Prediction of Sustained Virologic Response Based on Week 4 and Week 12 Response in Hepatitis C Virus Genotype 1 Patients Treated with Peginterferon and Ribavirin: Assessment in a Favorable *IL28B* Allele-Prevalent Area

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Key Words

Chronic hepatitis C • Virologic response • Sustained virologic response • Treatment-naïve • Genotype 1 • Peginterferon • Ribavirin • Positive predictive value • Negative predictive value

Abstract

Objectives: The aim of this study was to evaluate rapid virologic response (RVR) rate after peginterferon (PegIFN) and ribavirin (RBV) dual combination therapy in Korean hepatitis C virus (HCV) genotype 1 patients whose *IL28B* polymorphism is generally favorable. This study also assessed the value of RVR in predicting sustained virologic response (SVR). **Methods:** Treatment-naïve HCV genotype 1 patients who underwent initial treatment with either PegIFN- α -2a or α -2b and RBV were retrospectively evaluated. From 148 patients, 115 met inclusion criteria for the final analysis. **Results:** Overall RVR rate was 47.8% and SVR rate was 67.8% (78/115). Positive RVR had the highest positive predictive value (PPV) for achieving SVR, whereas it had the lowest negative predictive value (NPV). Undetectable HCV RNA at treatment week 12, namely complete early virologic response (cEVR), had high PPV as well as high NPV. Factors predisposing SVR were ab-

sence of liver cirrhosis and achievement of RVR or cEVR. **Conclusion:** This study showed RVR rate close to 50% in HCV genotype 1 patients treated with dual combination therapy in the region where favorable *IL28B* polymorphism is reported to be as high as 90%. Even for the patients who failed to achieve RVR, positive cEVR demonstrated a fair chance of achieving SVR.

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Introduction

Standard of care (SOC) therapy for patients with chronic hepatitis C virus (HCV) has been the use of peginterferon (PegIFN) combined with ribavirin (RBV). In cases of HCV genotype 1, this will lead to a sustained virologic response (SVR) rate of 40–50% in western countries [1, 2]. Recent introduction of direct-acting antiviral agents is reported to raise SVR rates. Two protease inhibitors, boceprevir and telaprevir, which are currently available in a limited number of countries, have been shown to improve SVR rates up to 63–72% in treatment-naïve HCV genotype 1 patients [3, 4]. A practice guideline established by the American Association for the Study of

Liver Diseases recommended the use of a protease inhibitor with PegIFN and RBV in treating previously untreated HCV genotype 1 patients [5]. However, introducing a protease inhibitor in the therapy would not only raise the efficacy of the treatment but also the frequency of adverse effects as well as the cost of the therapy [3–6]. There must be a proportion of patients that would successfully achieve SVR without adding a protease inhibitor. It has been suggested that treatment-naïve HCV genotype 1 patients with favorable *IL-28B* polymorphism or patients that showed undetectable HCV RNA at week 4 of PegIFN and RBV dual combination therapy have a considerably higher chance of achieving SVR without adding a protease inhibitor [6, 7].

Several reports suggest that Asian patients with chronic HCV have a better chance of achieving SVR, even in HCV genotype 1 [8–10]. This is partly attributed to a higher proportion of favorable *IL-28B* polymorphisms in Asians. As for Koreans, the proportion of patients with favorable allele is reported to be as high as 87.7–93.5% [11, 12]. Therefore, including a protease inhibitor in SOC therapy for treating all treatment-naïve HCV genotype 1 patients might not be cost-effective in Korea and other regions with similar clinical situations. Meanwhile, a recommendation has been put forward to use virologic response at treatment week 4, known as rapid virologic response (RVR), as an indicator for adding protease inhibitor to PegIFN and RBV dual combination therapy in treating HCV genotype 1 patients that have never been treated before [6, 7].

