Tolerability and efficacy of pegylated consensus interferon-α in the treatment of chronic hepatitis C

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Abstract. This study aimed to explore and evaluate the tolerability and antiviral activity of pegylated recombinant human consensus interferon-α (PEG-CIFN) in adults with hepatitis C virus (HCV) infection. A total of 48 adult subjects chronically infected with HCV were divided into five groups, which were treated separately with PEG-CIFN 1.0 μg/kg (n=10), 1.5 μg/kg (n=10), 2.0 μg/kg (n=9) or 3.0 μg/kg (n=10), or pegylated IFN α-2a (Pegasys) 180 μg (n=9) as controls. Symptoms were observed and laboratory results collected to monitor adverse reactions, adjust drug dosage and evaluate tolerability. The thrombocytopenic effects in all PEG-CIFN dose groups were less than that of pegylated IFN α-2a (at week 14, P<0.05). The rapid virologic response of the PEG-CIFN 1.5, 2.0 and 3.0 μg/kg groups and the pegylated IFN α-2a group were significantly higher than that of the PEG-CIFN 1.0 μg/kg group (P<0.05). Patients who had HCV genotype 1b infections had relatively high responses. The early virologic response of the PEG-CIFN 1.0, 1.5 and 2.0 μg/kg groups and the pegylated IFN α-2a group were 30, 90, 88.8 and 88.8% respectively. PEG-CIFN is well tolerated, and was found to have dose-dependent effectiveness in subjects with chronic hepatitis C. Virological response rates between PEG-CIFN 1.5 or 2.0 μg/kg, and pegylated IFNα-2a were similar, and not significantly different. It is concluded that 1.5 μg/kg PEG-CIFN may be the clinically recommended dose. PEG-CIFN is superior to pegylated IFN α-2a in maintaining platelet levels.

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Introduction

Hepatitis C virus (HCV) chronically infects ~180 million people worldwide, and is a frequent cause of liver diseases, including liver failure and hepatocellular carcinoma (1,2). The seroprevalence of hepatitis C infection in the general population of China is estimated to be 0.8-2.1% (3). The rate is much higher in certain subgroups such as injecting drug users or subjects with hemophilia (3).

The discovery of direct-acting antiviral agents (DAAs) in 2002 led to the development of small molecules to block the replication of HCV, including novel antiviral targets (4,5). Based on the impressive improvements in sustained virologic response (SVR) rates in phase III trials (6), the first two protease inhibitors telaprevir and boceprevir were recently approved by the US Food and Drug Administration, and are currently recommended first line agents for genotype 1 infections. However, while they are generally well-tolerated, adverse events are common, and the agents are very expensive. Furthermore, triple therapy is not approved for use in non-genotype 1 HCV infections, and there are numerous drug-drug interactions that preclude their use. Prior to the development of triple therapy, peginterferon α-2b or peginterferon α-2a alone, or in combination with weight-based ribavirin had been the standard treatment chronic hepatitis C resulting in SVRs of 30 and 50% (7,8) respectively, for genotype 1 cases, and 80% for genotypes 2 and 3 (9-12).

Two polyethylene glycol (PEG)-modified interferons, interferon (IFN)-α-2a containing a branched 40-kD PEG molecule (PEGASYS®; F. Hoffmann-La Roche, Inc., Basel, Switzerland) and IFN-α-2b containing a linear 12-kD PEG molecule (PEG-INTRON®; Merck & Co., Inc., Kenilworth, NJ, USA) are currently on the market. However, side effects are quite problematic, and the efficacy of PEG-IFN monotherapy is limited. Consensus interferon (CIFN) was designed in order to maximize efficacy, and minimize side effects. It is composed of the most frequently observed amino acids in each corresponding position in the natural α IFNs. CIFN shares an 89, 30, and 60% homology with IFN-α, IFN-β and IFN-ω, respectively (13). CIFN has been shown to be efficacious in HCV genotype 1 patients who have failed therapy with PEG-IFN (14). In order to increase the duration of action,

recombinant human CIFN was PEG-modified (pegylated) by Chongqing Fujin Biomedical Co., Ltd. (Chongqing, China). Compared with naturally occurring IFN-α, PEG-CIFN has demonstrated enhanced *in vivo* antiviral activity in cynomolgus monkeys; serum sample analyses from PEG-CIFN-treated monkeys showed a dose-dependent antiviral activity (15). The PEG-CIFN investigated in the current study was produced by the covalent attachment of a single 20-kDa methoxypolyethylene glycol-propionaldehyde molecule to the N-terminus of IFN, forming a molecule with an average molecular weight of ~40 kDa. This modification results in a longer half-life and sustained antiviral action (15). PEG-CIFN has exhibited improved pharmacokinetic properties compared with CIFN in monkeys and rats, with 12- and 15-fold increases in elimination half-life, and 100- and 10-fold reductions in serum clearance, as well as a 2.5- and 10-fold increases in the time to reach peak serum concentrations, respectively (15).

