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Pegylated Interferon and Ribavirin in the Retreatment of Chronic Hepatitis C in Korea

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Background/Aims: Pegylated interferon (peginterferon) and ribavirin is the current standard therapy for chronic hepatitis C. The aims of this study were to evaluate the efficacy of peginterferon and ribavirin and to identify predictors of a sustained virological response (SVR) to the retreatment of chronic hepatitis C in Korea. **Methods:** The clinical records of 91 patients with chronic hepatitis C who were retreated with peginterferon and ribavirin were retrospectively analyzed. None of the patients had previously attained a SVR, and the patients were categorized according to their previous responses (nonresponder, relapser, or inadequate treatment) to conventional interferon/ribavirin. **Results:** The overall SVR rate was 54.9%. Independent predictors of a SVR were genotypes 2 and 3, relapse, an adherence to peginterferon of over 80%, and an early virological response (EVR). For genotype 1 patients, an adherence to peginterferon of over 80% was an independent predictor of a SVR. **Conclusions:** Peginterferon and ribavirin therapy is effective for the retreatment of Korean chronic hepatitis C patients who have failed interferon/ribavirin, especially in patients with genotypes 2 and 3, relapse, an adherence to peginterferon over 80%, and an EVR. For genotype 1 patients, retreatment was effective in patients with an adherence to peginterferon over 80%. **(Gut Liver 2013;7:585-593)**

Key Words: Retreatment; Hepatitis C, chronic; Peginterferon; Ribavirin

INTRODUCTION

Over the past decade, therapy involving the combined use of pegylated interferon-α (PEG-IFNα) and ribavirin has become the standard antiviral treatment for chronic hepatitis C, regardless of hepatitis C virus (HCV) genotype. Initially the treatment of chronic hepatitis C was carried out with the combination of conventional IFNα and ribavirin over 24 to 48 weeks according to the genotype. Progressively, IFNα has been replaced by PEG-IFNα, due to the latter's superior efficacy.[1-3]

Patients who display sustained virological response (SVR) generally do not experience progression of fibrosis and may experience regression of established fibrosis.[4-6] Survival rates are significantly higher in patients with cirrhosis who attain SVR than in nonresponders in terms of liver failure and hepatocellular carcinoma.[7,8] Therefore, the primary goal of treating these patients is viral eradication.

Two large international studies, the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) study and the Evaluation of PegIntron in Control of Hepatitis C Cirrhosis 3 (EPIC3) study, involved retreatment of chronic hepatitis C patients who were non-responders or relapsers to previous treatment with IFN and ribavirin, with PEG-IFNα-2a/α-2b and ribavirin. SVR of 18% for nonresponders[9,10] and 43% for relapsers[10] were reported. Other studies on retreatment of chronic viral hepatitis C have been done mostly in Western countries.

The aims of this study were to evaluate the efficacy of the PEG-IFNα and ribavirin treatment in Korean chronic hepatitis C patients who had not achieved SVR after treatment with conventional IFNα with or without ribavirin. We also tried to identify predictors of SVR in these patients.

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MATERIALS AND METHODS

1. Patients

The Institutional Review Board of Samsung Medical Center approved this retrospective study. The clinical records of 91 patients with chronic hepatitis C who were retreated with PEG-IFNα and ribavirin from May 2004 to February 2009 were retrospectively analyzed. All patients in this study did not previously attain SVR and were categorized according to their previous response (nonresponder, relapser, or inadequate treatment) to IFNα with or without ribavirin based on documented HCV-RNA polymerase chain reaction (PCR) results.

Nonresponders were defined as having detectable HCV-RNA in serum after treatment for at least 12 weeks and at the end of therapy. Relapsers had undetectable HCV-RNA at the end of treatment and had subsequent detectable HCV-RNA during posttreatment follow-up. Patients who did not complete the previously scheduled treatment due to poor compliance or adverse events were designated as inadequate treatment.

Patients were excluded if they had an age less than 18 years, coinfection with human immunodeficiency virus or hepatitis B virus, decompensated liver disease (Child-Turcotte-Pugh score ≥7, a history of variceal bleeding, ascites, or hepatic encephalopathy), an autoimmune disease such as autoimmune hepatitis, a history of habitual alcohol ingestion (≥30 g/day), hepatic infiltrative disease, and malignancies, including hepatocellular carcinoma.

The diagnosis of liver cirrhosis was made in the event of histologically compatibility or compatible radiologic findings and platelet counts less than 100×10^3/μL.