Although several studies have reported relatively higher SVR rates in Koreans, studies of RVR rates in Korea, where the majority of patients have a favorable *IL-28B* polymorphism, are scarce. The aim of this study was to evaluate RVR rate in Korean HCV genotype 1 patients treated in a single center using PegIFN and RBV dual combination therapy. In addition, this study also assessed the positive predictive value (PPV) and negative predictive value (NPV) of RVR for SVR in Korean patients of whom the majority of *IL-28B* polymorphisms are reported to be favorable.

Patients and Methods

Patients

Treatment-naïve chronic hepatitis C patients with HCV genotype 1 that underwent initial treatment with either PegIFN- α -2a or α -2b combined with appropriate dose of RBV, were retrospectively evaluated. These patients were treated between January 2005 and August 2010 at Inha University Hospital (Incheon, Re-

public of Korea). Among these 148 patients, 115 patients who had their sustained virologic response available were included in the final analysis. These 115 patients were aged >18 years and with positive anti-HCV antibody (third generation, enzyme immunoassay, Abbott Laboratories, Chicago, Ill., USA) and detectable serum HCV RNA level evaluated by real-time RT-PCR analysis (Abbott RealTime HCV Assay; Abbott Laboratories) for more than 6 months. Patients were excluded from the analysis when they (i) currently had or had experienced malignant disease, (ii) had autoimmune disease, (iii) were co-infected with either HIV or hepatitis B virus, (iv) had a serum creatinine level >1.5 times the upper limit of normal, (v) had been put under immunosuppressive therapy or experienced organ transplantation or (vi) had evidence of decompensated liver disease at the time of the treatment.

The patients were treated with either pegylated IFN- α -2a (Pegasys, Hoffmann-La Roche Ltd, Basel, Switzerland) 180 μ g or α -2b (PegIntron, MSD) 1.5 μ g/kg, subcutaneously injected once a week, and concomitant daily administration of oral RBV for 48 weeks, unless the patient showed undetectable HCV RNA at treatment week 4.

Definition and Evaluation of the Treatment Response

On-treatment virologic response was evaluated at baseline, week 4, week 12, the end of treatment and 24 weeks after the end of treatment by assessing serum HCV RNA levels quantitatively. The test had a sensitivity limit of 15 IU/ml. RVR was defined as an undetectable serum HCV RNA level (<15 IU/ml) at treatment week 4. Early virologic response (EVR) was defined as at least a 2-log reduction in serum HCV RNA level from baseline to week 12 of treatment. Complete EVR (cEVR) was defined as undetectable serum HCV RNA level at week 12 of therapy. End of treatment response was defined as undetectable serum HCV RNA level at the end of treatment. SVR was declared if HCV RNA was absent at the end of treatment as well as at 24 weeks after the therapy had ended.

The patient was said to be adherent to the therapy when he/she received the therapy for more than 40 weeks unless the patient achieved RVR and decided to receive shortened therapy of 24 weeks. The patients with lack of EVR who had the treatment stopped at week 12 were also considered to be adherent to the therapy. Adherence to RBV administration was ensured when dose reduction less than 20% of the initial dose was undertaken.

Statistical Analysis

Univariate and multivariate analysis of factors that predisposed SVR were assessed using logistic regression models. Variables with $p < 0.05$ in univariate analysis were included in the multivariate model. These models were considered using conditional selection procedures. Hazard ratios are presented with 95% confidence interval. $p < 0.05$ was considered significant for multivariate analysis.

PPV is the probability that a patient with a given on-treatment virologic response will achieve an SVR, whereas NPV is the probability that a patient without a given on-treatment virologic response will not achieve an SVR. Statistical analyses were performed using SPSS software version 15.0 (SPSS, Chicago, Ill., USA).

