Efficacy and Tolerability of Pegylated Interferon- α_{2a} plus Ribavirin versus Pegylated Interferon- α_{2b} plus Ribavirin in Treatment-Naive Chronic Hepatitis C Patients

Seok Lee^a In Hee Kim^a Seong Hun Kim^a Sang Wook Kim^a Seung Ok Lee^a
Soo Teik Lee^a Dae Ghon Kim^a Chang Seop Lee^a Chang Soo Choi^b
Eun Young Cho^b Haak Cheoul Kim^b

^aDepartment of Internal Medicine, Research Institute for Medical Science, Chonbuk National University Medical School and Hospital, Jeonju, and ^bDepartment of Internal Medicine, Wonkwang University College of Medicine and Hospital, Iksan, South Korea

Key Words

Chronic hepatitis C • Pegylated interferon- α_{2a} • Pegylated interferon- α_{2b} • Ribavirin

Abstract

Objectives: The authors compared the efficacies and tolerabilities of pegylated interferon- α_{2a} (PEG-IFN- α_{2a}) + ribavirin and pegylated interferon- α_{2b} (PEG-IFN- α_{2b}) + ribavirin for the initial treatment of chronic hepatitis C. **Methods:** A total of 126 treatment-naive patients (29.4% genotype 1, 70.6% genotype non-1) were treated with PEG-IFN- α_{2a} 180 μ g/week (group A, n = 79) or PEG-IFN- α_{2b} 1.5 μ g/kg/week (group B, n = 47) with ribavirin (800 mg/day for genotype non-1 or 1,000–1,200 mg/day for genotype 1) for 24 (genotype non-1) or 48 weeks (genotype 1). **Results:** End-of-treatment virologic response, sustained virologic response, and biochemical response were not significantly different in groups A and B (84.8 vs. 89.4%, 70.9 vs. 72.3%, and 70.9 vs. 74.5%, respectively; $p > 0.05$). In patients with the HCV genotype 1 or non-1, treatment responses were not significantly different. Multivariate analysis showed that HCV genotype only was an independent factor that affected sustained virologic response ($p = 0.048$). The proportions of treatment discontinu-

ations in groups A and B were similar (10.1 vs. 10.6%; $p = 1.000$). **Conclusions:** PEG-IFN- α_{2a} or PEG-IFN- α_{2b} + ribavirin combination therapies showed similar efficacies and tolerabilities as initial treatments for chronic hepatitis C.

Copyright © 2010 S. Karger AG, Basel

Introduction

Chronic hepatitis C is a common condition, with a global prevalence of 1–2% [1]. It has been estimated that approximately 170 million people worldwide are infected with hepatitis C virus (HCV). Furthermore, approximately 85% of patients with a HCV infection go on to develop chronic disease, and of these, up to 20% will eventually develop cirrhosis, which may lead to liver failure and hepatocellular carcinoma [2, 3]. Furthermore, chronic hepatitis C is the leading cause of liver transplantation in the USA and Western Europe.

Therapy for chronic hepatitis C has advanced considerably during the past decade. The introduction of interferon- α (IFN- α) monotherapy in the early 1990s met with limited success, but the addition of ribavirin and the later development of pegylated IFN (PEG-IFN) markedly

improved response rates. The current standard treatment for HCV patients is a combination therapy consisting of PEG-IFN- α + ribavirin. In controlled trials, treatment for 48 weeks (HCV genotype 1 or 4) or for 24 weeks (HCV genotypes 2 or 3) achieved sustained virologic response (SVR) rates of ~ 50 and $\sim 80\%$, respectively [4–8]. Two types of PEG-IFNs, PEG-IFN- α_{2a} and PEG-IFN- α_{2b} , are now commercially available, and the majority of reported studies have used one of these agents in combination with ribavirin at different dosages or treatment durations. However, few comparative trials have been conducted on the relative efficacies and safeties of these two agents plus ribavirin in chronic hepatitis C.

The object of this study was to compare the tolerabilities and antiviral efficacies of PEG-IFN- α_{2a} + ribavirin and PEG-IFN- α_{2b} + ribavirin for treatment-naïve chronic hepatitis C in Korean patients.