2. Treatment protocol

PEG-IFNα-2a (Pegasys®; Roche, Basel, Switzerland) at a dosage of 180 μg/week was injected subcutaneously. Ribavirin (Viramid®; Ilsung Pharmaceuticals, Seoul, Korea) was given orally twice daily at a dose of 1,000 mg/day for patients who weighed 75 kg or less and at a dose of 1,200 mg/day for those weighing more than 75 kg for genotype 1; 800 mg/day was administered for genotype 2 and 3 patients. The duration of treatment was 48 weeks for the patients with genotype 1, and 24 weeks for the patients with genotypes 2 and 3. The patients with a genotype 1 infection, baseline viral load, and an early virological response (EVR), defined as a ≥2 $\log_{10}$ reduction of the serum HCV RNA level after 12 weeks of therapy, were assessed. Those who did not achieve an EVR had their treatment discontinued.

During antiviral therapy, all the patients were followed every 4 to 6 weeks and they were monitored for adverse reactions. A thyroid function test was performed every 12 weeks. Complete blood cell counts were assessed every 4 to 12 weeks, or more frequently if necessary. In this study, neutropenia was defined as an absolute neutrophil cell count below 750/mm^3, anemia was defined as a hemoglobin level below 10 g/dL, and thrombocytopenia was defined as a platelet counts below 50,000/mm^3.

The patients that developed anemia, neutropenia, and/or thrombocytopenia were generally managed with a dose reduction or permanent discontinuation of PEG-IFN or ribavirin as per the guidelines provided in the package inserts. Some patients who developed neutropenia and/or anemia had received subcutaneous granulocyte-colony stimulating factor (G-CSF, Leucostim®; Dong-A Pharmaceutical, Seoul, Korea), 300 μg twice a week and/or subcutaneous human recombinant erythropoietin (Eprex®; Janssen Korea, Seoul, Korea), 2,000 IU twice a week. G-CSF and erythropoietin were administered on an individual basis according to the physician's judgment.

3. Virologic assessment and definition of response

All the patients tested positive for serum anti-HCV antibodies (ADVIA centaur® XP assay; Bayer Healthcare LLC, Diagnostics Division, Tarrytown, NY, USA). The HCV RNA was amplified by RNA PCR and hybridization methods (COBAS® Amplicor HCV test version 2.0; Roche Molecular Systems, Branchburg, NJ, USA; lower limit of detection, 50 IU/mL), and the serum

Table 1. Clinical Characteristics of the Patients (N=91)

Variable	Value
Mean age, yr	52±10
Male	56 (61.5)
Genotype	
1	63 (69.2)
2, 3	28 (30.8)
Viral load, IU/mL	
≤600,000	26 (28.6)
>600,000	65 (71.4)
Previous therapy	
IFN monotherapy	23 (25.3)
IFN+RBV	68 (74.7)
Previous response	
Nonresponse	34 (37.4)
Relapse	37 (40.7)
Inadequate treatment	20 (22)
Liver cirrhosis	22 (24.2)
Mean weight, kg	66±10
Diabetes	7 (7.7)
Median alanine aminotransferase, U/L	64 (12-409)
Median aspartate aminotransferase, U/L	58 (16-625)
Median white blood cell count, $\times10^3$/μL	4.89 (2.83-9.82)
Mean absolute neutrophil cell count, $\times10^3$/μL	2.47±1.17
Mean hemoglobin, g/dL	14±2
Median platelets, $\times10^3$/μL	158 (52-265)

Data are presented as mean±SD, number (%), or median (range).
IFN, interferon; RBV, ribavirin.

concentration of HCV-RNA was measured by real-time PCR (COBAS® AmpliPrep/COBAS® TaqMan® HCV Test; Roche Molecular Systems). Serum HCV RNA was measured at screening; at weeks 12, 24, and 48 of treatment, and at 12 and 24 weeks posttreatment.

An end-of-treatment virological response (ETR) was defined as an undetectable level of HCV RNA as assessed by qualitative assay at the end of treatment. The SVR was defined as an undetectable level of HCV RNA as assessed by a qualitative assay at 24 weeks after the completion of the antiviral therapy and this level was maintained throughout the remaining documented follow-up period.

4. Statistical analysis

The analysis was performed by intention to treat analysis. To identify the factors associated with a SVR, multivariable binary logistic regression analysis was performed using the variables with p-values of <0.2 on the univariable analysis. For several factors, the previously reported cutoff values were used to identify the patients who are likely to show a SVR.[11] Based on these cutoff values, age (≤40 years vs >40 years), HCV RNA (≤600,000 IU/mL vs >600,000 IU/mL), body weight (≤75 kg vs >75 kg), serum alanine transaminase (≤120 U/L vs >120 U/L), and adherence to PEG-IFNα and ribavirin (≤80% vs >80%) were categorized into two groups, and these were tested in the univariable and/or multivariable analyses.