In vitro studies have shown that the antiviral mechanism of action of PEG-CIFN is identical to that of CIFN: Competitive inhibition of virus binding with receptors on target cells. Therefore, damage to target cells can be minimized. Studies in animals have suggested that PEG-CIFN has significant antiviral activity (16). The aim of the current study was to determine the tolerability and antiviral activity of PEG-CIFN in adults with HCV infection.

Materials and methods

Subjects. Forty-eight subjects from Jilin province, China were enrolled in the study, and the characteristics of the subjects are shown in Table I.

Inclusion criteria: Eligible subjects were 18-65 years old, with compensated liver disease due to chronic HCV infection, plasma HCV RNA levels >2,000 IU/ml, and no history of previous anti-HCV treatment, an absolute neutrophil count >1,500/ml^3, a platelet (PLT) count of >90,000/mm^3 and hemoglobin levels of >12 g/dl (for women) or >13 g/dl (for men), body mass index (BMI) between 18 and 26 kg/m^2 and alanine aminotransferase (ALT) level <240 IU/l.

Exclusion criteria: Co-infection with human immunodeficiency virus or hepatitis B, any other cause of liver disease, severe depression or a severe psychiatric disorder, active drug or alcohol abuse, liver cirrhosis, or hepatocellular carcinoma, abnormal serum creatinine level, serum total bilirubin level >34.2 µmol/l or serum albumin <35 g/l.

This clinical trial was approved by the Ethics Committee of the First Hospital of Jilin University (Jilin, China). All subjects provided signed informed consent prior to enrollment.

Study design. The 48 adult subjects infected with HCV were divided into five groups. The first group received weekly PEG-CIFN by subcutaneous injections at a dose of 1.0 µg/kg, and were observed for 4 weeks. If the subjects tolerated the dose, the next groups received 1.5 and 2.0 µg/kg PEG-CIFN weekly for 14 weeks, but were not given drug at weeks 2 and 14 due to pharmacokinetic experiments. Therefore, in total the patients received 12 doses of PEG-CIFN monotherapy. One group received the maximum dose of PEG-CIFN (3.0 µg/kg) only to evaluate tolerance according to the protocol. Pegylated IFNα-2a (peginterferon

α-2a; Pegasys) was administered at a dose of 180 µg using the same treatment protocol as the PEG-CIFN groups and served as a positive control.

Safety was assessed by physicians of the First Hospital of Jilin University, at weeks 2, 4 and 8 or other (emergency) visits. If >50% of subjects had any of the following adverse events, the dose escalation was terminated: Absolute neutrophil count (ANC) <0.5x10^9/l, PLT count <30x10^9/l, ALT >400 IU/l, persistent ALT rise or accompanied by bilirubin elevation after dose titration, serum total bilirubin >51.3 µmol/l, development of ascites, hepatic encephalopathy, or psychiatric disorders, allergic reactions, uncontrolled thyroid disease, diabetes mellitus, serious damage to the heart, kidney, brain, lung, etc.

If a serious adverse event occurred during the course of treatment, we discontinued or modified the dosage of PEG-CIFN until the adverse event abated or decreased in severity. The process for dose reduction consisted of two-steps. If the ANC or PLT count was 0.5x10^9-0.75x10^9/l or 30x10^9-50x10^9/l, respectively, the treatment dose of PEG-CIFN was reduced. If the ANC or PLT count fell below 0.5x10^9/l or 30x10^9/l, respectively, the drug was discontinued. Drug doses could be increased once the cytopenia resolved (when the ANC was ≥0.75x10^9/l or the PLT count was ≥50x10^9/l).

Study drugs. PEG-CIFN was developed by Chongqing Fujin Biomedical Co., Ltd., and produced by Beijing Kain Science and Technology Co., Ltd. (Beijing, China). Peginterferon α-2a was produced by F. Hoffmann-La Roche, Inc. Agents were stored until use under conditions recommended by the manufacturers.

Follow-up. The subjects were monitored every week by physical examination, vital signs, inquiries of adverse reactions and weight measurements. At weeks 4, 8 and 14, HCV RNA levels were measured by quantitative polymerase chain reaction using the COBAS TaqMan HCV test (Roche Molecular Systems, Pleasanton, CA, USA), which has a low limit of quantitation (15 IU/ml). Complete blood cell counts were measured weekly and drug dosages adjusted accordingly for abnormalities in hemoglobin levels, ANC and PLT count. Subjects were randomly assigned to groups. If subjects missed more than one follow-up visit, those persons were considered non-compliant and were removed from the study. Evaluation of tolerability index test results for PEG-CIFN and peginterferon α-2a groups were compared with the same dose group at week 0 (Fig. 1).

