follows: hepatocellular carcinoma in five patients, liver failure in four, spontaneous bacterial peritonitis in one, variceal bleed in one, cholangiocarcinoma in one, pneumonia in two, chronic kidney disease in one, myocardial infarction in one, pancreatic cancer in one, lung cancer in one, suicide in one.

Table 2. Multivariate Analysis for Factors Associated with SVR according to the HCV Genotype

Variable	HCV genotype 1		HCV genotype non-1	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Pretreatment variable				
Age, yr (>65 vs ≤65)	0.48 (0.23–1.03)	0.059	0.15 (0.05–0.43)	<0.001
Liver cirrhosis (yes vs no)	0.34 (0.16–0.73)	0.006		
HCV RNA, log IU/mL (>5 vs ≤5)			0.16 (0.04–0.63)	0.009
HCV RNA, log IU/mL (>7 vs ≤7)	0.24 (0.08–0.72)	0.011		
Total bilirubin, mg/dL (>1 vs ≤1)	0.45 (0.23–1.03)	0.059	0.19 (0.05–0.64)	0.008
Type of peginterferon* (α-2b vs α-2a)	0.35 (0.16–0.75)	0.007		
Interleukin-28B genotype* rs12979860 (CC vs TC/TT)	6.6 (1.4–32.1)	0.019		
Adherence and virological response to treatment*				
Treatment dose, % of target dose (>75% vs ≤75%)	14.6 (4.5–47.3)	<0.001		
Treatment duration, % of planned duration (>75% vs ≤75%)			33.2 (2.2–510.1)	0.012
RVR (yes vs no)	8.0 (2.7–23.5)	<0.001	12.0 (1.9–77.0)	0.009

The p-values were obtained by multivariate logistic regression analysis.
SVR, sustained virological response; HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval; Treatment dose, peg-IFN and ribavirin administration dose; Treatment duration, peg-IFN and ribavirin administration duration; RVR, rapid virological response.
*Adjusted with pretreatment variables.

When expressed as events per 10^4 person-years, incidence rates of death were remarkably higher in patients with cirrhosis (F4) than that in those without (353 vs 48 for all-cause death, 277 vs 10 for liver-related death, both p<0.001 using Cox regression analysis) (Table 3). Additionally, the rates of all-cause death and liver-related death were significantly lower in patients with SVR than that in those without (all-cause death: 87 vs 257; hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.14 to 0.83; p=0.018; liver-related death: 48 vs 180 per 10^4 person-years; HR, 0.27; 95% CI, 0.09 to 0.86; p=0.026). When we considered the degree of hepatic fibrosis, the impact of SVR on mortality was only obvious in a subgroup of patients with advanced fibrosis (F3+F4) who maintained well-compensated liver functions (Child-Pugh score, 5) at baseline (p=0.006 and 0.016 for all-cause and liver-related death, respectively) (Table 3). Multivariate Cox regression analysis demonstrated an interaction between SVR and well-compensated cirrhosis for all-cause (p=0.063) and liver-related deaths (p=0.04), suggesting that a substantial reduction in liver-related death due to SVR would be expected only in patients with well-compensated cirrhosis at baseline (Table 4). In fact, the difference in cumulative incidence rates of liver-related death between the SVR and non-SVR groups was statistically significant only in patients with well-compensated cirrhosis (p=0.034 by log-rank test), and not in cirrhotic groups including patients with Child-Pugh scores >5 (Fig. 2A and B, Supplementary Table 5).

Table 3. Clinical Outcomes according to the Hepatic Fibrosis Stage and Treatment Response

