Efficacy and Tolerability of Peginterferon Alpha Plus Ribavirin in the Routine Daily Treatment of Chronic Hepatitis C Patients in Korea: A Multi-Center, Retrospective Observational Study


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Background/Aims: We aimed to evaluate the efficacy and safety of peginterferon plus ribavirin for chronic hepatitis C (CHC) patients under real life setting in Korea. Methods: We retrospectively analyzed the medical records of 758 CHC patients treated with peginterferon plus ribavirin between 2000 and 2008 from 14 university hospitals in the Gyeonggi-Incheon area in Korea. Results: Hepatitis C virus (HCV) genotype 1 was detected in 61.2% of patients, while genotype 2 was detected in 35.5%. Baseline HCV RNA level was ≥8×10⁵ IU/mL in 51.6% of patients. The sustained virological response (SVR) rate was 59.6% regardless of genotype; 53.6% in genotype 1 and 71.4% in genotype 2/3. On multivariate analysis, male gender (p=0.011), early virological response (p<0.001), genotype 2/3 (p<0.001), HCV RNA <6×10⁵ IU/mL (p=0.005) and adherence to the drug >80% of the planned dose (p=0.001) were associated with SVR. The rate of premature discontinuation was 35.7%. The main reason for withdrawal was intolerance to the drug due to common adverse events or cytopenia (48.2%). Conclusions: Our data suggest that the efficacy of peginterferon and ribavirin therapy in Koreans is better in Koreans than in Caucasians for the treatment of CHC, corroborating previous studies that have shown the superior therapeutic efficacy of this regimen in Asians. (Gut Liver 2012;6:98-106)

Key Words: Chronic hepatitis C; Pegylated interferon alpha; Ribavirin; Korean

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease worldwide. Although the prevalence of anti-HCV has remained stable around 1% since 1991, chronic hepatitis C (CHC) is the third most common etiology of chronic liver disease and hepatocellular carcinoma (HCC) in Korea. After publication of three pivotal, randomized clinical trials, the combination of pegylated interferon alpha (peginterferon) and ribavirin is currently recommended as the standard of care for treatment of CHC. Recent well-designed clinical trials demonstrated variable rates of sustained virological response (SVR) between 39.8% and 66%, regardless of the genotype, and suggested several predictive variables for successful treatment and rates of common adverse events. However, the study subjects in clinical trials are usually highly selected individuals meeting complicated inclusion and exclusion criteria, so they may not reflect the general population of CHC patients encountered in...
routine clinical practice. Moreover, special attention may be given to the patients enrolled in clinical trials and this can be a factor influencing compliance or notification of adverse events.

There have been several Korean studies that evaluated the treatment efficacy of the peginterferon plus ribavirin regimen in CHC patients. These studies reported overall SVR rates of 63% to 81%, a range that seems to be somewhat higher than in Western countries. However, because there are a smaller proportion of CHC patients compared to chronic hepatitis B patients in Korea, it is difficult to perform a well-designed study to survey treatment efficacy for CHC in a single institution. Previous studies have limitations in that they were conducted in single institutions and do not have sufficiently large study populations to accurately reflect the Korean CHC population.

K(G)yeonggi-Incheon Peginterferon Alpha and Ribavirin Effect in CHC Treatment (KIPECT) is a multicenter study group from 14 university hospitals in the Gyeonggi and Incheon areas (a large province and a city surrounding Seoul) in Korea. The aims of this study were to evaluate the efficacy and safety of peginterferon plus ribavirin for the treatment of Korean CHC patients in routine clinical practice and to confirm that the treatment efficacy of this regimen in Korean CHC patients is superior to that reported in Western countries.

MATERIALS AND METHODS

1. Subjects

The study subjects were retrospectively included from 14 large-volume university hospitals in Gyeonggi and Incheon. CHC patients 18 years or older with detectable serum HCV RNA and/or elevated serum alanine aminotransferase (ALT) levels for more than 6 months, who had been treated with peginterferon plus ribavirin from January 2000 to September 2008 were included. Exclusion criteria were acute hepatitis C, history of prior exposure to interferon or pegylated interferon alfa-2b plus ribavirin, and no available data on HCV genotype. Patients with normal serum ALT levels, patients co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), patients with chronic renal disease, and intravenous drug users were all included. Baseline clinical and virologic characteristics were obtained by retrospective review of medical records, and when available, pre-treatment histologic data were also recorded. HCV RNA levels measured in copies/mL were converted into IU/mL using a conversion factor according to the particular assay used at each hospital. Hepatic steatosis was categorized as present or absent, and the degree of hepatic fibrosis was classified as recommended by the Korean Study Group for the Pathology of Digestive Disease: grade 0, no fibrosis; grade 1, portal fibrosis; grade 2, perportal fibrosis; grade 3, septal fibrosis; and grade 4, cirrhosis. Data collection was performed with an Excel-based case report form by physicians at each individual hospital from April 2009 to August 2009. The study protocol was approved by the Institutional Review Boards at each hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

2. Treatment of CHC

Patients were treated with either pegylated interferon alfa-2a or pegylated interferon alfa-2b plus ribavirin. The starting dosage and dose modification of peginterferon and ribavirin were determined based on the current guidelines suggested by the Korean Association for the Study of the Liver. The duration of treatment was planned to be 24 weeks for genotype 2/3 and 48 weeks for non-genotype 2/3. However, according to the nature of this retrospective study, selection and discontinuation as well as dosing and treatment duration of peginterferon and ribavirin were not controlled, but reflected the clinical practice of the attending physicians.

3. Definition and evaluation of the treatment response

Virological responses during therapy were defined and evaluated according to the current guidelines. Quantitative HCV RNA values at baseline, 12 weeks after treatment, and at the end of treatment for HCV genotype 1/4 were recorded. The achievement of early virological response (EVR) was judged to be either complete (HCV RNA negative) or partial (more than 2 log10 reduction in HCV RNA level compared to baseline) based on the HCV RNA level at 12 weeks. For CHC patients infected with genotype 2/3 HCV, quantitative HCV RNA levels at baseline and at the end of treatment were recorded. Regardless of genotype, end-of-treatment response (ETR) was defined as HCV RNA negative status at the end of treatment. SVR was defined as HCV RNA negativity measured at 24 weeks after treatment cessation for all genotypes. HCV RNA negativity after 4 weeks of treatment was considered a rapid virological response (RVR), if tested. The same algorithm used for genotype 1/4 was applied in patients with genotype 5/6 HCV infection.

All analyses were made on an intention-to-treat basis.

4. Adverse events

Adverse events were categorized as flu-like symptoms, emotional friability including depression or insomnia, alopecia, dermatologic reactions such as pruritus or rash, gastrointestinal disorders including nausea, vomiting, or diarrhea, and thyroid dysfunction. They were graded based on the severity: Grade I, mild symptoms that require no dose reduction; Grade II, dose reduction required due to an adverse event; Grade III, treatment discontinuation due to an adverse event. The incidence of hematologic events in terms of serum absolute neutrophil count <500/mm3, hemoglobin level <8.5 g/dL, or platelet count <25,000/mm3 were recorded. Serious adverse events were defined as death or problems requiring hospitalization.

5. Statistical analysis

Baseline clinical characteristics are presented as means±stan-