Patients and Methods

Study Population and Study Design

This retrospective, non-randomized, comparative study was conducted at the Chonbuk National University and Wonkwang University Hospitals between May 2004 and February 2009. We selected chronic hepatitis C patients that had been treated with PEG-IFN + ribavirin during the period of study. Treatment-naïve adults of both sexes aged 18 years or more that met the following conditions were considered eligible: seropositivity for HCV antibody (anti-HCV), quantifiable serum HCV RNA by polymerase chain reaction (PCR) assay (Cobas Amplicor HCV monitor test, version 2.0; Roche Diagnostics, Branchburg, N.J., USA), an elevated serum alanine aminotransferase (ALT) level within the previous 6 months, and compensated liver disease. Exclusion criteria included: decompensated liver disease, uncontrolled depressive illness, drug or alcohol abuse within 6 months of study commencement, prior organ transplantation, positivity for hepatitis B virus or human immunodeficiency virus, a pregnant status or an unwillingness/inability to comply with adequate contraception, untreated hyperthyroidism, autoimmune hepatitis, a hemoglobin level of ≤ 10 g/dl, an absolute neutrophil count of $\leq 750/\text{mm}^3$, a platelet count of $\leq 50,000/\text{mm}^3$, or a concurrent medical condition, such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, or obstructive pulmonary disease. Patients with known hypersensitivity to drugs used to treat HCV were also excluded.

In total, 177 patients were enrolled from two Korean sites. Of these 177 patients, 51 were excluded from the analysis because 38 patients were under treatment, 11 patients were incompletely followed up for 6 months after treatment completion, and 2 patients were lost to follow-up for undetermined reasons. Finally, 126 patients were included in the analysis. The 126 patients were divided into two groups by PEG-IFN type (group A members ($n = 79$) received PEG-IFN- α_{2a} , and group B members ($n = 47$) PEG-IFN- α_{2b}). Study subjects received once weekly subcutaneous injections of either PEG-IFN- α_{2a} (Pegasys; Hoffmann-La Roche Ltd, Basel,

Switzerland) 180 μg or PEG-IFN- α_{2b} (PegIntron; Shering Plough Corp., Kenilworth, N.J., USA) 1.5 $\mu\text{g}/\text{kg}$ for 24 weeks (for HCV genotype non-1) or 48 weeks (for HCV genotype 1). In addition, all 126 participants received daily oral ribavirin; 800 mg/day for genotype non-1, or 1,000 mg/day (body weight < 75 kg) or 1,200 mg/day (body weight ≥ 75 kg) for genotype 1. Data were retrospectively analyzed by an independent investigator unaware of study and treatment details. The study protocol was approved by the respective institutional review boards and all participants provided written informed consent.

Laboratory Tests

Baseline clinical and demographic characteristics data, adverse events during treatment, and serum assay values (especially ALT, serum HCV RNA levels, and HCV genotypes) were stored in a database. Serum HCV RNA levels were determined using a quantitative PCR assay (Cobas Amplicor HCV monitor test, version 2.0; Roche Diagnostics) at baseline and assessed using another qualitative PCR assay (Cobas Amplicor HCV test, version 2.0, detection limit 50 IU/ml; Roche Diagnostics) after treatment initiation. HCV genotyping was performed by reverse hybridization (Innolipa HCV; Innogenetics, Ghent, Belgium). A liver biopsy was not mandatory.

Efficacy and Tolerability Assessments

Biochemical response (BR) and virological responses were assessed at weeks 12 and 24 (end of treatment), and at week 48 (end of follow-up) in patients with HCV genotype non-1, and at weeks 12, 24, and 48 (end of treatment), and at week 72 (end of follow-up) in patients with HCV genotype 1. Patients that received at least one dose of study medication were entered in the analysis, which was conducted on an intention-to-treat basis. The following variables were used to assess treatment efficacies. Early virologic response (EVR) was defined as a $\geq 2 \log_{10}$ reduction or complete absence of serum HCV RNA after 12 weeks of treatment versus baseline. End-of-treatment response (ETR) was defined as a single undetectable serum HCV RNA measurement by qualitative PCR at treatment completion. SVR was defined as a single undetectable serum HCV RNA measurement by qualitative PCR after 24 weeks of follow-up. BR was defined as serum ALT normalization after 24 weeks of follow-up. Relapse was defined as the reappearance of HCV RNA in serum after treatment was discontinued and ETR was documented.