	No. of patients, SVR/NR	PY of follow-up, SVR/NR	No. of events, SVR/NR	Incidence /10^4 PY, SVR/NR	SVR/NR		F4/F0-3	
					HR (95% CI)	p-value	HR (95% CI)	p-value
Overall death								
F0-2	122/37	593/174	2/1	34/57	0.58 (0.05–6.40)	0.657		
F3	41/12	216/51	0/2	0/392	NA			
F4	55/37	232/165	7/7	302/424	0.80 (0.28–2.31)	0.682	7.6 (2.7–21.0)	<0.001
cF4	46/27	195/115	2/6	103/522	0.24 (0.05–1.21)	0.083		
F3+cF4	87/39	411/166	2/8	49/482	0.11 (0.02–0.52)	0.006		
Total	218/86	1040/389	9/10	87/257	0.34 (0.14–0.83)	0.018		
Liver-related death								
F0-2	122/37	593/174	0/0	0/0	NA			
F3	41/12	216/51	0/1	0/392	NA			
F4	55/37	232/165	5/6	216/364	0.64 (0.19–2.11)	0.460	29.7 (3.8–230)	<0.001
cF4	46/27	195/115	1/5	51/435	0.13 (0.02–1.17)	0.068		
F3+cF4	87/39	411/166	1/6	24/361	0.07 (0.01–0.61)	0.016		
Total	218/86	1040/389	5/7	48/180	0.27 (0.09–0.86)	0.026		
Hepatic decompensation								
F0-2	122/37	590/174	0/0	0/0	NA			
F3	41/12	216/51	0/2	0/392	NA			
F4	51/37	213/143	8/16	376/1119	0.34 (0.14–0.79)	0.012	35.3 (8.3–150)	<0.001
F3+F4	92/49	429/194	8/18	187/928	0.20 (0.09–0.46)	<0.001		
Total	214/86	1019/367	8/18	79/491	0.16 (0.07–0.36)	<0.001		
Hepatocellular carcinoma								
F0-2	121/37	590/174	0/0	0/0	NA			
F3	41/12	210/49	2/2	95/408	0.13 (0.01–1.40)	0.093		
F4	50/35	199/139	6/11	302/791	0.38 (0.14–1.03)	0.057	13.9 (4.7–41.4)	<0.001
F3+F4	91/47	409/189	8/13	196/688	0.28 (0.12-0.68)	0.057		
Total	212/84	998/361	8/13	80/360	0.22 (0.09-0.54)	0.001		

The p-values and hazard ratios were obtained by a univariate Cox regression analysis. The progression of hepatic fibrosis was divided into five stages, F0, F1, F2, F3, and F4, according to Batts-Ludwig classification; F4 and cF4 refer to cirrhosis and well-compensated cirrhosis (compensated cirrhosis corresponding to Child-Pugh score 5), respectively. Hepatic decompensation was defined as the development of ascites, hepatic encephalopathy, or variceal bleeding.

SVR, sustained virological response; NR, no sustained virological response; PY, person-years; HR, hazard ratio; CI, confidence interval; NA, not available.

Table 4. Multivariate Analysis for Risk Factors Associated with Mortality, Hepatic Decompensation Development, and Hepatocellular Carcinoma

	Variable	HR	95% CI	p-value
Overall death	Liver cirrhosis (yes vs no)	6.4	2.0–20.5	0.002
	SVR (yes vs no) * Well compensated cirrhosis (yes vs no)	0.23	0.05–1.08	0.063
Liver-related death	Liver cirrhosis (yes vs no)	39.2	4.9–311.7	<0.001
	Bilirubin, mg/dL	4.9	1.3–18.8	0.022
	SVR (yes vs no) * Well compensated cirrhosis (yes vs no)	0.12	0.02–0.90	0.040
Hepatic decompensation	SVR (yes vs no)	0.24	0.10–0.60	0.002
	Liver cirrhosis (yes vs no)	12.7	2.7–59.0	0.001
	Albumin, g/dL	0.35	0.15–0.83	0.018
	Bilirubin, mg/dL	3.2	1.2–9.0	0.025
Hepatocellular carcinoma	SVR (yes vs no)	0.37	0.15–0.91	0.032
	Liver cirrhosis (yes vs no)	10.9	3.6–33.1	<0.001

The p-values and hazard ratios were obtained by a multivariate Cox regression analysis, which included variables at p<0.10 in the univariate model. Hepatic decompensation was defined as the development of ascites, hepatic encephalopathy, or variceal bleeding. Well-compensated cirrhosis refers to the state of compensated cirrhosis corresponding to a Child-Pugh score of 5.
HR, hazard ratio; CI, confidence interval; SVR, sustained virological response.