A $p<0.05$ was considered significant and it was corrected by Bonferroni's method to correct the inflated type I error due to multiple testing. All the statistical analysis was run on SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinical characteristics

The clinical features of the chronic viral hepatitis C patients who were retreated with PEG-IFN and ribavirin are shown in Table 1. The mean age was 52±10 years and 61.5% of the patients were male. Overall, 69.2% (63/91) of the patients had gen-

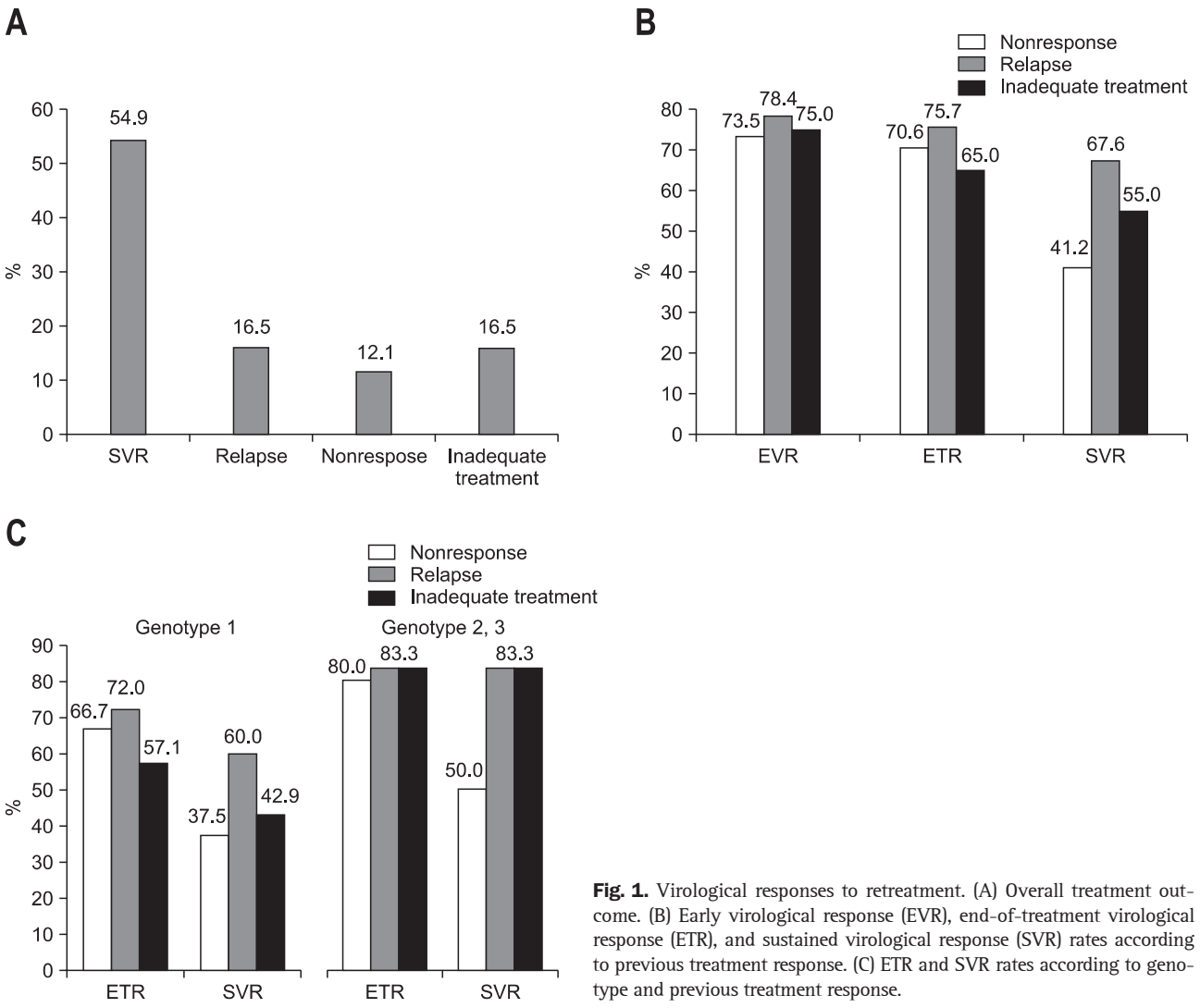

Fig. 1. Virological responses to retreatment. (A) Overall treatment outcome. (B) Early virological response (EVR), end-of-treatment virological response (ETR), and sustained virological response (SVR) rates according to previous treatment response. (C) ETR and SVR rates according to genotype and previous treatment response.