Laboratory abnormalities, drug discontinuations, dose modifications, and adverse events were evaluated. Treatment was discontinued if adverse events were intolerable, or laboratory findings, such as severe neutropenia $< 500/\text{mm}^3$ or anemia (hemoglobin < 6 g/dl), were abnormal in two consecutive samples. Dose modifications of ribavirin or PEG-IFN were implemented if neutropenia ($< 750/\text{mm}^3$), anemia (hemoglobin < 10 g/dl), or thrombocytopenia ($< 50,000/\text{mm}^3$) occurred; scheduled doses were re-administered after recovery from cytopenia. In addition, we assessed all visit records for the presence of adverse events, such as flu-like symptoms (fever, headache, myalgia), fatigue, anorexia/nausea, itching, rash, insomnia, alopecia, depression, or diarrhea.

Statistical Analysis

Results are reported as mean $\pm$ SD values. Continuous variables were compared using the two-tailed Student's *t* test, and

Table 1. Baseline and demographic characteristics of the study patients

	Total (n = 126)	PEG-IFN- α_{2a} (n = 79)	PEG-IFN- α_{2b} (n = 47)	p value
Age, years	53.5 $\pm$ 13.1	53.4 $\pm$ 12.9	53.6 $\pm$ 13.5	0.943
Females, n (%)	49 (38.9)	28 (35.4)	21 (44.7)	0.304
Body mass index	23.9 $\pm$ 2.8	24.1 $\pm$ 2.6	23.6 $\pm$ 3.0	0.340
Cirrhosis, n (%)	20 (15.9)	15 (19.0)	5 (10.6)	0.215
Platelet count, $\times 10^3/\text{mm}^3$	162.1 $\pm$ 57.2	156.9 $\pm$ 56.4	170.8 $\pm$ 58.1	0.188
AST, IU/l	72.4 $\pm$ 55.2	78.2 $\pm$ 57.5	62.5 $\pm$ 50.0	0.122
ALT, IU/l	86.6 $\pm$ 90.8	91.7 $\pm$ 101.3	78.0 $\pm$ 70.0	0.417
GGT, IU/l	72.4 $\pm$ 161.8	83.8 $\pm$ 199.5	52.4 $\pm$ 45.8	0.306
Total bilirubin, mg/dl	0.8 $\pm$ 0.2	0.8 $\pm$ 0.4	0.7 $\pm$ 0.3	0.220
Albumin, g/dl	4.2 $\pm$ 0.5	4.2 $\pm$ 0.5	4.2 $\pm$ 0.4	0.407
Total cholesterol, mg/dl	158.7 $\pm$ 30.1	157.0 $\pm$ 32.9	160.9 $\pm$ 27.9	0.502
APRI score	1.4 $\pm$ 1.3	1.5 $\pm$ 0.4	1.1 $\pm$ 1.2	0.107
Serum HCV RNA level, $\times 10^6$ IU/ml	1.5 $\pm$ 1.9	1.3 $\pm$ 1.5	1.6 $\pm$ 2.4	0.376
Serum HCV RNA level, $\log_{10}$ IU/ml	5.7 $\pm$ 0.8	5.8 $\pm$ 0.8	5.7 $\pm$ 0.9	0.698
HCV genotype, n (%)				0.374
Type 1	37 (29.4)	21 (26.6)	16 (34.0)	
Type non-1	89 (70.6)	58 (73.4)	31 (66.0)	

Values are means $\pm$ SDs. ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ -glutamyl transpeptidase; APRI = AST platelet ratio index, calculated as AST (U/l)/upper normal $\times$ 100/platelet count ($10^9/\text{l}$); HCV = hepatitis C virus.

categorical data using the χ^2 test or Fisher's exact test. Factors associated with SVR were analyzed by uni- and multivariate analysis using a logistic regression model. p values <0.05 were considered statistically significant. Data were transferred into a Microsoft Excel database (Microsoft Excel 2003), and analyzed using SPSS for Windows, version 15.0 (SPSS, Inc., Chicago, Ill., USA).