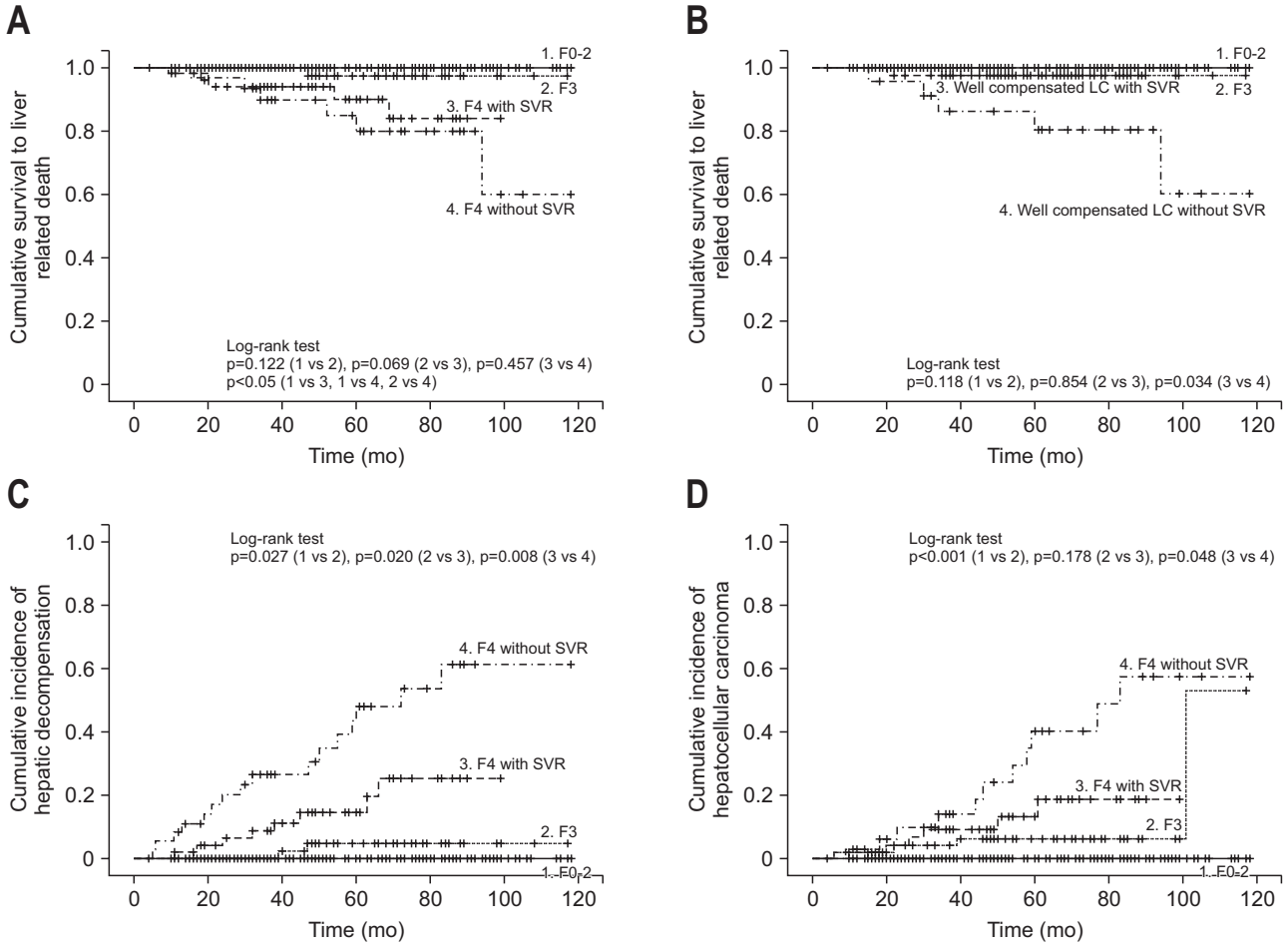

Fig. 2. Kaplan-Meier curves showing the occurrence of clinical events according to the hepatic fibrosis stage and sustained virological response (SVR). (A) The cumulative incidence rates of liver-related deaths tended to differ between the F3 group and F4 group with SVR (p=0.069) but did not differ significantly between the F4 groups with and without SVR. (B) The cumulative incidence rates of liver-related deaths did not differ between the F3 group and the well-compensated F4 group with SVR but did differ significantly between the well-compensated F4 groups with and without SVR. (C) Among patients without hepatic decompensation at baseline, the cumulative incidence rates of hepatic decompensation consistently increased with progression of fibrosis and lack of SVR (p=0.027 between the F0–2 and F3 groups, p=0.020 between the F3 group and the F4 group with SVR, p=0.008 between the F4 groups with and without SVR). (D) The cumulative incidence rates of hepatocellular carcinoma significantly increased with fibrosis progression and lack of SVR (p<0.001 between the F0–2 and F3 groups, p=0.048 between the F4 groups with and without SVR by log-rank test).