otype 1, 27 patients had genotype 2, and only one patient had genotype 3. More than two-thirds (71.4%) of the patients had a viral load of more than 600,000 IU/mL. Almost three-fourths (74.7%) of the patients were previously treated with IFNα and ribavirin, and 25.3% of the patients were previously treated with IFNα monotherapy. Overall, 40.7% of the patients were relapsers to previous treatment, 37.4% were nonresponders, and 22% were inadequate treatment. Approximately one-fourth of the patients (24.2%) had liver cirrhosis.

2. Response to treatment

Overall treatment outcome is shown in Fig. 1A. After retreatment with PEG-IFNα and ribarivin, 54.9% (50/91) of the patients attained a SVR, 12.1% (11/91) were nonresponders, and 16.5% (15/91) were relapsers. Overall EVR was 76.9% (70/91) and an ETR was 71.4% (65/91).

Virological responses to retreatment according to previous treatment responses are as shown in Fig. 1B. Previous relapsers had a higher virologic response, especially compared with previous nonresponders, with an EVR of 78.4%, an ETR of 75.7%, and a SVR of 67.6%. Virological responses to retreatment according to genotypes and previous treatment responses are as shown in Fig. 1C. Genotype 2 and 3 patients who were previous relapsers and inadequate treatment had a higher virologic response compared with previous nonresponders, with an ETR of 83.3% and a SVR of 83.3%.

Table 2. Predictors of a Sustained Virological Response to Retreatment Evaluated by Univariate and Multivariate Binary Logistic Regression Analyses

Variable	SVR	OR (95% CI)	p-value
Univariable analysis			
Age ≤40 yr	4/8 (50)	0.804 (0.188-3.436)	0.769
Female	23/35 (65.7)	2.059 (0. 860-4.928)	0.105
Genotype 2, 3	20/28 (71.4)	2.750 (1.056-7.164)	0.038
HCV RNA ≤600,000 IU/mL	17/26 (65.4)	1.832 (0.71-4.703)	0.208
Previous therapy: IFN+RBV	34/68 (50)	0.438 (0.160-1.198)	0.108
Previous response			0.038
Nonresponse	14/34 (41.2)	1	
Relapse	25/37 (67.6)	2.976 (1.129-7.848)	0.027
Inadequate treatment	11/20 (55)	1.746 (0.573-5.323)	0.327
Absence of liver cirrhosis	42/69 (60.9)	2.722 (1.007-7.357)	0.048
Body weight ≤75 kg	43/76 (56.6)	1.536 (0.505-4.673)	0.450
Absence of diabetes	46/84 (54.8)	0.908 (0.191-4.309)	0.903
ALT >120 U/L	11/21 (52.4)	0.874 (0.329-2.324)	0.788
Adherence to PEG-IFN >80%	38/52 (73.1)	6.107 (2.445-15.254)	<0.001
Adherence to RBV >80%	38/54 (70.4)	4.948 (2.006-12.203)	0.001
EVR	48/70 (68.6)	20.727 (4.435-96.871)	<0.001
Multivariable analysis			
Female	23/35 (65.7)	1.548 (0.485-4.935)	0.461
Genotype 2, 3	20/28 (71.4)	5.787 (1.277-26.222)	0.023
Previous therapy: IFN+RBV	34/68 (50)	0.540 (0.128-2.289)	0.403
Previous response			0.027
Nonresponse	14/34 (41.2)	1	
Relapse	25/37 (67.6)	6.609 (1.667-26.206)	0.007
Inadequate treatment	11/20 (55)	2.785 (0.628-12.343)	0.178
Absence of liver cirrhosis	42/69 (60.9)	2.628 (0.586-11.790)	0.207
Adherence to PEG-IFN >80%	38/52 (73.1)	4.011 (1.232-16.087)	0.048
Adherence to RBV >80%	38/54 (70.4)	0.713 (0.160-3.176)	0.657
EVR	48/70 (68.6)	27.491 (3.026-249.72)	0.003

Data are presented as number (%).
SVR, sustained virological response; OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; ALT, alanine aminotransferase; PEG-IFN, pegylated interferon; EVR, early virological response.

