Durability of a sustained virological response in chronic hepatitis C patients treated with pegylated interferon alfa and ribavirin

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Background/Aims: The reappearance rates of hepatitis C virus (HCV) RNA after a sustained virological response (SVR) have been reported to be 1-2%. We investigated the reappearance rate of HCV RNA after SVR in chronic hepatitis C (CHC) patients treated with pegylated interferon (PEG-IFN) and ribavirin. Methods: In total, 292 CHC patients who achieved an SVR after PEG-IFN and ribavirin treatment were included. They were treated with subcutaneous injections of either PEG-IFN-α 2a or 2b plus ribavirin orally. Liver function tests and qualitative HCV RNA assays were performed every 6 months during the follow-up period after an SVR. Results: Among the 292 patients, 224 (genotype 1, 92; genotype non-1, 132) were followed up for more than 6 months after SVR. These 224 patients were aged 48.1±11.5 years (mean±SD), and 129 of them were male. The median follow-up duration was 18 months (range 6-60 months). The reappearance rate of HCV RNA during follow-up was 0%. Two patients who achieved an SVR developed hepatocellular carcinoma during the follow-up period. Conclusions: An SVR was maintained in all CHC patients treated with PEG-IFN plus ribavirin during a median follow-up of 18 months. However, a screening test for hepatocellular carcinoma is needed for patients with an SVR. (Korean J Hepatol 2011;17:183-188)

Keywords: Durability; Sustained virological response; Chronic hepatitis C; Pegylated interferon; Ribavirin

INTRODUCTION

Globally, it has been estimated that 170 million people are chronically infected with the hepatitis C virus (HCV), and 3 to 4 million are infected each year. The HCV is a major public health problem and a leading cause of chronic liver disease. Natural history studies indicate that 55% to 85% of individuals who develop acute hepatitis C will remain HCV-infected. The risk of developing cirrhosis ranges from 5% to 25% over periods of 25 to 30 years.

The currently recommended therapy for chronic HCV infection is the combination of pegylated interferon (PEG-IFN) and ribavirin. The sustained virological response (SVR) rates in patients treated with PEG-IFN and ribavirin are 50% in HCV genotype 1 and 80-90% in HCV genotype 2 or 3. The achievement of the SVR in patients with chronic hepatitis C (CHC) has been associated with improvements in liver histology as well as a reduced risk of hepatocellular carcinoma (HCC) and liver-related mortality.

Previous studies reported that the SVR after PEG-IFN and ribavirin combination therapy was maintained up to 99-100% during the long-term follow-up. However, a Korean study recently reported that the reappearance rate of HCV RNA after SVR was as high as 11%. Therefore, we investigated the...
reappearance rate of HCV RNA after SVR in CHC patients treated with PEG-IFN and ribavirin.

PATIENTS AND METHODS

Patients and treatments
Three hundred forty three consecutive patients with CHC were treated with PEG-IFN and ribavirin at Paik Hospital, Busan, Korea, between April 2004 and December 2008. Among them, 292 patients (85.1%) with SVR were included in this study.

They were treated with subcutaneous injections of either PEG-IFN-α 2a (Pegasys®; F. Hoffmann-La Roche, Ltd., Basel, Switzerland), at a dose of 180 μg/week or PEG-IFN-α 2b (PegIntron®; Schering Plough Corp., Kenilworth, NJ), at a dose of 1.5 μg/kg/week and ribavirin orally. The ribavirin dose was determined according to the HCV genotype and the patients’ body weight, as follows: dose of 1,000 mg/day (for patients weighing ≤75 kg) or 1,200 mg/day (for patients weighing >75 kg) in genotype 1 and 800-1,000 mg/day in genotype non-1. The standard treatment duration was 48 weeks in infections with the HCV genotype 1 and 24 weeks in those with the genotype non-1.

For the quantitative HCV-RNA assay, before February 2009, we used the Cobas Amplicor HCV Monitor Version 2.0 (Roche diagnostic, IN, USA), with the lower limit of detection of 600 IU/mL. From February 2009, we used the Cobas Amplicore/Cobas TaqMan system (Roche Molecular Systems, Pleasanton, CA), with the lower limit of detection of 15 IU/mL. The HCV RNA was measured at baseline (i.e. before treatment) and during the treatment, at weeks 4 and 12. To assess the efficacy of the treatment, the qualitative HCV RNA assay (Cobas Amplicor HCV Test Version 2.0, Roche diagnostic, IN, USA, lower limit of detection, 50 IU/mL) was performed at the end of treatment and 24 weeks after completing the therapy. HCV genotyping was performed in all patients before treatment initiation, using the INNO-LiPA HCV II kit (Bayer Diagnostics, Emeryville, CA).

The dose of PEG-IFN was reduced to 75% of the initial dose if the neutrophil count decreased under 750/mm³ or the platelet count were under 50,000/mm³, the dose was reduced to 50% if there was no improvement of cytopenia, and the treatment with PEG-IFN was discontinued if the neutrophil count further decreased under 500/mm³ or the platelet count decreased under 30,000/mm³. Ribavirin was reduced stepwise from the initial dose to 600 mg if the hemoglobin decreased under 10 g/dL, and was discontinued if the hemoglobin further decreased under 8 g/dL. When medication-related adverse effects occurred, such as flu-like symptoms, depression or insomnia, non-steroidal anti-inflammatory drugs, anti-depressant and hypnotics were administered to improve the patients’ symptoms. During the follow-up period after SVR, qualitative HCV RNA assays and liver function tests were performed every 6 months. We called the patients lost to follow-up within the past one year and asked for checking their liver function and HCV RNA test.

Definitions of virological responses

Rapid virological response was defined as HCV RNA negative at treatment week 4 by a sensitive PCR based quantitative assay. Early virological response was defined as qualitative HCV RNA negative or a reduction from baseline HCV RNA level of 2 log₁₀ IU/mL at week 12. End of treatment response and SVR were defined, respectively, as a negative qualitative HCV RNA level at the end of treatment and after 24 weeks of untreated follow-up.

Relapse was defined as reversion to HCV RNA positive status in patients who had an undetectable HCV RNA positive status at the end of treatment, and reappearance was defined as HCV RNA positive after SVR.

RESULTS

Among the 343 patients treated with PEG-IFN and ribavirin, the numbers of genotype 1 and non-1 patients were 151 and 192, respectively. Three hundred thirty eight patients (98.5%) achieved the end of treatment response and 292 patients (85.1%) achieved the SVR. The SVR was 75.5% (114/151) in genotype 1 and 92.7% (178/192) in genotype non-1. The numbers of patients who were followed-up with HCV RNA assays and liver function tests for more than 6 months after SVR was 224. Sixty five patients were lost to follow-up. The remaining three patients were less than 6 months of follow-up period, so they didn't perform HCV RNA assays. These 224 patients were actually followed-up for a median period of 18 months (range 6-60 months). The baseline characteristics and treatment doses of the patients were shown in Table 1. During the follow-up period, ALT increased in 149 (66.5%) and was maintained within normal limits in 75 (33.5%). Pre-treatment abdominal ultrasonography was performed in 220 patients, 22/220 (10%) had liver cirrhosis and 196/220 (89.1%) did not. Two patients already had HCC. SVR was maintained in all patients (n=224, 100%) during the