6. Development of hepatic decompensation

Among the 300 patients without hepatic decompensation at baseline, 26 developed hepatic decompensation during the follow-up period. The incidence rate was significantly higher in patients with cirrhosis than in those without (674 vs 19 per 10^4 person-years, p<0.001), but was significantly lower in patients who attained SVR compared to those who did not (79 vs 491 per 10^4 person-years; HR, 0.16; 95% CI, 0.07 to 0.36; p<0.001) (Table 3). The effect of SVR on hepatic decompensation in relation to hepatic fibrosis stage was only significant in patients with cirrhosis (F4) (p<0.012) and advanced fibrosis (F3+F4) (p<0.001) (Table 3). Multivariate analysis showed independent relationships between the occurrence of hepatic decompensation and achievement of SVR (p=0.002) or the presence of cirrhosis (p=0.001) (Table 4). The cumulative incidence rates of hepatic decompensation consistently increased with progression of fibrosis and with lack of SVR, as shown in Fig. 2C and Supplementary Table 5 (p=0.027 between F0-2 and F3 groups, p=0.020 between F3 group vs F4 group with SVR, and p=0.008 between F4 groups with and without SVR).

7. Development of hepatocellular carcinoma

Among the 296 patients without past history of hepatocellular carcinoma at baseline, 21 developed hepatocellular carcinoma during the follow-up period. The incidence rate of hepatocellular carcinoma was remarkably higher in cirrhotic patients than that in noncirrhotic patients (503 vs 39 per 10^4 person-years, p<0.001), and significantly lower in patients who attained SVR compared to those who did not (80 and 360 per 10^4 person-years; HR, 0.22; 95% CI, 0.09 to 0.54; p<0.001) (Table 3). This SVR effect against hepatocellular carcinogenesis was only evident (p=0.005) in patients with advanced fibrosis (F3+F4) compared to other stages of hepatic fibrosis (Table 3). Multivariate analysis corroborated the independent impact of cirrhosis (p<0.001) and SVR (p=0.032) on hepatocellular carcinogenesis (Table 4). Reflecting these findings, the cumulative incidence rates of hepatocellular carcinoma increased significantly with the progression of fibrosis and lack of SVR, as shown in Fig. 2D and Supplementary Table 5 (p<0.001 between F0-2 and F3 groups, p=0.048 between F4 groups with and without SVR by log-rank test).

DISCUSSION

In the present study, standard peginterferon and ribavirin combination therapy resulted in fairly high SVR rates in CHC patients with cirrhosis, including 36.7% among those with HCV genotype 1 and 86.0% for non-1 genotypes. These results were better than those reported in Western studies (13% to 33% for genotype 1/4 and 31% to 57% for genotype 2/3)[8,17-19] and in small Korean studies (21% to 24% for genotype 1 and 33% to 53% in non-1 genotypes).[20,21] In addition, SVR rates in the current study reached 67% among patients without cirrhosis with HCV genotype 1 and 86% in those with non-1 genotypes, also better results compared to large-scale Western studies (57% to 60% for genotype 1 and 76% for non-1 genotype groups),[8,22] but similar to other Korean data (74% for HCV genotype 1 and 83% in genotype non-1).[11]

The improved treatment responses in Korean patients with CHC could be partly attributed to a higher frequency of the specific IL28B genotype (rs12979860 CC type and rs8099917 TT type) in Koreans, which is closely linked to favorable responses to interferon treatment among patients with HCV genotype 1. The frequency of IL28B rs12979860 CC genotype in the present study was 88%, markedly higher than the 39% prevalence in European Americans, 16% in African Americans, and 35% in Hispanic Americans reported in a previous study.[23] Indeed, in the present study, SVR achievement among patients with HCV genotype 1 was significantly higher in those with IL28B CC genotype than in those with non-CC genotypes (Fig. 1C).

Another factor accounting for better SVR rates in the present study, especially in patients with cirrhosis, might be higher treatment adherence. Previous studies on patients with cirrhosis showed that the rate of premature drug cessation was as high as 67% and 33% in patients with and without HCV genotype 1, respectively.[19] In comparison, the premature withdrawal rate in this study was 43% among cirrhotic patients with HCV genotype 1 and only 16% among those with non-1 HCV genotypes. This higher adherence to treatment in our cirrhotic patients, especially in those with non-1 HCV genotype, must have contributed to a higher SVR rate despite the presence of cirrhosis. Concordant with a previous study,[24] treatment response in patients with HCV genotype 1 improved with drug exposures >75% of the total target dose in the present study, with the SVR rate reaching 58% even in cirrhotic patients; it further increased to 83.3% in the presence of RVR. Therefore, a combination therapy of peginterferon and ribavirin might be cost-effective in some subgroups. Unfortunately, however, the proportion of patients who received >75% of the total target dose was only 38% in cirrhotic patients with HCV genotype 1, as compared to 55% in noncirrhosis patients with the same genotype (p=0.056), probably resulting in a far lower SVR rate in cirrhotic patients (37% vs 67%).