3. Predictors of SVR

Univariable logistic regression analyses identified genotype 2 and 3, previous treatment response, absence of liver cirrhosis, adherence to PEG-IFN over 80%, adherence to ribavirin over 80%, and an EVR as significant predictors of a SVR (Table 2). In multivariable regression analysis, genotype 2 and 3 (p=0.023), relapse in previous treatment response (p=0.007), adherence to PEG-IFN over 80% (p=0.048), and an EVR (p=0.003) were statistically significant independent predictors of a SVR (Table 2).

Subgroup analysis for genotype 1 patients is shown in Table 3. Univariable logistic regression analyses identified absence of liver cirrhosis, adherence to PEG-IFN over 80%, and adherence to ribavirin over 80% as significant predictors of a SVR. In multivariable regression analysis, adherence to PEG-IFN over 80% (p=0.035) was statistically significant independent predictor of a SVR.

4. Safety, treatment modification, or discontinuation

PEG-IFNα and ribarivin combination therapy was completed by 74.7% (68/91) of the patients. In eight patients, treatment was stopped at week 12 due to nonresponse and in 11, therapy was discontinued due to treatment intolerance and adverse events. In three patients, treatment was stopped due to detection of hepatocellular carcinoma and in one patient, therapy was discontinued due to an economic problem. Among the patients who completed the treatment, 33.8% (23/68) of the patients needed dose reduction of PEG-IFNα and 27.9% (19/68) of the patients needed dose reduction of ribavirin due to treatment intolerance and adverse events. Among the patients who completed the treatment, 76.5% (52/68) of the patients showed over 80% adherence to PEG-IFNα and 79.4% (54/68) of the patients showed over 80% adherence to ribavirin.

Discontinuation and dose modification of PEG-IFNα and ribarivin according to genotype and previous treatment responses are shown in Fig. 2.

DISCUSSION

PEG-IFNα-2a and ribavirin combination therapy was effective in a substantial proportion of patients who failed conventional IFN with or without ribavirin therapy. The overall SVR rate was 54.9% (50/91) and responses varied depending on a number of predictors of response. Relapser group had higher SVR (67.6%) compared with nonresponder (41.2%) or inadequate treatment group (55%), and genotype 2 and 3 patients had higher SVR (71.4%) compared with genotype 1 patients (47.6%). Patients without liver cirrhosis showed higher SVR

Table 3. Predictors of a Sustained Virological Response to the Retreatment of Genotype 1 Chronic Hepatitis C Patients Evaluated by Univariate and Multivariate Binary Logistic Regression Analyses

Variable	SVR	OR (95% CI)	p-value
Univariable analysis			
Age ≤40 yr	3/6 (50)	1.111 (0.207-5.978)	0.902
Female	12/21 (57.1)	1.778 (0.617-5.124)	0.287
HCV RNA ≤600,000 IU/mL	10/19 (52.6)	1.333 (0.453-3.920)	0.601
Previous therapy: IFN+RBV	21/48 (43.8)	0.519 (0.159-1.687)	0.275
Previous response			0.272
Nonresponse	9/24 (37.5)	1	
Relapse	15/25 (60)	2.500 (0.791-7.898)	0.118
Inadequate treatment	6/14 (42.9)	1.250 (0.326-4.788)	0.745
Absence of liver cirrhosis	27/51 (52.9)	3.375 (0.818-3.930)	0.093
Body weight ≤75 kg	26/53 (49.1)	1.444 (0.365-5.713)	0.600
Absence of diabetes	26/56 (46.4)	0.650 (0.133-3.176)	0.595
ALT >120 U/L	9/17 (52.9)	1.339 (0.439-4.085)	0.608
Adherence to PEG-IFN >80%	23/33 (69.7)	7.557 (2.452-23.292)	<0.001
Adherence to RBV >80%	22/33 (66.7)	5.500 (1.857-16.287)	0.002
Multivariable analysis			
Absence of liver cirrhosis	27/51 (52.9)	1.738 (0.349-8.648)	0.500
Adherence to PEG-IFN >80%	23/33 (69.7)	4.691 (1.118-19.679)	0.035
Adherence to RBV >80%	22/33 (66.7)	1.824 (0.416-8.003)	0.426

Data are presented as number (%).
SVR, sustained virological response; OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; ALT, alanine aminotransferase; PEG-IFN, pegylated interferon.