Efficacy. The primary efficacy criterion was the percentage of subjects whose HCV RNA levels were undetectable at week 14 [early virologic response (EVR) after 12 doses of PEG-CIFN]. The secondary efficacy criterion was the percentage of subjects whose HCV RNA levels were undetectable at week 4 and after a further 3 doses of PEG-CIFN at week 8. Reductions in HCV RNA levels at weeks 4, 8 and 14 were expressed as log$_{10}$.

Statistical analysis. The results were analyzed with analysis of variance tests or Kruskal-Wallis tests using SAS software, version 9.0 (SAS Institute, Cary, NC, USA). The results were presented as means ± standard deviations. Multivariable logistic regression analyses involving age, gender, baseline

Table I. Characteristics of the study subjects.

Characteristic	Peginterferon α-2a (Pegasys)	PEG-CIFN 1.0 μg/kg	PEG-CIFN 1.5 μg/kg	PEG-CIFN 2.0 μg/kg	PEG-CIFN 3.0 μg/kg
Male/female ratio	7/2	5/5	7/3	6/3	8/2
Age (years, mean ± SD)	46.56±8.82	46.60±12.55	51.90±9.15	48.44±7.28	44.60±3.57
Body mass index (kg/m^2, mean ± SD)	23.38±2.62	23.83±2.16	23.92±1.87	22.64±2.28	22.83±2.82
AST (IU/l, mean ± SD)	47.11±24.60	35.85±16.46	42.90±22.53	45.22±34.56	30.60±11.28
ALT (IU/l, mean ± SD)	80.11±58.67	52.90±29.18	58.50±38.43	53.44±40.93	49.00±27.07
Hemoglobin (g/dl, mean ± SD)	159.88±12.18	141.40±14.10	157.80±12.55	149.00±11.98	159.30±17.73
White blood cells (/mm^3, mean ± SD)	5.81±0.91	4.54±2.25	6.44±1.81	6.82±1.77	5.59±0.98
Platelet count (/mm^3, mean ± SD)	171.50±31.92	161.25±58.70	181.80±43.57	175.22±51.00	185.6±38.28
Genotype (n)					
1b	2	10	6[a]	2	10
2a	7	0	5	7[b]	0
Viral count (log$_{10}$IU/l, mean ± SD)	5.90±1.12	6.58±0.59	6.27±0.95	6.65±0.63	6.50±0.74
Fibroscan	7.83±4.12	6.36±2.45	7.20±5.75	6.46±2.09	6.36±2.45

[a]One subject had genotype 1b/2a. [b]One subject had a genotype that could not be determined. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PEG, polyethylene glycol; CIFN, consensus interferon; SD, standard deviation.

HCV RNA levels, baseline ALT levels, baseline aspartate aminotransferase levels, BMI and treatment regimens were performed to determine virologic responses at weeks 4, 8 and 14. Virologic response was defined as an undetectable HCV RNA level (<15 IU/ml). P<0.05 in two-sided tests were considered to indicate a statistically significant difference.

Results

Baseline characteristics. The study enrolled 48 HCV-infected subjects of whom 15 subjects were female (31.2%). The average age of the patients was 47.4 years, ranging from 20 to 65 years. There were no significant differences between the dose groups at baseline for any of these characteristics (Table I).

Tolerance
PLT counts. The PLT counts of each group decreased from the baseline to week 8, and then began to rebound at week 9. The PLT counts of all PEG-CIFN dose groups were significantly higher than that of the peginterferon α-2a group at weeks 4, 8 and 14. Actual numbers and percentage changes are listed in Table II.

It was observed that the thrombocytopenic effect of PEG-CIFN was more moderate compared with that of peginterferon α-2a (180 μg) group. Therefore, subjects with cirrhosis and pre-treatment thrombocytopenia may be more suitably treated with PEG-CIFN rather than with the currently approved pegylated IFNs. However, even in the PEG-CIFN groups, PLT counts decreased until week 8, and then became relatively stable. This suggests that the clinical observation time should be extended from to 4 to 8 weeks (16).

Hemoglobin levels. The hemoglobin levels in each group remained >100 g/dl. None of the groups required adjustments in dosage due to anemia.

Neutrophil counts. ANCs at weeks 4, 8 and 14 were significantly lower than that at baseline (P<0.05). There were no statistically significant differences in ANCs between any dose group at baseline, and weeks 4, 8 and 14.