Table 1. Baseline characteristics of Korean patients infected with chronic HCV genotype 1 who received therapy with PegIFN- α combined with RBV

Patients, n	115
Median age	47 (27–74)
Male	82 (71.3)
Median BMI	24.7 (17.3–54.9)
HCV subtype	
1a	10 (8.7)
1b	99 (86.1)
Other	6 (5.2)
Baseline serum HCV RNA level	
<800,000 IU/ml	91 (79.1)
$\geq$ 800,000 IU/ml	24 (20.9)
Median baseline AST $\times$ ULN	1.67 (0.34–10.5)
Median baseline ALT $\times$ ULN	1.98 (0.19–17.7)
DM	29 (25.2)
Liver cirrhosis	24 (20.9)
Patients that adhered to the therapy ¹	107 (93.0)
Patients that had RBV reduced by more than 20% ²	11 (9.6)

Figures in parentheses represent ranges or n (%). AST = Aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

¹ The patient was considered to be adherent to the therapy when he/she was put under therapy for more than 40 weeks unless the patient achieved RVR and had shortened therapy of 24 weeks or had treatment stopped due to lack of EVR.

² Reduction was made from the initial dose of RBV.

Table 2. PPV and NPV for SVR of serum HCV RNA level tested at week 4 and 12 of the therapy

	PPV (%)	NPV (%)
RVR	98.2	60.0
cEVR	80.2	94.7
EVR	73.9	100.0

Results

Patient Characteristics

Among 148 HCV genotype 1 patients that underwent initial treatment with a weekly injection of PegIFN and concomitant daily administration of RBV, 33 cases were dropped due to lack of an SVR check. These dropout patients had a median treatment period of 10 weeks. Six patients received the treatment for longer than 24 weeks, among whom 1 patient completed the study with neither

Fig. 1. Duration of the treatment, considering virologic response.

end of treatment response nor SVR checked after the treatment.

Excluding 33 patients, 115 patients were included for the final analysis. The demographic characteristics of these 115 patients are summarized in table 1. The majority of the patients had HCV genotype 1b (99/115, 86.1%), with low baseline HCV RNA levels, <800,000 IU/ml (91/115, 79.1%; table 1). Treatment was stopped if the patient failed to achieve EVR at week 12, and 9 patients fell into this category (fig. 1). Out of 106 patients that had EVR, 55 patients also achieved RVR. From these 55, 10 chose to receive shortened therapy of 24 weeks. The other 45 patients with RVR and 51 patients that had EVR without RVR, were intended to be treated for 48 weeks (fig. 1). Out of these 96 patients intended to be treated for 48 weeks, 88 patients adhered to the therapy for more than 40 weeks and 8 patients received the treatment for less than 40 weeks (table 1). The reasons for premature cessation of the treatment included adverse events (5/8, 62.5%) such as neutropenia, anemia, generalized weakness and depression, and failure to return for the therapy (3/8, 37.5%).

Table 3. Factors predisposing SVR

	Univariate analysis	Multivariate analysis		
	p value	hazard ratio	95% CI	p value
Age (<40 versus ≥40)	0.003*			
Gender	1.000			
HCV subtype ¹	0.628			
Baseline serum HCV RNA (<800,000 versus ≥800,000 IU/ml)	0.810			
Positive RVR	0.000*	39.20	4.79–321.00	0.001*
Positive cEVR	0.000*	18.65	2.20–158.44	0.007*
Positive EVR	0.000*			
BMI (<25 versus ≥25)	1.000			
DM, present versus absent	0.000*			
Liver cirrhosis (present versus absent)	0.000*	0.135	0.02–0.92	0.041*
Treatment adherence (<40 versus ≥40 weeks) ²	0.57			
Reduction of RBV (≤20 versus >20%)	0.304			
Baseline AST	0.330			
Baseline ALT	0.071			

* $p < 0.05$. AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

¹ HCV subtype consists of genotype 1a, 1b or others.

² The patient was said to be adherent to the therapy when he/she was put under the therapy for more than 40 weeks unless the patient achieved RVR and had shortened therapy of 24 weeks or had treatment stopped due to lack of EVR.

Fig. 2. SVR (undetectable serum HCV RNA ≥24 weeks after the end of therapy) in patients with a virologic response by week 4 (RVR) and week 12 (EVR). cEVR is achieved when serum HCV RNA becomes undetectable at week 12.

