Recombinant Interferon-Beta-1α Plus Ribavirin for the Treatment of Chronic HCV Infection: A Prospective, Randomized, Comparative Pilot Study

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Background/Aims: Interferon beta (IFN-β) has been shown to have antiviral activity, and thus could be useful in treating viral infections. Therefore, we compared the efficacy and safety of recombinant IFN-β (IFN-β-1a) plus oral ribavirin versus interferon alpha (IFN-α) plus ribavirin therapy for the treatment of chronic hepatitis C (HCV). Methods: Twenty treatment-naïve patients were randomized into two equal-sized treatment groups. Both IFN-β-1a (44 μg) and IFN-α (3 MIU) were given subcutaneously three times a week, while ribavirin was given orally at 1,000-1,200 mg/day. Patients were treated for 24 weeks and followed for an additional 24 weeks. Results: After 24 weeks of treatment, six (60%) and four patients (40%) in the IFN-β-1a group and IFN-α groups, respectively, achieved viral clearance. The sustained virological response (SVR) at the end of the observation period was similar in both groups (40%). However, the baseline viral load was significantly higher (p=0.034) in the IFN-β-1a group than in the IFN-α group, and there were more HCV genotype 1 patients in the IFN-β-1a group (eight versus seven). The IFN-β-1a group was associated with similar adverse events in terms of frequency and severity. Conclusions: The SVR rate and safety profile were similar for the combination of IFN-β-1a and ribavirin and that of IFN-α and ribavirin. (Gut and Liver 2009;3:20-25)

INTRODUCTION

Since the isolation of hepatitis C virus (HCV) genome back in 1989 and the establishment of consequences of the infection, treatment modalities have undergone several changes over the last decade.1-4 From the early era when interferon alpha (IFN-α) monotherapy was given at 3 MIU for 24 week with a sustained virological response (SVR) rate of less than 10% to the current treatment of 48-week pegylated IFN-α plus ribavirin combined where 56% of SVR rate could be obtained, significant progresses have been achieved to counter this chronic infectious disease.5-7

Despite this achievements, there remains a large cohort of patients who do not have their viruses cleared even after 48 weeks of treatment with pegylated IFN-α plus ribavirin therapy. This includes approximately 50% of the difficult-to-treat HCV genotype 1 cohort and about 20% of the HCV genotype type 2 or 3 cohort.8 Re-treatment with similar regimen after the initial failure is not an optimal choice as the outcome is relatively poor.9,10

Furthermore, the IFN-α based treatment is not without side effects. Patients often have to discontinue treatment due to intolerable side effects or reduce the treatment dosages to minimize such effects.11 Indeed, there is an urgent need to investigate other treatment options to close the gaps on efficacies and safety profiles of the current regimens.

Interferon beta (IFN-β) is classified under the same type I IFN family with IFN-α since both molecules share
a common cell surface receptor.\textsuperscript{12,13} Due to its antiviral activities, natural IFN-\(\beta\) produced by fibroblast cells has been used extensively in Japan for the treatment of HCV infection.\textsuperscript{14-17} Unfortunately, the intravenous administration route of the current natural IFN-\(\beta\) did not offer the same convenience compared to the subcutaneous route used in the IFN-\(\alpha\) administration. Hence, the usage of natural IFN-\(\beta\) has largely been confined to Japan.

Recombinant IFN-\(\beta\) (IFN-\(\beta\)-1a), produced by mammalian cells, has a similar structure and glycosylation as the naturally occurring IFN-\(\beta\).\textsuperscript{18} Early study in HCV infection showed that it had similar antiviral properties as IFN-\(\alpha\) monotherapy.\textsuperscript{19} Recently, it has been shown to be safe and efficacious when combined with ribavirin.\textsuperscript{20} Another recent report has highlighted its potential therapeutic properties in Chinese population.\textsuperscript{21} However, all of these studies had been performed without a comparative IFN-\(\alpha\) treatment arm.

We had conducted a prospective, randomized, comparative pilot study with two arms consisting of IFN-\(\beta\)-1a plus ribavirin versus IFN-\(\alpha\) plus ribavirin in Korean population to investigate the efficacy and safety of both combination therapies in the same clinical setting.

**MATERIALS AND METHODS**

1. Patients

We included patients at the age 18 or above with chronic HCV infection confirmed by HCV-RNA reverse transcriptase-polymerase chain reaction (RT-PCR). Patients should have an elevated serum alanine aminotransferase (ALT) with level between 1.5 times and 10 times the upper limit of normal. All had adequate bone marrow reserve and organ function.

Patients were excluded if they had undergone previous treatment with an IFN, clinical evidence of liver cirrhosis defined by a Child-Pugh score of 7 and above, history of hepatic failure, other viral hepatitis, history of immunologically mediated disease, chronic renal impairment, history of cancer.

2. Study design

This was an open, randomized, comparative pilot study conducted in a gastroenterology unit of a university-affiliated hospital in Korea. The study was reviewed and approved by the hospital Ethics Committee. Each patient was provided with his/her written consent prior to the start of the study.

After confirmation of patient’s eligibility, he/she would be randomized to receive IFN-\(\beta\)-1a (Rebif\textsuperscript{22}, Serono international, Geneva, Switzerland) plus ribavirin or IFN-\(\alpha\) (Intermax-alpha\textsuperscript{23}, LG Biotech, Taejeon, Korea) plus ribavirin. IFN-\(\beta\)-1a at 44 mcg per dose and IFN-\(\alpha\) at 3 MIU per dose were given three times a week subcutaneously. Ribavirin was given orally twice a day with a total daily dosage of 1,000-1,200 mg depending on the weight of the patient. The treatment duration was 24 weeks followed by a 24-week observation phase. However, at treatment week 12, patient who did not achieve a virological response, defined as a decrease of at least 2 log viral load from the baseline, was removed from the treatment but would be included in the 24-week observation phase. Sustained virological response (SVR) was defined as a viral clearance, measured by a qualitative HCV RNA assay, at both the end of treatment and end of observation phase.

Baseline assessments included hematology, blood chemistry, HCV genotyping and serum HCV RNA measurement. Virological responses were assessed at treatment week 12, treatment week 24 and end of the observation period using both qualitative and quantitative HCV RNA assays. Qualitative HCV RNA measurement was performed using a polymerase chain reaction assay with primers specific for the 5' untranslated region of the HCV genome (COBAS Amplicor, version 2.0; Roche Diagnostics, Branchburg, NJ, USA) with a lower sensitivity of 50 IU/ml while the quantitative HCV RNA measurement was done using the COBAS Monitor Amplicor HCV 2.0 (Roche Diagnostics, Meylan, France) with a lower detection limit of 600 IU/mL. Safety was assessed by monitoring the adverse events and changes in the laboratory parameters at each study visits.

3. Statistical analysis

Data from both groups were analyzed and presented in a descriptive manner in terms of percentages and ranges. The assessments of baseline characteristics were performed for the total study population. HCV genotype and gender were assessed by Chi-square test. Baseline parameters, for example, ALT and HCV RNA levels were assessed by the nonparametric test Mann-Whitney U-test. The two-tailed significance level was set at 5%.

**RESULTS**

1. Patient characteristics

A total of 20 patients, 10 for each treatment group, were enrolled and completed the study between December 2003 and March 2005. One patient with genotype 1b from each arm was considered as a non-responder at treatment week 12. In the IFN-\(\alpha\) group, another patient decided to withdraw her consent after 8 weeks.