At weeks 4, 8 and 14, there were 5 subjects whose ANCs were <0.75/mm^3 but >0.5/mm^3 in the PEG-CIFN 1.0, 1.5 and 2.0 μg/kg groups and the peginterferon α-2a group combined. According to the protocol, their doses were reduced by 25%. After 1 week, the neutrophil counts rose to >0.75x10^9/l. Original doses were then re-instated.

PLT counts and ANCs decreased following the initiation of treatment, and then slowly rose with increasing treatment time or dose adjustment. The rebound in counts was significant in all PEG-CIFN groups compared with the peginterferon α-2a group.

Total bilirubin levels. Total bilirubin levels did not change significantly between any group at any time point.

Fibroscan values. Fibroscan values were tested at screening and week 14 of the study. FibroScan use the vibration control of the instantaneous elastic imaging to assess the hardness of the liver. The larger the value of elasticity, the greater the value of liver tissue hardness. For viral hepatitis, fibrosis was staged on a scale as follows: F2 (stiffness 0-7.3 kPa); F2-F3 (stiffness 7.3-12.4 kPa); F3-F4 (stiffness 12.4-17.5 kPa) and ≥F4 (stiffness ≥17.5 kPa). In the PEG-CIFN 2.0 μg/kg group, the Fibroscan values increased significantly compared with that at baseline (P<0.05). There were no statistically significant differences between the baseline value and the value at week 14 in any of the other dose groups.

Ophthalmologic complications. It has been reported that IFN-associated retinopathy occurs in 15-64% of IFN-treated patients (17). In the current study, it was found that 35.4% of subjects had ocular adverse reactions. These were mostly mild or moderate and gradually diminished. These events consisted
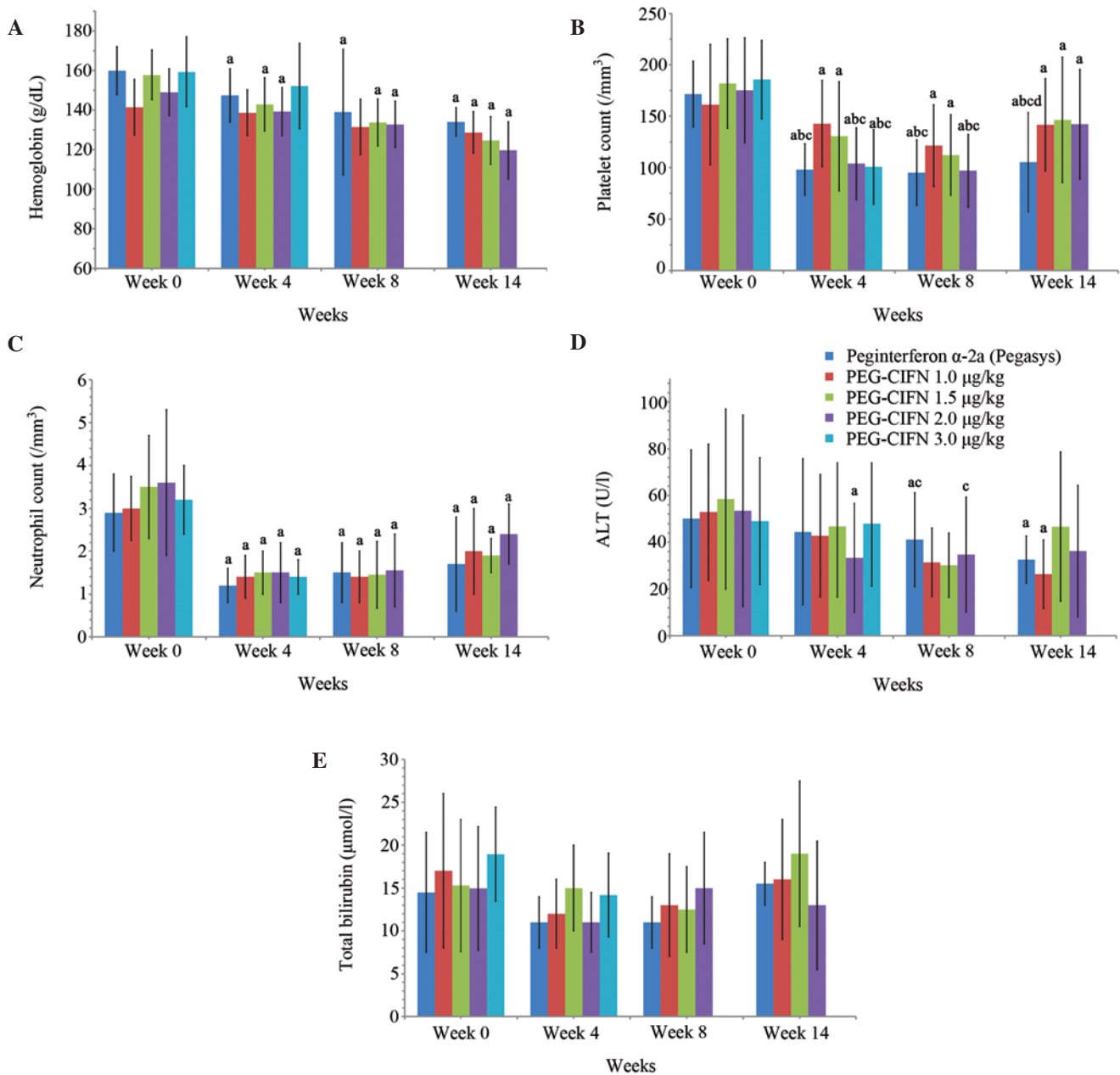
Figure 1. Evaluation of tolerability index test results for the PEG-CIFN and peginterferon α-2a groups. (A) Hemoglobin levels, (B) platelet counts, (C) neutrophil counts, (D) ALT levels and (E) total bilirubin levels at weeks 0, 8, 8 and 14. [a]$P<0.05$ vs. the same dose group at week 0; [b]$P<0.05$ vs. PEG-CIFN 1.0 µg/kg at the same week; [c]$P<0.05$ vs. PEG-CIFN 1.5 µg/kg at the same week; [d]$P<0.05$ vs. PEG-CIFN 2.0 µg/kg at the same week. PEG, polyethylene glycol; CIFN, consensus interferon; ALT, alanine aminotransferase.