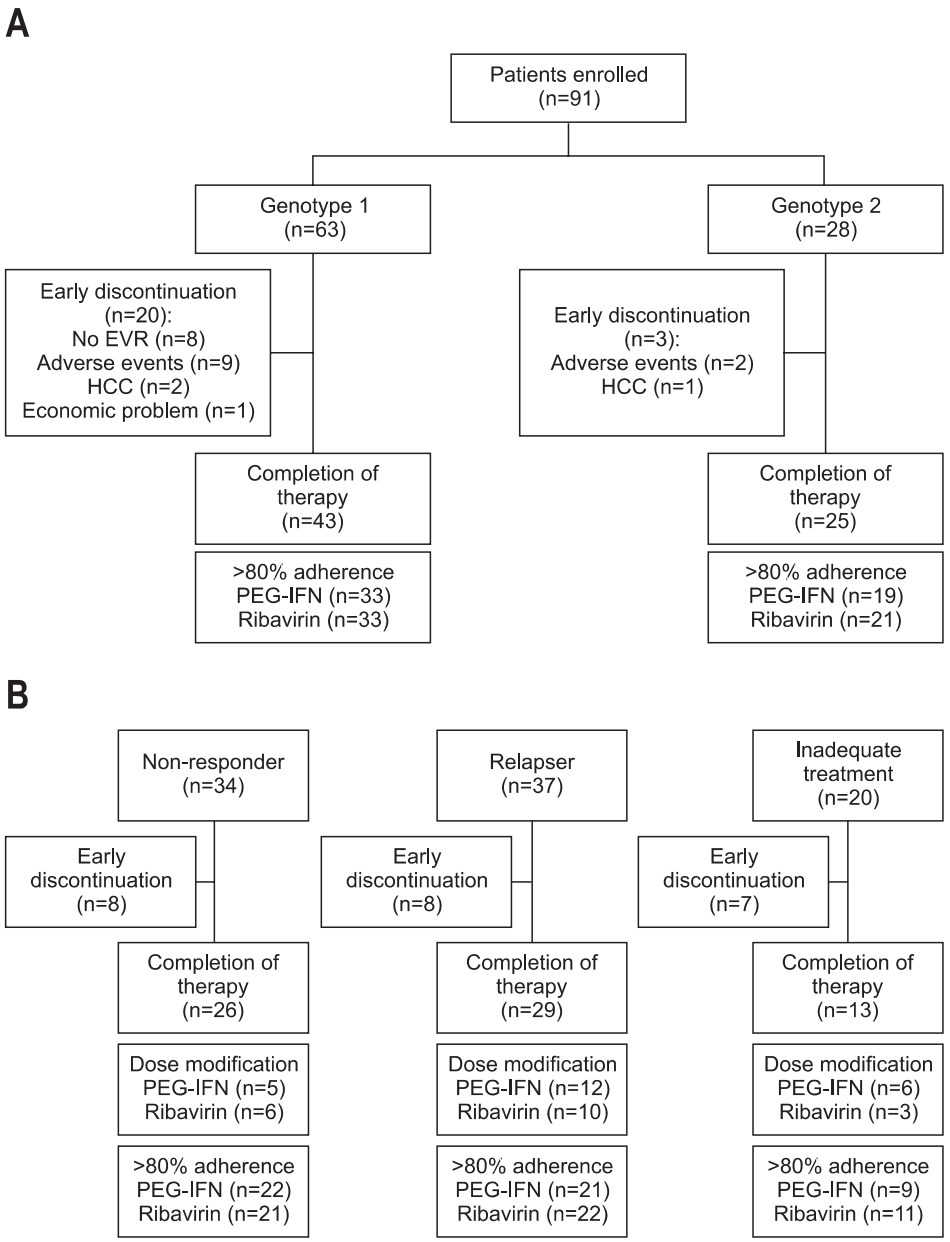

Fig. 2. Discontinuation and dose modification of pegylated interferon α (PEG-IFNα) and ribavirin. (A) Discontinuation of PEG-IFNα and ribavirin according to genotype. (B) Discontinuation and dose modification of PEG-IFNα and ribavirin according to previous treatment response.
EVR, early virological response; HCC, hepatocellular carcinoma.

(60.9%) than patients with liver cirrhosis (36.4%). Patients with adherence to PEG-IFN over 80% showed higher SVR (73.1% vs 30.8%), and patients with adherence to ribavirin over 80% showed higher SVR (70.4% vs 32.4%). Patients with an EVR showed higher SVR (68.6% vs 9.5%). The SVR rate was 37.5% in genotype 1 patients who were nonresponders to previous IFNα/ribavirin, and 83.3% in genotype 2 and 3 patients who experienced relapse after a previous IFNα/ribavirin. Independent predictors of a SVR were genotype 2 and 3, relapse in previous treatment response, adherence to PEG-IFN over 80%, and an EVR. For genotype 1 patients, adherence to PEG-IFN over 80% was independent predictor of a SVR.