Results

Patient Baseline Characteristics

A total of 126 patients (mean age 54 years, 49 female) were included in this study. 79 patients received PEG-IFN- α_{2a} + ribavirin and the remaining 47 patients received PEG-IFN- α_{2b} + ribavirin. These two treatment groups were comparable with respect to the following demographic and baseline laboratory features: age, sex, presence of cirrhosis, baseline serum ALT levels, baseline serum HCV RNA levels, and proportions of HCV genotypes (table 1). 20 patients with compensated cirrhosis were treated; 15 with PEG-IFN- α_{2a} + ribavirin (19.0%) and 5 with PEG-IFN- α_{2b} + ribavirin (10.6%). No patient had decompensated cirrhosis or HCC. Mean baseline serum HCV RNA levels were 5.8 $\log_{10}$ IU/ml in the PEG-IFN- α_{2a} + ribavirin group (group A) and 5.7 $\log_{10}$ IU/ml

in the PEG-IFN- α_{2b} + ribavirin group (group B). Of the 126 patients, 37 (29.4%) had HCV genotype 1 and 89 (70.6%) had a HCV non-1 genotype. Patients with the 1 and non-1 genotypes were also similar with respect to baseline characteristics (data not shown).

Treatment Responses

The overall treatment responses in terms of EVR, ETR, SVR, BR and relapse rates are summarized in figure 1. By intention-to-treat analysis, 90 (71.4%) of the 126 patients achieved SVR, and proportions were similar in groups A and B (70.9 vs. 72.3%, $p = 0.861$) (fig. 1a). Furthermore, patients with HCV genotype 1 and non-1 showed similar SVR patterns. For those with genotype 1, the rate of SVR among those on PEG-IFN- α_{2a} + ribavirin was lower than that of those on PEG-IFN- α_{2b} + ribavirin, but this was not significant (38.1 vs. 62.5%, $p = 0.141$) (fig. 1b). Similarly, for genotype non-1 patients, no significant differences were found between the two treatments (82.8 vs. 77.4%, $p = 0.542$) (fig. 1c).

For the 126 study subjects, EVR, ETR, and BR rates were 73.0, 86.5, and 72.2%, respectively, and these rates were similar in groups A and B (73.4 vs. 72.3%, 84.8 vs. 89.4%, and 70.9 vs. 74.5%, $p = 0.895$, 0.470, and 0.664, re-

Table 2. Factors associated with SVR by univariate analysis

	Patients with SVR (n = 90)	Patients without SVR (n = 36)	p value
Age, years	50.6 ± 13.2	60.9 ± 9.2	0.000
≥60, n (%)	24 (26.7)	20 (55.6)	0.002
<60, n (%)	66 (73.3)	16 (44.4)	
Females, n (%)	32 (35.6)	17 (47.2)	0.225
Body mass index	23.7 ± 2.7	24.8 ± 2.7	0.062
Cirrhosis, n (%)	9 (10.0)	11 (30.6)	0.004
Platelet count, × 10 ³ /mm ³	172.2 ± 56.7	136.7 ± 50.7	0.001
AST, IU/l	68.9 ± 53.8	81.0 ± 58.4	0.267
ALT, IU/l	85.3 ± 97.9	89.9 ± 71.2	0.798
GGT, IU/l	77.4 ± 189.3	60.0 ± 51.3	0.593
Total bilirubin, mg/dl	0.8 ± 0.3	0.9 ± 0.4	0.186
Albumin, g/dl	4.3 ± 0.5	4.1 ± 0.4	0.048
Total cholesterol, mg/dl	158.0 ± 32.2	160.5 ± 24.1	0.704
APRI score	1.2 ± 1.1	1.83 ± 1.7	0.033
Serum HCV RNA level,			
× 10 ⁶ IU/ml	1.3 ± 1.6	1.8 ± 2.4	0.190
≥800,000 IU/ml, n (%)	49 (54.4)	24 (66.7)	0.070
<800,000 IU/ml, n (%)	41 (45.6)	12 (33.3)	
HCV genotype			
Type 1, n (%)	18 (20.0)	19 (52.8)	0.000
Type non-1, n (%)	72 (80.0)	17 (47.2)	
PEG-IFNs			
PEG-IFN-α _{2a} , n (%)	56 (62.2)	23 (63.9)	0.861
PEG-IFN-α _{2b} , n (%)	34 (37.8)	13 (36.1)	

Values are means ± SDs. ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transpeptidase; APRI = AST platelet ratio index, calculated as AST (U/l)/upper normal × 100/platelet count (10⁹/l); HCV = hepatitis C virus.