of papilledema (5 subjects), retinopathy (5 subjects), arteriosclerosis (5 subjects), intraocular pressure and fundus cup-disc ratio, C/D≥0.5 (2 subjects).

Other adverse events. Adverse reactions were monitored and recorded weekly. Common adverse reactions were fatigue, poor appetite, feverishness, musculoskeletal pain, hair loss and depression. The incidence of the majority of the psychiatric and physical adverse events increased with increasing doses of PEG-CIFN, and they were higher than those of the pegylated IFN-2a group. All the events were mild or moderate and did not result in discontinuation of treatment.

The incidence of adverse reactions increased with increasing dose (Table III). The incidence of adverse reactions

was highest in the 3.0 µg/kg group, and some adverse reactions occurred in all participants in this group (100%).

Efficacy
Virologic response. There were no significant differences in baseline HCV RNA levels between any of the groups (Table IV). Serum HCV RNA levels decreased significantly at weeks 4, 8 and 14 for all groups compared with baseline ($P<0.05$; Fig. 2).

The RVR rates for the PEG-CIFN 1.5, 2.0 and 3.0 µg/kg groups and for the peginterferon α-2a group were 70% (7/10), 77.8% (7/9), 60% (6/10) and 77.8% (7/9), respectively. These rates were all significantly higher than that in the PEG-CIFN 1.0 µg/kg group (10%, 1/10) ($P<0.05$).

Table II. Evaluation of tolerability results for the PEG-CIFN and Peg interferonα-2a groups.

Evaluation index	Time (week)	Peginterferon α-2a (n=9)	PEG-CIFN 1.0 µg/kg (n=10)	PEG-CIFN 1.5 µg/kg (n=10)	PEG-CIFN 2.0 µg/kg (n=9)	PEG-CIFN 3.0 µg/kg (n=10)
Hemoglobin <100 g/dl, n (%)	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	8	0 (0)	0 (0)	0 (0)	0 (0)	
	14	0 (0)	0 (0)	0 (0)	0 (0)	
ANC <0.75 and >0.5/mm³, n (%)	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	4	0 (0)	1 (10)	0 (0)	1 (11.11)	0 (0)
	8	1 (11.11)	0 (0)	1 (10)	0 (0)	
	14	0 (0)	1 (10)	0 (0)	0 (0)	
Platelet count, /mm³, mean ± SD	0	171.50±31.92	161.25±58.70	181.80±43.57	175.22±51.00	185.6±38.28
	4	98.11±25.10	142.70±42.05[a]	130.40±53.18[a]	103.78±35.13[a]	100.80±36.41[a]
	8	95.11±31.80[a]	121.40±39.79[a]	112.30±39.27[a]	97.00±35.40[a]	
	14	105.33±48.07[a,b]	141.80±44.98[a,c,d]	146.50±60.92[a,c,e]	142.30±53.21[a,c,f]	
ALT IU/l, mean ± SD	0	110.11±37.34[a]	52.90±29.18	58.50±38.43	53.44±40.93	49.00±27.07
	4	80.11±58.67	42.80±26.28[a]	46.80±30.29[a]	33.33±23.36[a]	
	8	44.44±30.82[a]	31.40±14.70[a]	66.60±30.57	34.78±24.60[a]	
	14	41.11±16.80[a]	26.33±14.65[a]	46.70±31.97[a]	36.20±28.14[a]	
Total bilirubin>34.2 µmol/l, n (%)	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	4	0 (0)	0 (0)	1 (10)	0 (0)	
	8	0 (0)	0 (0)	0 (0)	0 (0)	
	14	0 (0)	0 (0)	0 (0)	0 (0)	