Previous studies have shown that some patients who are nonresponsive to IFNα with or without ribavirin can be retreated with PEG-IFNα/ribavirin; SVR rates ranging from 4% to 37% in nonresponders to 50% or more in relapsers.[9,12-25]

Two large international studies, HALT-C and EPIC3, that used PEG-IFNα-2a/α-2b and ribavirin to retreat chronic hepatitis C patients who were nonresponders or relapsers to previous treatment with IFN and ribavirin, obtained 18% of SVR for nonresponders[9,10] and 43% of SVR for relapsers.[10] In the HALT-C study, all patients had bridging fibrosis or cirrhosis on liver biopsy and the population who previously received IFN with ribavirin (n=385) attained a SVR rate of 12%.[9] In the EPIC3 study, all patients had significant hepatic fibrosis/cirrhosis (METAVIR score F2, F3, or F4), and the retreatment results were better in relapsers than in nonresponders and, mainly, in those who received IFN and ribavirin previously as compared to those

who received PEG-IFN and ribavirin.[10] In EPIC3, SVR predictors included genotypes 2/3, F2/F3 fibrosis stage by METAVIR score, baseline viral load ≤600,000 UI/mL, previous treatment with IFN monotherapy and relapsers after the first treatment.

In the current study, the overall ETR was 71.4%, and the SVR rate was 54.9%. The SVR rates of genotype 1 patients were 37.5% in previous nonresponders and 60% in previous relapsers. The SVR rates of genotype 2 patients were 50% in previous nonresponders and 80.3% in previous relapsers (Fig. 1C). They were similar but somewhat higher than results of other reported studies. Krawitt *et al*.[12] treated 182 nonresponder and relapse patients with PEG-IFNα-2b and ribavirin during 48 weeks and achieved a SVR rate of 20% and 55%, respectively. They also observed SVR in 53% of the relapsing patients infected by genotype 1 and in 59% of the relapsing patients infected by genotypes 2/3. Of the previous nonresponders, only 17% of patients infected by genotype 1 presented SVR, as compared to 57% of the infected by the genotypes 2/3. Parise *et al*.[13] reported SVR rates of 51% and 26%, respectively, in a study of 134 patients in which relapsers and nonresponders to IFNα/ribavirin were retreated with PEG-IFNα-2a/ribavirin. Sherman *et al*.[14] obtained a SVR rate of 23% for nonresponders and 41% for relapsers to prior treatments with IFN monotherapy or combined with ribavirin after a therapy with PEG-IFNα-2a plus ribavirin. The reported SVR rate of Korean is higher than the SVR rate of other ethnicity. There is increasing evidence that Asians have a higher likelihood of achieving a SVR than their Caucasians counterparts.[26] Several factors such as host genetic variation (i.e., *IL28B* polymorphism), geographic variations of HCV, and lower weight of Asian patients have been suggested to explain this.[26,27] The patients in the current study might have a basal lower stage of fibrosis compared to other studies, but histologic data was not available for most of patients. Relatively high adherence to PEG-IFN and ribavirin could also affect the results.

Studies from Asia (Japan in particular) showed the importance of the *IL28B* genotype in patients with HCV genotype 1 infections.[28,29] Sinn *et al*.[30] reported that the favorable allele frequency in Korean patients was 0.85. Patients with the unfavorable homozygote allele were extremely rare, comprising only 1% of the total patients. In that study, the authors concluded that genotyping of the *IL28B* genotype may help identify genotype 1 HCV infected patients who will show a nonresponse to PEG-IFN and ribavirin therapy, but not in genotype 2. Among 91 patients of the current study, 19 patients were included in the previous study[30] and tested for single nucleotide polymorphism genotyping (data not shown). Among 15 genotype 1 patients, 12 patients had major homozygotes (TT) and three patients had heterozygotes (GT). Two patients out of three GT patients showed a SVR and eight patients out of 15 major TT patients showed a SVR. Although the role of the *IL28B* polymorphism in retreatment of chronic hepatitis C could not be fully evaluated in the current study due to lack of data, the *IL28B* polymorphism may play a role in these patients.