Fig. 1. Rates of treatment responses by intention-to-treat analysis. **a** Overall. **b** HCV genotype 1. **c** HCV genotype non-1. EVR = Early virologic response; ETR = end-of-treatment response; SVR = sustained virologic response; BR = biochemical response.

spectively) (fig. 1a). Furthermore, for patients with HCV genotype 1 and non-1, EVR, ETR, and BR rates were also similar for the two treatments (fig. 1b, c).

The proportion of study subjects in whom ETR was documented but serum HCV RNA relapsed after treatment discontinuation was 15.9%, and rates were similar in the two groups (15.2 vs. 17.0%, $p = 0.786$) (fig. 1a). For genotype 1 patients, the rate of relapse among those on PEG-IFN-α_{2a} + ribavirin was greater than that for those on PEG-IFN-α_{2b} + ribavirin, but this was not significant (38.1 vs. 18.8%, $p = 0.202$) (fig. 1b).

Factors Associated with Sustained Virologic Response

To identify predictors of SVR, we examined the following variables by univariate analysis (table 2): age (≥60 vs. <60 years), sex, body mass index, presence of cirrho-

Table 3. Factors associated with SVR by multivariate analysis

	Patients with SVR (n = 90)	Patients without SVR (n = 36)	p value	Odds ratio	95% CI
HCV genotype					
Type 1, n (%)	18 (20.0)	19 (52.8)	0.048	6.862	1.014–46.418
Type non-1, n (%)	72 (80.0)	12 (50.0)			

sis, platelet count, baseline serum aminotransferase level, GGT, total bilirubin, albumin, total cholesterol, APRI (AST platelet ratio index) score, baseline serum HCV RNA level ($\geq 800,000$ vs. $< 800,000$ IU/ml), HCV genotypes (type 1 vs. non-1), and PEG-IFN type (PEG-IFN- α_{2a} vs. PEG-IFN- α_{2b}). The mean age of patients with SVR was higher than that of patients without SVR (50.6 vs. 60.9 years, $p = 0.000$), and the percentage of patients over 60 years of age was significantly lower among patients with SVR (26.7 vs. 55.6%, $p = 0.002$). Liver cirrhosis ($p = 0.004$), platelet count ($p = 0.001$), serum albumin level ($p = 0.048$), APRI score ($p = 0.033$), and HCV genotype ($p = 0.000$) were also found to be associated with SVR, but sex, body mass index, serum AST, ALT, GGT, total bilirubin, and total cholesterol were not. The mean baseline serum HCV RNA level was lower in those with SVR than in those without, but this was not significant (1.3 ± 1.6 vs. $1.8 \pm 2.4 \times 10^6$ IU/ml, $p = 0.190$) (table 2). Multivariate analysis showed that only HCV genotype was significantly associated with SVR ($p = 0.048$, odds ratio 6.862, 95% confidence interval 1.014–46.418) (table 3).

Adverse Events and Tolerability

Of the 126 study subjects, only 13 patients (10.3%) discontinued prematurely (8 patients (10.1%) in group A and 5 patients (10.6%) in group B, $p = 1.000$) (table 4). Rates of the adverse events and laboratory abnormalities, which caused discontinuation, were not statistically different in the two study groups. However, the rate of dose modification was significantly greater in group A (59.5 vs. 34.0%, $p = 0.006$). Furthermore, those in group A had a significantly higher incidence of fatigue (16.5 vs. 4.3%, $p = 0.041$) and non-significantly higher incidence of neutropenia ($\leq 750/\text{mm}^3$) (35.4 vs. 19.1%, $p = 0.052$). However, the incidence of flu-like symptoms was significantly higher in group B (22.8 vs. 46.8%, $p = 0.005$).