[a]P<0.05 vs. the corresponding 0 day outcome at the same dose; [b]reduced vs. the week 8 value in 3 subjects; [c]P<0.05 vs. the corresponding peginterferon α-2a outcome on the same day; [d]reduced vs. the week 8 value in 1 subject; [e]reduced vs. the week 8 value in 0 subjects; [f]reduced vs. the week 8 value in 1 subject. SD, standard deviation; ANC, absolute neutrophil count; ALT, alanine aminotransferase; PEG, polyethylene glycol; CIFN, consensus interferon.

Table III. Common adverse reactions [n (%)].

Event	PEG-CIFN 1.0 µg/kg (%)	PEG-CIFN 1.5 µg/kg (%)	PEG-CIFN 2.0 µg/kg (%)	PEG-CIFN 3.0 µg/kg (%)	Peginterferon α-2a (%)
Fatigue	5 (50)	3 (30)	9 (100)	10 (100)	4 (40)
Headache	5 (50)	3 (30)	8 (88.9)	8 (80)	5 (50)
Insomnia	1 (10)	1 (10)	2 (22.2)	4 (40)	1 (10)
Feverishness	2 (20)	2 (20)	3 (33.3)	8 (80)	0
Musculoskeletal pain	7 (70)	5 (50)	6 (66.7)	10 (10)	5 (50)
Xerostomia	6 (60)	4 (40)	9 (100)	10 (100)	5 (50)
Injection site reaction	0	4 (40)	9 (100)	9 (90)	0
Indigestion	0	0	2 (22.2)	0	1 (10)
Flu-like symptoms	0	1 (10)	0	4 (40)	0
Poor appetite	0	7 (70)	6 (66.7)	3 (30)	1 (10)
Hair loss	1 (10)	0 (0)	0 (0)	4 (40)	1 (10)
Depression	3 (30)	0 (0)	2 (22.2)	1 (10)	0 (0)

PEG, polyethylene glycol; CIFN, consensus interferon.

At week 8, the extended RVR rates of the PEG-CIFN 1.0, 1.5 and 2.0 µg/kg groups and for the peginterferon α-2a group were 10% (1/10), 70% (7/10), 77.8% (7/9) and 66.7% (6/9), respectively.
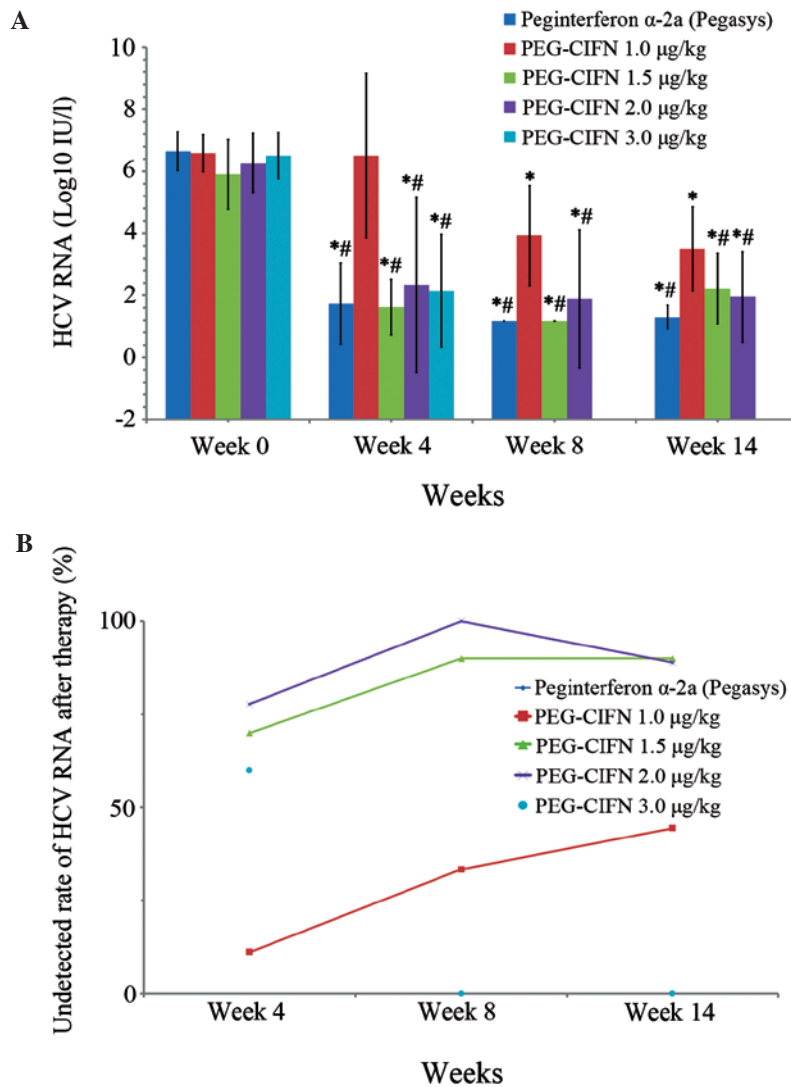
Figure 2. (A) Effects of PEG-CIFN and peginterferon α-2a (Pegasys) on adults with HCV infections. #P<0.05 vs. the PEG-CIFN 1.0 µg/kg group outcome at the same time point (4, 8 or 14 weeks); *P<0.05 vs. the corresponding week 0 outcome in the same dose group,. (B) Effects of PEG-CIFN and peginterferon α-2a (Pegasys) on virologic response. HCV, hepatitis C virus; PEG, polyethylene glycol; CIFN, consensus interferon.