Furthermore, a relatively lower level of viremia observed in non-1 HCV genotype cirrhotic patients in the present study, as compared to those reported in previous studies (4.90 vs 6.04 to 6.11 log HCV RNA IU/mL),[20,21] probably had a positive influence on SVR rate, for viral load is a well-known predictive factor of SVR as confirmed in the present study.

Some of our study results are also noteworthy in view of factors affecting the effect of peginterferon and ribavirin on CHC. First, there has been controversy about the therapeutic effects of different peginterferon types.[25-27] In the present study,

peginterferon α-2a exhibited a significantly higher SVR rate in patients with HCV genotype 1, particularly those without cirrhosis, compared to peginterferon α-2b. Secondly, some studies reported very low SVR rates of 13% to 14% in compensated cirrhosis patients with HCV genotype 1 and portal hypertension.[17,18] However, in the present study, the SVR rate in these patients was as high as 40%, and did not differ significantly from the SVR rate in those without portal hypertension. This might be owing to their relatively high adherence to treatment, not inferior to that in patients without portal hypertension as shown in Supplementary Table 3. Thirdly, Bruno et al. demonstrated a decrease in SVR rate with progression of hepatic fibrosis in patients without cirrhosis.[8] In the present study, however, no significant difference in the SVR rate was observed between those with and without bridging fibrosis (F3 vs F0-2), irrespective of HCV genotypes. Yet, the results of present study on the therapeutic efficacy according to the type of peginterferon and patients' characteristics should be interpreted with caution as our study has unavoidable limitations arising from its nature of retrospective study design.

Sporadic reports have demonstrated that SVR achievement reduces the occurrence of liver-related death, hepatic decompensation, and hepatocellular carcinoma in patients with CHC.[5,6] A recent meta-analysis reported that SVR achievement reduced liver-related death (0.23-fold), risk of hepatic decompensation (0.21-fold), and risk of hepatocellular carcinoma (0.21-fold) in patients with CHC in all stages of fibrosis.[7] A large-scale observational study conducted in the United States reported that SVR achievement reduced all-cause mortality 0.51- to 0.70-fold.[28] In the present study, we also confirmed that SVR achievement reduced the risk of overall death 0.34-fold; liver-related death 0.27-fold; risk of hepatic decompensation 0.16-fold; and risk of hepatocellular carcinoma 0.22-fold in patients with CHC in all stages of fibrosis.

However, it should be noted that pretreatment fibrosis stages in the present study greatly affected patient prognosis after successful treatment. Hepatic decompensation or liver-related death did not occur during the follow-up period in patients without cirrhosis who achieved SVR. In contrast, the risk of hepatic decompensation, while reduced, still existed in patients with cirrhosis even after achieving SVR. Particularly, the risk of liver-related death was reduced only in patients with cirrhosis with Child-Pugh scores of 5. This suggests that SVR needs to be achieved before liver function deteriorates beyond a Child-Pugh score of 5 in order to improve the prognosis of patients with HCV-related cirrhosis. In addition, it is noteworthy that hepatocellular carcinoma did not occur in patients without advanced fibrosis (F0-2) once they achieved a SVR, but did develop at a high rate in patients with advanced fibrosis (F3+F4) even after they achieved a SVR. This indicates that, irrespective of SVR achievement, patients with advanced hepatic fibrosis due to CHC should undergo continued surveillance for hepatocellular carcinoma.

In summary, we were able to achieve a high SVR rate in Korean patients with CHC, including those with cirrhosis, using a standard peginterferon and ribavirin combination therapy, and showed that SVR achievement could reduce the incidence of liver-related death, hepatic decompensation, and hepatocellular carcinoma. However, the risk of liver-related complications still exists in patients with advanced fibrosis even after achieving SVR. Therefore, all patients with HCV-related advanced hepatic fibrosis should receive close follow-up irrespective of successful antiviral treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333-1342.
2. Shin HR. Epidemiology of hepatitis C virus in Korea. Intervirology 2006;49:18-22.
3. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol 2012;26:401-412.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529-538.
5. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579-587.
6. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2011;9:923-930.
7. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-288.e1.
8. Bruno S, Shiffman ML, Roberts SK, et al. Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. Hepatology 2010;51:388-397.
9. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756-1765.
10. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir

for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-1493.
11. Jin YJ, Lee JW, Lee JI, et al. Multicenter comparison of PEG-IFN alpha2a or alpha2b plus ribavirin for treatment-naïve HCV patient in Korean population. BMC Gastroenterol 2013;13:74.
12. Heo NY, Lim YS, Lee HC, et al. High effectiveness of peginterferon alfa-2a plus ribavirin therapy in Korean patients with chronic hepatitis C in clinical practice. Clin Mol Hepatol 2013;19:60-69.
13. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology 2009;49:729-738.
14. Batts KP, Ludwig J. Chronic hepatitis: an update on terminology and reporting. Am J Surg Pathol 1995;19:1409-1417.
15. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
16. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014;60:392-420.
17. Di Marco V, Almasio PL, Ferraro D, et al. Peg-interferon alone or combined with ribavirin in HCV cirrhosis with portal hypertension: a randomized controlled trial. J Hepatol 2007;47:484-491.
18. Giannini EG, Basso M, Savarino V, Picciotto A. Predictive value of on-treatment response during full-dose antiviral therapy of patients with hepatitis C virus cirrhosis and portal hypertension. J Intern Med 2009;266:537-546.
19. Syed E, Rahbin N, Weiland O, et al. Pegylated interferon and ribavirin combination therapy for chronic hepatitis C virus infection in patients with Child-Pugh Class A liver cirrhosis. Scand J Gastroenterol 2008;43:1378-1386.
20. Kim KH, Jang BK, Chung WJ, et al. Peginterferon alpha and ribavirin combination therapy in patients with hepatitis C virus-related liver cirrhosis. Korean J Hepatol 2011;17:220-225.
21. Cheong HR, Woo HY, Heo J, et al. Clinical efficacy and safety of the combination therapy of peginterferon alpha and ribavirin in cirrhotic patients with HCV infection. Korean J Hepatol 2010;16:38-48.
22. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346-355.
23. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
24. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061-1069.
25. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.
26. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology 2010;138:108-115.
27. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology 2010;138:116-122.
28. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509-516.e1.

Supplementary Table 1. Detailed Methods and Results

Diagnostic methods

CHC infection was diagnosed based on seropositivity by the antihepatitis C virus (anti-HCV) test (Architect 2000 system; Abbott Laboratories, Chicago, IL, USA) and HCV RNA quantification analysis (Amplicor HCV Monitor Test, version 2.0; Roche Molecular Diagnostics, Pleasanton, CA, USA). HCV genotypes were assessed using a commercial HCV genotype sequencing test (2500 series; Applied Biosystems, Waltham, MA, USA) or restriction fragment mass polymorphism (RFMP) assay using matrix assisted laser desorption ionization time-of-flight (MALDI-TOF, Autolfex II; Bruker Daltonics, Bremen, Germany). A retrospective analysis of the IL28B genotypes (rs12979860) was performed on 137 patients by RFMP assay of stored frozen serum, and direct sequencing was also conducted for more accurate genotyping in cases with heterozygous alleles.

Modification of treatment

The peginterferon dosage was reduced if leukocyte counts decreased to ≤1,000/mm^3 or if neutrophil counts decreased to ≤750/mm^3, treatment discontinuation was considered if neutrophil counts decreased to ≤500/mm^3. In addition, peginterferon dosage was reduced if platelet counts decreased to ≤50,000/mm^3; treatment discontinuation was considered if counts decreased to ≤25,000/mm^3. For anemia with hemoglobin levels ≤10 g/dL, ribavirin dosage was reduced and administration of erythropoietin was considered; for anemia with hemoglobin levels ≤8.0 g/dL, ribavirin discontinuation was considered.

Definition of virological response

Rapid virological response (RVR) were defined as negative for HCV RNA at treatment week 4; early virological response (EVR) was defined as ≥2 log IU/mL reduction in HCV RNA levels or negative for HCV RNA at treatment week 12. End-of-treatment response (ETR) was defined as HCV RNA negative at the end of treatment; sustained virological response (SVR) was defined as undetectable levels of HCV RNA 24 weeks after treatment cessation. In addition, complete EVR (cEVR) was defined as negativity for HCV RNA during EVR.

Baseline characteristics

Patients with cirrhosis were older than those without cirrhosis, regardless of their HCV genotype, and they showed lower serum albumin levels, lower platelet counts, higher serum bilirubin levels, and longer prothrombin time (all $p<0.05$). Among patients without cirrhosis, the proportion of women was higher for those with non-1 HCV genotypes than the genotype 1 group, which probably resulted in lower mean hemoglobin levels in those with non-1 HCV genotypes (Table 1).