Table 4. Treatment discontinuation and dose modification

	PEG-IFN- α_{2a} (n = 79)	PEG-IFN- α_{2b} (n = 47)	p value
Premature discontinuation, n (%)	8 (10.1)	5 (10.6)	1.000
Adverse events	3 (3.8)	4 (8.5)	0.264
Laboratory abnormalities	4 (5.1)	1 (2.1)	0.117
Other causes	1 (1.3)	0 (0)	0.708
Dose modification, n (%)	47 (59.5)	16 (34.0)	0.006
Anemia (≤ 10 g/dl)	6 (7.6)	4 (8.5)	0.854
Neutropenia (≤ 750 cells/mm ³)	28 (35.4)	9 (19.1)	0.052
Thrombocytopenia ($\leq 5 \times 10^5$ cells/mm ³)	3 (3.8)	2 (4.3)	0.899
Other adverse events, n (%)			
Flu-like symptoms	18 (22.8)	22 (46.8)	0.005
Fatigue	13 (16.5)	2 (4.3)	0.041
Anorexia/nausea	11 (13.9)	12 (25.5)	0.103
Itching	4 (5.1)	6 (12.8)	0.122
Rash	10 (12.7)	5 (10.6)	0.735
Insomnia	10 (12.7)	7 (14.9)	0.722
Alopecia	5 (6.3)	4 (8.5)	0.646
Depression	5 (6.3)	1 (2.1)	0.284
Diarrhea	0 (0)	3 (6.4)	0.023

Discussion

PEG-IFN is produced by covalently bonding polyethylene glycol (PEG) to IFN, and has lower renal clearance and a longer half-life in plasma than IFN [9, 10]. Currently, two types of PEG-IFN preparations are commercially available for the treatment of hepatitis C, namely, PEG-IFN- α_{2a} and PEG-IFN- α_{2b} . PEG-IFN- α_{2a} consists of IFN- α_{2a} molecule bound to a large, branched 40-kDa PEG chain by an amide bond, which is not subject to hydrolysis [11], whereas PEG-IFN- α_{2b} is linked to a linear 12-kDa PEG chain by a urethane bond, which is susceptible to hydrolysis [12]. These two agents have significantly different pharmacokinetic and pharmacodynam-

ic properties. PEG-IFN- α_{2a} is absorbed slowly (absorption half-life 50 h), has a restricted distribution volume (8 liters), a narrow peak-to-trough ratio of 1.5, and a low rate of clearance (60 ml/h) [13]. On the other hand, PEG-IFN- α_{2b} is absorbed rapidly (absorption half-life 4.6 h), has a wide distribution volume (0.99 l/kg), and a peak-to-trough ratio of >10. Furthermore, the clearance of PEG-IFN- α_{2b} is greater than that of PEG-IFN- α_{2a} (725 vs. 60 ml/h) [14]. In practice, the above-mentioned distribution volume differences mean that PEG-IFN- α_{2a} can be administered at a fixed dose of 180 μ g/week, whereas PEG-IFN- α_{2b} must be dosed on a body weight basis.

Despite the different pharmacologic properties of these two PEG-IFNs, few studies have compared the efficacies of PEG-IFN- α_{2a} + ribavirin and PEG-IFN- α_{2b} + ribavirin in chronic hepatitis C. In the present study, the overall rate of SVR was similar in groups A and B (70.9 vs. 72.3%, $p = 0.861$). For patients with HCV genotype 1, the SVR rate was non-significantly lower than in those on PEG-IFN- α_{2a} (38.1 vs. 62.5%, $p = 0.141$), whereas for patients with a HCV non-1 genotype, SVR rates were similar for both treatments (82.8 vs. 77.4%, $p = 0.542$). Rates of ETR, BR, and relapse were also similar in groups A and B, and were not affected by HCV genotype. Furthermore, rate of relapse was higher among patients with genotype 1 on PEG-IFN- α_{2a} , though this was not significant (38.1 vs. 18.8%, $p = 0.202$).

Recently, three prospective randomized clinical trials compared the efficacies and safeties of PEG-IFN- α_{2a} + ribavirin versus PEG-IFN- α_{2b} + ribavirin in chronic hepatitis C [15–17]. In an Italian study [15], 320 treatment-naive patients were randomized to receive either PEG-IFN- α_{2a} at 180 μ g/week or PEG-IFN- α_{2b} at 1.5 μ g/kg/week + ribavirin 1,000 mg/day (<75 kg) or 1,200 mg/day (≥ 75 kg) for 48 weeks (genotypes 1/4) or 24 weeks (genotypes 2/3). The results obtained showed that patients on PEG-IFN- α_{2a} achieved a significantly higher SVR rate than those on PEG-IFN- α_{2b} (68.7 vs. 54.4%, $p = 0.008$), and in a subset analysis by HCV genotype, SVR rates were also found to be higher for those on PEG-IFN- α_{2a} (54.8 vs. 39.8% for genotypes 1 or 4, $p = 0.04$; 88.1 vs. 74.6% for genotypes 2 or 3, $p = 0.046$). In the Milan Safety Tolerability (MIST) study [16], 431 patients were randomly assigned to receive either PEG-IFN- α_{2a} 180 μ g/week + daily ribavirin 800–1,200 mg or PEG-IFN- α_{2b} 1.5 μ g/kg/week + daily ribavirin 800–1,400 for the HCV genotype durations mentioned above. The results obtained showed that overall ETR and SVR rates were higher for PEG-IFN- α_{2a} (78 vs. 67% for ETR, $p = 0.009$; 66 vs.