Comparisons between studies are very difficult as each author stratifies in a different way. Previous studies showed heterogeneous SVR rates and they also showed differences in design and power of the studies, potential biases in the selection of patients with different demographic, clinical and virologic characteristics, the variability in the doses of IFN and ribavirin, and the different treatment stopping rule of the first course of therapy. Camma *et al*.[31] conducted meta-analysis of 14 trials on retreatment with PEG-IFN and ribavirin in chronic hepatitis C patients who failed to respond to IFN or PEG-IFN and ribavirin. This meta-analysis of data from 14 studies, comprising nearly 4,000 nonresponders to combination therapy, reported that retreatment with a course of 48 weeks of PEG-IFN and ribavirin achieved a SVR in 16% of patients with a 12% withdrawal rate due to adverse reactions or intolerance to drugs. Although the number of retreated patients in the available studies was high, suggesting that the estimate of the cumulative SVR rate could be robust, the confidence intervals of the effect were wide (8.3% to 29.6%) due to the heterogeneity of the trials. This analysis showed that studies that included patients with normal baseline BMI, and low prevalence of genotype 1 infection, and in which PEG-IFNα-2a was administered, showed a higher SVR rate.

Previous studies showed that an EVR can help predict the likelihood of achieving a SVR and the treatment stopping role could be anticipated at week 12.[10,18,20,32,33] The current study showed that among patients who achieved an EVR, 68.6% of the patients achieved a SVR compared with only 9.5% of patients who did not achieve an EVR. Univariable and multivariable analyses showed that an EVR is a statistically significant predictor of a SVR. In the current study, the treatment stopping rule at week 12 was applied for genotype 1 patients, so the result may be little wonder. In subgroup analysis for genotype 1, an EVR could not be included in the univariable and multivariable analyses and this may be attributable to the fact that none of the patients who did not have an EVR had a SVR. Although an EVR was a statistically significant predictor of a SVR in univariable analysis for genotype 2 patients (p=0.032), multivariable analysis could not be done due to the small number of patients who did not have a SVR (data not shown).

Some previous studies included 48 week regimen of PEG-IFN and ribavirin for retreatment of genotype 2 or 3 patients, but relatively small numbers of the nongenotype 1 patients were included in those studies.[9,10,12,13,15,17,23,33] The rates of SVR in this study may have been affected by the 48 week treatment regime, further large scale studies are needed to prove benefits.

Jensen *et al*.[32] showed that retreatment with PEG-IFN and ribavirin for an extended duration of 72 weeks was successful in those patients who cleared HCV RNA by week 12 of retreatment. The rates of SVR in this study may have been higher had the treatment regimen been extended to 72 weeks. Further large scale multicenter RCTs will prove useful in substantiating the

benefit of retreatment with a prolonged course of therapy.

In the current study, inadequate treatment group showed relatively high SVR. This is probably attributable to the advances in management of adverse events of PEG-IFN and ribavirin. Thus, the decision to retreat patients should depend on the reasons for why they may have failed, such as inadequate drug dosing or side effect management.

Although the American Association for the Study for Liver Disease Practice Guidelines recommend that retreatment with PEG-IFN and ribavirin be considered for nonresponders who have undergone previous regimens of combination treatment using conventional IFN,[11] retreatment of chronic hepatitis C patients is still a great challenge in some patients. Triple combination therapy including a protease inhibitor such as telaprevir or boceprevir or other direct acting agents to the present therapy may be considered in such patients.[34,35]

Many studies have been published on retreatment of chronic viral hepatitis C, but most of them were from Western countries. To our knowledge, this is the first published article on PEG-IFNα plus ribavirin combination therpay in the retreatment of chronic hepatitis C patients who did not achieve SVR to previous IFNα/ribavirin in Korea.

There are several limitations to this study. First, this study is a retrospective study. There is a possibility of a bias in which better candidates for retreatment were more likely to be selected. This study was conducted in the tertiary care hospital, substantial numbers of the patients were referred from the other hospitals. So, the precise protocol of previous treatments was not clear. Second, histologic data was not available for most of patients, so we could not analyze a SVR according to the fibrosis stage. Third, the number of patients was relatively small, the patients may not be representative of the whole population of Korea. Moreover, subgroup analyses according to genotypes could not be done effectively. A larger-scale prospective study is required to evaluate clinical outcomes of retreatment. Fourth, the rapid virological response (RVR), are gaining importance in guiding further therapy.[36] In this study, the RVR assessment was not done for many patients, because many patients underwent therapy before the introduction of the RVR. Guiding therapy with RVR can be beneficial in retreatment of chronic viral hepatitis C patients, but this needs further clarification.

In conclusion, PEG-IFNα-2a and ribavirin combination therapy is effective in patients who have failed conventional IFN with or without ribavirin therapy in patients with genotype 2 and 3, relapse in previous treatment response, adherence to PEG-IFN over 80% and an EVR. For genotype 1 patients, retreatment was effective especially in patients with adherence to PEG-IFN over 80%.

CONFLICTS OF INTEREST

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

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