Results of virological response

Among 103 patients with HCV genotype 1 without cirrhosis, RVR was attained in 51% (42/82), EVR in 80%, cEVR in 75%, ETR in 79%, and SVR in 67%. Among 49 patients with HCV genotype 1 with cirrhosis, RVR was reached in 35% (15/43), EVR in 76%, cEVR in 71%, ETR in 74%, and SVR in 37%. Among 109 patients with non-1 HCV genotypes and without cirrhosis, RVR was achieved in 90% (83/92), EVR in 94%, cEVR in 92%, ETR in 95%, and SVR in 86% of patients. Among 43 patients with non-1 HCV genotypes and cirrhosis, RVR was accomplished in 83% (30/36), EVR in 97%, cEVR in 88%, ETR in 95%, and SVR in 86% of patients. For all categories of virological response, the rates of achievement were significantly lower in patients with HCV genotype 1 than that in those with non-1 genotypes for patients with and without cirrhosis. Among patients with genotype 1, the rates of virological responses were significantly lower in those with cirrhosis than those without ($p<0.001$), while there was no significant difference between those with and without cirrhosis among patients with non-1 genotypes (Table 1).

Supplementary Table 2. Adverse Events

Variable	HCV Genotype 1 (n=152)		HCV Genotype non-1 (n=152)	
	Non-LC (n=103)	LC (n=49)	Non-LC (n=109)	LC (n=43)
Anorexia	29 (28.2)	19 (38.8)	32 (29.4)	12 (27.9)
Nausea	11 (10.7)	7 (14.3)	13 (11.9)	2 (4.7)
Diarrhea	5 (4.9)	1 (2.0)	2 (1.8)	4 (9.3)
Flu-like symptom	74 (71.8)	33 (67.3)	72 (66.1)	30 (69.8)
Itching or rash	57 (55.3)	25 (51.0)	53 (48.6)	17 (39.5)
Insomnia	27 (26.2)	2 (4.1)	12 (11.0)	6 (14.0)
Depression	10 (9.7)	2 (4.1)	5 (4.6)	1 (2.3)
Personality change	8 (7.8)	2 (4.1)	3 (2.8)	1 (2.3)
Alopecia	18 (17.5)	5 (10.2)	16 (14.7)	4 (9.3)
Weakness	34 (33.0)	12 (24.5)	30 (27.5)	11 (25.6)
Weight loss	37 (35.9)	8 (16.3)	26 (23.9)	6 (14.0)
Dyspnea	18 (17.5)	10 (20.4)	13 (11.9)	6 (14.0)
Headache	8 (7.8)	5 (10.2)	8 (7.3)	1 (2.3)
Dizziness	13 (12.6)	10 (20.4)	13 (11.9)	9 (20.9)
Anemia (Hb ≤10 g/dL)	49 (47.6)	32 (65.3)	44 (40.4)	23 (53.5)
Neutropenia (ANC ≤750/μuL)	42 (40.8)	26 (53.1)	22 (20.2)	18 (41.9)
Thrombocytopenia (platelet ≤50,000/mm^3)	0	15 (30.6)	0	16 (37.2)

Data are presented as number (%).
HCV, hepatitis C virus; LC, liver cirrhosis; Hb, hemoglobin; ANC, absolute neutrophil count.
The most common adverse events in the present study were flu-like symptoms, which occurred in 67.3% to 71.8% of patients, followed by hematologic adverse events, such as anemia (40.4% to 65.3%) and neutropenia (20.2% to 53.1%). The other adverse events included itching, rash, anorexia, fatigue, weight loss, dizziness, and headache. The occurrence rates of hematologic adverse events, such as anemia, neutropenia, and thrombocytopenia, were higher in patients with cirrhosis than in those without.