54% for SVR, $p = 0.02$). In contrast, in the IDEAL trial study conducted in the USA [17], 3,070 HCV genotype 1 treatment-naive patients were randomized and treated for 48 weeks with PEG-IFN- α_{2b} (1.5 or 1.0 μ g/kg/week) + ribavirin 800–1,400 mg/day or PEG-IFN- α_{2a} (180 μ g/week) + ribavirin 1,000–1,200 mg/day. SVR rates were found to be similar for these regimens: 39.8% for standard-dose PEG-IFN- α_{2b} , 38.0% for low-dose PEG-IFN- α_{2b} , and 40.9% for PEG-IFN- α_{2a} ($p = 0.20$ for standard-dose vs. low-dose PEG-IFN- α_{2b} ; $p = 0.57$ for standard-dose PEG-IFN- α_{2b} vs. PEG-IFN- α_{2a}). The response rate at the end of the treatment phase was higher for PEG-IFN- α_{2a} than for either PEG-IFN- α_{2b} regimen, but its virologic relapse rate was also higher. We considered that discrepancies between the results of these clinical trials with respect to the efficacies of PEG-IFN- α_{2a} + ribavirin versus PEG-IFN- α_{2b} + ribavirin warranted further study.

In a previous study, the absence of EVR was found to be strongly correlated with non-response in treatment-naive subjects with a genotype 1 infection [6, 18]. In fact, 97% of treatment-naive patients with genotype 1 HCV who failed to achieve EVR also failed to achieve SVR. In the present study, EVR rates were similar in groups A and B (73.4% for group A and 72.3% for group B, $p = 0.706$). EVR rates were also not significantly different for patients with genotype 1 or non-1 genotype infections ($p = 0.393$ and 0.173 , respectively). However, previous comparative studies on EVR of the two PEG-IFNs produced discordant results. Bruno et al. [19] showed that mean HCV RNA level at week 12 was significantly lower in those treated with PEG-IFN- α_{2a} than in those treated with PEG-IFN- α_{2b} ($p < 0.01$). In contrast, Silva et al. [20] found that the average rate of viral decline per week during an 8-week trial period was significantly greater for those on PEG-IFN- α_{2b} than for those on PEG-IFN- α_{2a} (0.346 vs. 0.233 $\log_{10}$ per week, $p < 0.002$).

Predictors of response prior to treatment commencement are useful for advising patients of the likelihood of achieving SVR. In the present study, only HCV genotype was found to predict SVR significantly by multivariate analysis ($p = 0.048$, odds ratio 6.862, 95% confidence interval 1.014–46.418). In three above-mentioned randomized controlled trials [6–8], multivariate analyses identified viral genotype and pretreatment viral load as predictors of SVR, and in one of these studies [8] SVR rates were higher for a non-1 infection genotype (mostly genotypes 2 and 3) and for those with a viral load of <600,000 IU/ml [8].

Previous findings also diverge regarding safety and tolerability. Ascione et al. [15] reported more withdrawals for side effects for PEG-IFN- α_{2b} . On the other hand, Silva et al. [20] reported that neutropenia and treatment discontinuation due to an adverse event were more frequent for PEG-IFN- α_{2a} , which they suggested might be explained by the administration of a fixed dose. In this previous study, flu-like symptoms were the most frequently encountered adverse events for both treatments, but the frequency of this symptom was greater for PEG-IFN- α_{2b} , which they suggested might have been due to a physiologic response to free IFN [20]. In the present study, treatment withdrawal rates were similar in both study groups (10.1% for group A and 10.6% for group B, $p = 1.000$). However, dose modifications, because of laboratory abnormalities or adverse events, were more common in group A (59.5 vs. 34.0%, $p = 0.006$). Similarly, neutropenia (≤ 750 cells/mm³) was also more frequent in this group, though with borderline significance (35.4 vs. 19.1%, $p = 0.052$). Overall, flu-like symptoms, anorexia/nausea, and insomnia were more frequent adverse events, but the frequencies of these adverse events differed in our two study groups; for example, fatigue was significantly more frequently encountered in group A, but flu-like symptoms and diarrhea were significantly more common in group B.