Treatment Outcomes

Overall SVR rate was 67.8% (78/115) and overall recurrence rate was 21.2% (21/99). On-treatment virologic response rate at week 4, week 12 and at the end of treatment

was 47.8% (55/115), 93.0% (107/115) and 86.1% (99/115), respectively. Overall cEVR was achieved in 96 patients (96/115), which was 89.7% (96/107) of positive EVR patients.

Overall SVR rate was highest among patients that had RVR (fig. 2). Positive RVR had highest PPV for SVR whereas absence of EVR had highest NPV (table 2).

Predictors of SVR

Although having positive RVR demonstrated highest PPV for achieving SVR, it had relatively low NPV. Among patients that failed to show RVR, 40% (24/60) of patients achieved SVR. Univariate analysis showed that achieving RVR, cEVR or EVR, longer duration of treatment, lower age, absence of diabetes mellitus (DM) or liver cirrhosis might predict positive SVR (table 3). Multivariate analysis showed that achieving RVR, cEVR and not having liver cirrhosis were favorable predictive factors for achieving SVR (table 3).

Discussion

This study showed RVR rate of 47.8% and SVR rate of 67.8%. In accordance with previous studies [13, 14], this study also suggested that achievement of RVR had high

PPV for SVR which was over 90%. This virtue of RVR allowed some experts to recommend addition of a protease inhibitor depending on the result of RVR achievement in treating treatment-naïve HCV genotype 1 patients [6, 7]. However, our study as well as other investigations demonstrated that a considerable number of patients that failed to achieve RVR might successfully acquire SVR [15, 16] without adding a protease inhibitor. More careful considerations might be necessary in the regions where favorable *IL-28B* polymorphism prevails, since this, along with RVR, has consistently been suggested as a strong predictor for SVR [6]. Achieving undetectable HCV RNA at treatment week 12, namely cEVR, might be a candidate predictive factor for SVR before taking the decision to start protease inhibitor-based therapy. In this study, cEVR showed both considerably high PPV and NPV, as was also reported by a previous study [16]. In addition, absence of liver cirrhosis can act as a favorable predictor for SVR in accordance with other studies [3, 4].

Among 115 patients that were included for the final analysis, 55 achieved RVR. These patients could choose between shortened treatment of 24 weeks and completion of 48 weeks of therapy. Ten patients chose to receive shortened therapy and 9 patients achieved SVR. The patient that failed to achieve SVR had relapsed chronic HCV. However, this result may not be significant regarding the efficacy of tailored therapy in Koreans since too few patients received shortened therapy.

In our study, high baseline serum HCV RNA level failed to play a role in predicting SVR achievement. This result may be attributable to a larger proportion of low baseline serum HCV RNA levels, <800,000 IU/ml in this study.

Although presence of DM did not show statistical significance in multivariate analysis as a factor predicting SVR in this study, it did show some significance in univariate analysis. Reports suggested that insulin resistance hinders SVR achievement [17, 18], and a recent study even showed that insulin resistance may undermine the advantages of favorable *IL-28B* polymorphism in PegIFN and RBV dual combination therapy [19]. Since our study consists of patients from a single center, another study with a larger number of patients might validate the role of DM in predicting the SVR of a population with favorable *IL-28* polymorphism more clearly.

Since treatment outcome using PegIFN and RBV in HCV genotype 1 patients is known to be less satisfactory, addition of a protease inhibitor has been proposed as a SOC therapy in some countries. However, in a population where favorable *IL-28B* polymorphism is dominant, and where SVR rate is relatively high, the introduction of protease inhibitors may require some caution since this will also enhance the frequency of adverse effects as well as the economic burden. Our study was performed over a population with mostly favorable *IL-28B* polymorphism, and demonstrated that RVR rate was close to 50% in HCV genotype 1 patients treated with dual combination therapy. In addition, even patients that failed to achieve RVR seemed to have a fair chance of achieving SVR if they succeeded in achieving undetectable serum HCV RNA at treatment week 12, known as positive cEVR. A study analyzing the cost-effectiveness of a protease inhibitor in treatment-naïve HCV genotype 1 patients may be necessary before establishing a new SOC therapy in Korea where favorable *IL-28B* polymorphism is dominant.

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