Table IV. Baseline HCV RNA levels in the treatment groups.

Group	n	HCV RNA level ($\log_{10}$IU/l, mean ± SD)
Peginterferon α-2a	9	5.90±1.12
PEG-CIFN 1.0 µg/kg	10	6.58±0.59
PEG-CIFN 1.5 µg/kg	10	6.27±0.95
PEG-CIFN 2.0 µg/kg	9	6.65±0.63
PEG-CIFN 3.0 µg/kg	10	6.50±0.74

P>0.05 among the groups. HCV, hepatitis C virus; PEG, polyethylene glycol; CIFN, consensus interferon.

At week 8, the HCV RNA levels decreased rate for the PEG-CIFN 1.0, 1.5 and 2.0 µg/kg groups and for the peginterferon α-2a group were 30% (3/10), 90% (9/10), 88.8% (8/9) and 88.8% (8/9), respectively.

Multivariable logistic regression analyses were performed to study the virologic responses. The virologic responses at weeks 4, 8 and 14 were higher for the PEG-CIFN 1.5 and 2.0 µg/kg groups and for the peginterferon α-2a group than that for the PEG-CIFN 1.0 µg/kg group. There was no difference in virologic response between the peginterferon α-2a and PEG-CIFN 2.0 µg/kg groups at weeks 4 and 8. Virologic response rates increased with increasing duration of drug administration.

Biochemical response. There were no statistically significant differences in ALT levels between any dose groups at baseline, or at weeks 4, 8 or 14. The ALT levels were observed to decrease as the duration of treatment increased, with no significant differences among all values in the same dose group (P>0.05).

Discussion

In the past, treatment with pegylated IFN α-2a or pegylated IFN α-2b, plus ribavirin, for 48 weeks was recommended for patients infected with HCV genotype 1, the most common

genotype in the United States and Europe (18). By contrast, patients infected with HCV genotypes 2 or 3 may be treated with ribavirin (800 mg/day) and for just 24 weeks without compromising efficacy. These findings are reflected in treatment guidelines for chronic hepatitis C (19,20). The discovery of protease inhibitors as DAAs in 2002 led to the development of numerous small molecules that block the replication of HCV at novel antiviral targets (4,5). In patients with HCV genotype 2 or 3 infection for whom treatment with peginterferon and ribavirin was not an option, 12 or 16 weeks of treatment with sofosbuvir and ribavirin was found to be effective in early studies (21). Triple therapy including direct-acting antiviral agents, other than protease inhibitors, combined with pegylated IFN α-2a or pegylated IFN α-2b, plus ribavirin) are showing promising results in clinical trials. The possibility of decreased side effects and tolerability with the same efficacy for PEG-CIFN indicate that it may play a role in combination with new direct acting agents in the future.

The virologic response rate for genotype 1 HCV treated with dual therapy (pegylated IFN combined with ribavirin) has been reported to be between 30 and 50% (7,8). In the current study, the RVR rate at week 4 was 10% in the PEG-CIFN 1.0 µg/kg group, but 60% in the PEG-CIFN 3.0 µg/kg group. These results suggest that the higher dose of PEG-CIFN may be the optimal dose for genotype 1, and that PEG-CIFN monotherapy compares favorably with dual therapy.

Host, virologic, and treatment factors such as viral load, age, gender, race, state of fibrosis, BMI and HCV genotyping have been reported to be associated with differences in response rates to HCV treatment (22-24). In particular, the virologic response to antiviral treatment in women has been reported to be higher with standard-dose or high-dose peginterferon compared with low-dose peginterferon α-2a (22,23). However, in the current study, no significant effect of these factors on virological response was found.