The present study is intrinsically limited by its retrospective, non-randomized design. Furthermore, the number of patients in the two groups differed and group

A contained greater proportions of patients with genotype non-1 and with cirrhosis than group B, although it should be added that these differences were not significant. In addition, the data collected, the treatment strategies used regarding initial ribavirin doses, and the modifications of doses during treatment differed slightly at the two centers. Finally, our study lacks information regarding the actual doses administered, and our investigation of adverse events was limited to medical records. Nevertheless, we believe that this study offers valuable information regarding the therapeutic efficacies and tolerabilities of PEG-IFN- α_{2a} and PEG-IFN- α_{2b} . A further large, randomized, prospective trial is warranted to confirm our results.

Summarizing, the present study shows that PEG-IFN- α_{2a} and PEG-IFN- α_{2b} , in combination with ribavirin, have comparable antiviral efficacies in treatment-naïve patients with chronic hepatitis C. However, dose modifications were more commonly required for those being treated with PEG-IFN- α_{2a} , usually because of neutropenia, and the incidence of flu-like symptoms was higher among those treated with PEG-IFN- α_{2b} .

Acknowledgement

This study was supported in part by research funds of the Chonbuk National University Hospital in 2008.

References

- 1 Lauer GM, Walker BD: Hepatitis C virus infection. *N Engl J Med* 2001;345:41–52.
- 2 Poynard T, Yuen MF, Ratziu V, Lai CL: Viral hepatitis C: review. *Lancet* 2003;362:2095–2100.
- 3 Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH: Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 2000;132:296–305.
- 4 Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases: Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335–1374.
- 5 Farrell GC: New hepatitis C guidelines for the Asia-Pacific region: APASL consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J Gastroenterol Hepatol* 2007;22:607–610.
- 6 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–982.
- 7 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001;358:958–965.
- 8 Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group: Peginterferon- α_{2a} and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346–355.
- 9 Harris JM, Martin NE, Modi M: Pegylation – a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* 2001;40:539–551.
- 10 Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O’Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ: Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666–1672.
- 11 Foster GR: Pegylated interferons: chemical and clinical differences. *Aliment Pharmacol Ther* 2004;20:825–830.
- 12 Glue P, Fang J, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Saif M, Jacobs S: Pegylated interferon- α_{2b} : pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. *Clin Pharmacol Ther* 2000;68:556–567.

- 13 Peginterferon- α_{2a} Prescribing Information. Roche Laboratories, Inc., Nutley, NJ, USA.
- 14 Peginterferon- α_{2b} Prescribing Information. Schering-Plough Corp., Kenilworth, NJ, USA.
- 15 Ascione A, De Luca M, Tartaglione MT, Lampasi F, Galeota Lanza A, Picciotto FP, Di Costanzo GG, Leandro G: Peginterferon- α_{2a} plus ribavirin versus peginterferon- α_{2b} plus ribavirin in naive patients with chronic hepatitis C virus infection: results of a prospective randomised trial. *J Hepatol* 2008;48(suppl 2):S370.
- 16 Rumi M, Aghemo A, Prati GM, D'Ambrosio R, Donato MF, Russo A, Cerami N, Soffredini R, Colombo M: Randomized study comparing peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin in naive patients with chronic hepatitis C: final results of the Milan Safety Tolerability (MIST) study. *Hepatology* 2008;48(suppl 1):404A.
- 17 McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS; for the IDEAL Study Team: Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580–593.
- 18 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J: Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;38:645–652.
- 19 Bruno R, Sacchi P, Ciappina V, Zochetti C, Patruno S, Maiocchi L, Filice G: Viral dynamics and pharmacokinetics of peginterferon- α_{2a} and peginterferon- α_{2b} in naive patients with chronic hepatitis C: a randomized, controlled study. *Antiviral Ther* 2004;9:491–497.
- 20 Silva M, Poo J, Wagner F, Jackson M, Cutler D, Grace M, Borden R, Cullen C, Harvey J, Laughlin M: A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). *J Hepatol* 2006;45:204–213.