Supplementary Table 3. Sustained Virological Response in Subgroups Defined by the Genotype of HCV, the Presence of Liver Cirrhosis, and the Patients' Adherence to Treatment

			Treated for ≥12 wk			
		Treated for <12 wk	EVR (–)	EVR (+)		
				≤75% of planned duration	>75% of planned duration	
					≤75% of target dose	>75% of target dose
Genotype 1	Cirrhosis (n=49)	0/8 (0)	0/4 (0)	3/8 (38)	4/10 (40)	11/19 (58)
	Decompensated (n=1)	-	-	-	-	1/1 (100)
	Compensated (n=48)	0/8 (0)	0/4 (0)	3/8 (38)	4/10 (40)	10/18 (56)
	With CRPH (n=29)	0/5 (0)	0/3 (0)	2/4 (50)	3/6 (50)	6/11 (55)
	Without CRPH (n=19)	0/3 (0)	0/1 (0)	1/4 (25)	1/4 (25)	4/7 (57)
	Noncirrhosis (n=103)	1/16 (6)	1/6 (17)	8/11 (73)	10/14 (71)	49/56 (88)
Genotype non-1	Cirrhosis (n=43)	3/4 (75)	0/1 (0)	2/2 (100)	14/17 (82)	18/19 (95)
	Decompensated (n=3)	1/1 (100)	-	-	-	2/2 (100)
	Compensated (n=40)	2/3 (67)	0/1 (0)	2/2 (100)	14/17 (82)	16/17 (94)
	With CRPH (n=19)	1/1 (100)	0/1 (0)	2/2 (100)	6/9 (67)	5/6 (83)
	Without CRPH (n=21)	1/2 (50)	-	-	8/8 (100)	11/11 (100)
	Noncirrhosis (n=109)	0/4 (0)	1/3 (33)	1/1 (100)	22/23 (96)	70/78 (90)

Data are presented as number (%). Decompensation refers to the presence of ascites or variceal bleeding and/or a Child-Pugh score ≥7. CRPH refers to the presence of esophagogastric varices or thrombocytopenia ($<10^5/mm^3$) with splenomegaly.
HCV, hepatitis C virus; EVR, early virological response; CRPH, clinically relevant portal hypertension.

Supplementary Table 4. Sustained Virological Response in Subgroups Defined by HCV Genotype and Relevant Predictors

Genotype 1		≤75% of target dose	>75% of target dose	p-value
Cirrhosis	RVR negative	1/17 (5.9)	6/11 (54.5)	0.007
	RVR positive	4/9 (44.4)	5/6 (83.3)	0.287
Noncirrhosis	RVR negative	2/22 (9.1)	13/18 (72.2)	<0.001
	RVR positive	10/14 (71.4)	26/28 (92.9)	0.155
Genotype non-1		HCV RNA >5 log IU/mL	HCV RNA ≤5 log IU/mL	p-value
Age >65 yr		15/25 (60.0)	17/19 (85.9)	0.042
Age ≤65 yr		59/67 (88.1)	40/41 (97.6)	0.149

Data are presented as number (%).
HCV, hepatitis C virus; RVR, rapid virological response.
Among patients with HCV genotype 1, only those with early virological responses who were assessed for RVR were included. The p-values were obtained by Fisher exact test.

Supplementary Table 5. Occurrence of Clinical Events according to the Hepatic Fibrosis Stage and Treatment Response

Time	1 Year	3 Years	5 Years	7 Years
Liver-related death		Survival rates (%)/no. of patients at risk (n)		
F0–2	100/153	100/116	100/75	100/36
F3	100/53	100/45	97.6/24	97.6/9
F4 SVR	98.2/52	94.2/39	90.1/19	84.1/7
F4 NR	100/35	89.9/22	80.1/16	80.1/8
cF4 SVR	100/45	97.6/33	97.6/16	97.6/6
cF4 NR	100/26	86.2/17	80.5/14	80.5/7
Hepatic decompensation		Cumulative incidence (%)/no. of patients at risk (n)		
F0–2	0/153	0/116	0/75	0/36
F3	0/53	0/45	4.7/24	4.7/9
F4 SVR	2.0/49	8.5/37	14.3/17	25.4/6
F4 NR	8.1/33	26.4/20	47.9/12	61.4/5
Hepatocellular carcinoma		Cumulative incidence (%)/no. of patients at risk (n)		
F0–2	0/153	0/116	0/75	0/36
F3	0/53	4.0/43	6.3/23	6.3/9
F4 SVR	2.0/46	9.2/33	13.3/16	18.7/5
F4 NR	2.9/32	13.8/19	40.2/10	57.3/5

Hepatic fibrosis progression was divided into five stages—F0, F1, F2, F3, and F4—according to Batts-Ludwig classification. F4 and cF4 refer to cirrhosis and well-compensated cirrhosis with a Child-Pugh score of 5, respectively. Hepatic decompensation was defined as the development of ascites, hepatic encephalopathy, or variceal bleeding.
SVR, sustained virological response; NR, no sustained virological response.