In conclusion, the rates of favorable virologic response were similar, while the adverse event profile, particularly the decreased degree of thrombocytopenia, was better in patients who received PEG-CIFN compared with pegylated IFNα-2a. This locally produced PEG-CIFN may make the treatment available to many more patients. Limitations of this study include a small sample size and a short observation period. Larger studies particularly comparing PEG-CIFN in dual and triple therapy regimens may be helpful in determining the role of PEG-CIFN in future treatment of HCV infections.

Acknowledgements

References

1. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, et al: IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 41: 1100-1104, 2009.

2. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, et al: Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 41: 1105-1109, 2009.

3. Zhang H, Jiang YF, He SM, Sun J, Gu Q, Feng XW, DU B, Wang W, Shi XD, Wang CY, et al: Etiology and prevalence of abnormal serum alanine aminotransferase levels in a general population in Northeast China. Chin Med J (Engl) 124: 2661-2668, 2011.

4. Hinrichsen H, Benhamou Y, Wedemeyer H, Reiser M, Sentjens RE, Calleja JL, Forns X, Erhardt A, Crönlein J, Chaves RL, et al: Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. Gastroenterology 127: 1347-1355, 2004.

5. Pawlotsky JM, Chevaliez S and McHutchison JG: The hepatitis C virus life cycle as a target for new antiviral therapies. Gastroenterology 132: 1979-1998, 2007.

6. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, et al: Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 364: 2405-2416, 2011.

7. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS, Hsu CS, Tseng TC, Wang CC, Lai MY, et al: Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: A multicenter, randomized controlled trial. Clin Infect Dis 47: 1260-1269, 2008.

8. de Segadas-Soares JA, Villela-Nogueira CA, Perez RM, Nabuco LC, Brandão-Mello CE and Coelho HS: Is the rapid virologic response a positive predictive factor of sustained virologic response in all pretreatment status genotype 1 hepatitis C patients treated with peginterferon-alpha2b and ribavirin? J Clin Gastroenterol 43: 362-366, 2009.

9. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, et al: Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461: 798-801, 2009.

10. Ahlenstiel G, Booth DR and George J: IL28B in hepatitis C virus infection: Translating pharmacogenomics into clinical practice. J Gastroenterol 45: 903-910, 2010.

11. Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, Urban T, Afdhal NH, Jacobson IM, Esteban R, et al: Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology 139: 120-129. e18, 2010.

12. Clark PJ, Thompson AJ and McHutchison JG: IL28B genomic-based treatment paradigms for patients with chronic hepatitis C infection: The future of personalized HCV therapies. Am J Gastroenterol 106: 38-45, 2011.

13. Melian EB and Plosker GL: Interferon alfacon-1: A review of its pharmacology and therapeutic efficacy in the treatment of chronic hepatitis C. Drugs 61: 1661-1691, 2001.

14. Moore CM, George M and Van Thiel DH: Consensus interferon used to treat prior partial-responders to pegylated interferon plus ribavirin. Dig Dis Sci 56: 3032-3037, 2011.

15. Cai Y, Zhang Z, Fan K, Zhang J, Shen W, Li M, Si D, Luo H, Zeng Y, Fu P and Liu C: Pharmacokinetics, tissue distribution, excretion, and antiviral activity of pegylated recombinant human consensus interferon-α variant in monkeys, rats and guinea pigs. Regul Pept 173: 74-81, 2012.

16. Cheng J: New progress in therapy of patients with chronic hepatitis C. Zhonghua Lin Chuang Gan Ran Bing Za Zhi 4: 1-5, 2010 (In Chinese).

17. Bajaire BJ, Paipilla DF, Arrieta CE and Oudovitchenko E: Mixed vascular occlusion in a patient with interferon-associated retinopathy. Case Rep Ophthalmol 2: 23-29, 2011.

18. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, et al: Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 361: 580-593, 2009.

19. Dienstag JL and McHutchison JG: American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterology 130: 225-230, 2006.

20. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, et al: Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. Ann Intern Med 140: 346-355, 2004.

21. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, *et al*: Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 368: 1867-1877, 2013.
22. Rodriguez-Torres M, Jeffers LJ, Sheikh MY, Rossaro L, Ankoma-Sey V, Hamzeh FM and Martin P; Latino Study Group: Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. N Engl J Med 360: 257-267, 2009.
23. Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, Luketic VA and Sanyal AJ: Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology 46: 371-379, 2007.
24. Daw MA, Elasifer HA, Dau AA and Agnan M: The role of hepatitis C virus genotyping in evaluating the efficacy of INF-based therapy used in treating hepatitis C infected patients in Libya. Virol Discov 1: 3, 2013.