Original Article

A Follow-up Study for Chinese Chronic Hepatitis C Patients Treated with the Combination of PEG-IFN α -2a (PEGASYS) and Ribavirin

Zhu Chen, Yi-lan Zeng*, Li Wang, Rong Hu, Yan Wang, Yu-zhen Tang, Li Zhu and Bei Wu

Objective To compare the efficacy of peginterferon alfa-2a (PEGASYS) plus ribavirin (RBV) with interferon alfa-2a plus RBV, and evaluate the safety.

Methods Total of 117 patients with chronic hepatitis C were enrolled to receive either PEGASYS (135 μ g or 180 μ g) subcutaneously once per week, plus RBV (800 mg-1 200 mg) per day for 48 weeks (79 patients, PEGASYS group), or 5 million units of interferon alfa-2a subcutaneously every other day, plus RBV as above dosage for 48 weeks (38 patients, IFN α group).

Results Sixty-three of 79 (79.7%) patients reached sustained virological response (SVR) in PEGASYS group, while 14 of 38 (36.8%) patients reached SVR in IFN α group. PEGASYS group was associated with a higher rate of virologic response than IFN α group at week 4, 12, 36, 48 and week 72. Sustained normalization of serum ALT concentrations at week 36, 48 and week 72 was also more common in PEGASYS group than in IFN α group. Baseline levels of ALT and HCV RNA had no effect on SVR in either PEGASYS group or IFN α group. Both groups were similar in the frequency and severity of adverse events.

Conclusions PEGASYS plus RBV produced similar adverse events but higher rate of SVR. Meanwhile, complications should be prevented and treated promptly in order to increase compliances and effects.

Key words: Chronic hepatitis C; Interferon-alpha, Ribavirin, Treatment outcome

The world-wide spread of hepatitis C virus infection is enormous. It is estimated that approximately 3% of the world's population was infected with HCV, as well as 30 million people in China (mostly with HCV-1b). The majority (55%-85%) of patients with acute HCV infection will develop into chronic hepatitis and approximately 5%-25% of these patients will develop into cirrhosis. These patients are at high risk of liver failure, liver decompensation or hepatocellular carcinoma. Today, a combination of pegylated interferon alfa plus ribavirin (RBV) is considered as the standard of care (SOC) for patients with chronic hepatitis C, while the combination of interferon alfa and RBV is the second option. The purpose of this article is to evaluate

the safety and efficacy of PEGASYS plus RBV, compared with interferon alfa-2a (IFN α) plus RBV in the treatment of patients with chronic hepatitis C. The primary end point was SVR defined as an undetectable level of HCV RNA (< 1 000 IU/ml). Univariate analyses were performed to determine the factors associated with response.

PATIENTS AND METHODS

Patients

Adults (18 years or elder) with positive detection for anti-HCV antibody, HCV RNA level higher than 1 000 IU/ml on polymerase-chain-reaction analysis (Roche Diagnostics), a serum ALT concentration above the upper limit of normal but below tenfold of the upper limit were eligible for this study. Total of 117 patients with chronic hepatitis C were enrolled to

The Public Health Clinical Center of Chengdu, Chengdu, Sichuan Province, China.

Correspondence: Yi-lan Zeng, E-mail: 277796360@qq.com.

receive treatment from January 2009 to January 2012 (68 men and 49 women; median age, 42 years old).

Criteria for exclusion were neutropenia (neutrophil count $<1\,500$ per cubic millimeter); thrombocytopenia (platelet count $<90\,000$ per cubic millimeter); a creatinine concentration higher than 1.5 times of the upper limit of normal; coinfection with hepatitis A or B virus; decompensated liver disease; organ transplant; neoplastic disease; severe cardiac or chronic pulmonary disease; autoimmune disease (except well-controlled thyroid disease); a psychiatric disorder; women with pregnancy or lactation; an unwillingness for contraception.

Design

Eligible patients were assigned to receive either PEGASYS (135 μg or 180 $\mu\text{g}/\text{week}$, F. Hoffmann–La Roche, Shanghai, China) subcutaneously plus weight-based RBV (800 mg/d–1 200 mg/d, Shanghai Huashi Pharmaceutical Company) per os for 48 weeks, or 5 million units of interferon alfa-2a (Shenyang Sunshine Pharmaceutical Co., LTD) subcutaneously every other day, plus RBV as above for 48 weeks. Data on virology and biochemistry for all patients before treatment and at week 4, 12, 24, 36, 48 during treatment, and week 24 after treatment were collected. The differences between both groups were compared and ALT and HCV RNA were quantified.

Characteristics

The two groups were matched for sex, age, weight, baseline ALT and AST levels and viral level (Table 1).

Assessment and end points

Efficacy was assessed by measuring plasma HCV RNA and serum ALT. Virologic response was defined as undetectable levels of HCV RNA (with a lower limit of detection as 1 000 IU/ml). Biochemical

response was defined as the presence of normal ALT and AST values (normalization of serum ALT and AST concentrations to a value $\leq$ upper limit of normal). The primary efficacy end points were a virologic and a biochemical response at week 72 (SVR). The differences between the two groups was compared and ALT, AST and HCV RNA were detected.

Statistical analysis

Numerical data were described by mean $\pm$ standard deviation and analyzed by *t* test; while measurement data were analyzed by chi-square test. Two-sided *P* values were calculated for pairwise comparisons of the two treatment methods (accepting $P < 0.05$). All data were analyzed through statistic software SPSS (Statistical Program for Social Sciences) 16.0.

RESULTS

Efficacy

Virological response between the two groups

PEGASYS group was associated with a higher rate of virological response than IFN α group at week 4 (74.7 percent vs. 31.6 percent, $P < 0.001$), week 12 (77.2 percent vs. 36.8 percent, $P < 0.001$), week 36 (89.9 percent vs. 57.9 percent, $P < 0.001$), week 48 (93.7 percent vs. 57.9 percent, $P < 0.001$) and week 72 (79.7 percent vs. 36.8 percent, $P < 0.001$) (Table 2).

Biochemical response between the two groups

Sustained normalization of ALT concentrations at week 36, 48 and 72 were also more common in PEGASYS group than in IFN α group (Table 3).

Effective factors influencing the virological response

We also explored the correlation between baseline HCV RNA level (<1 million vs ≥ 1 million IU per milliliter) or ALT level and virological response. Base-line ALT level was calculated as the average of

Table 1. Characteristics of the patients at baseline

	Male sex [no. (%)]	Age ($\bar{x} \pm s$, yr)	Weight ($\bar{x} \pm s$, kg)	ALT ($\bar{x} \pm s$, U/L)	AST ($\bar{x} \pm s$, U/L)	Mean of HCV RNA ($\bar{x} \pm s$, 10^6 IU/ml)
PEGASYS group (n=79)	45 (55.6)	44.31 $\pm$ 7.03	63.44 $\pm$ 9.05	145.38 $\pm$ 51.77	103.31 $\pm$ 40.86	23.97 $\pm$ 7.75
IFN α group (n=38)	18 (56.3)	43.41 $\pm$ 6.52	63.22 $\pm$ 7.36	142.62 $\pm$ 53.31	112.07 $\pm$ 38.00	25.94 $\pm$ 5.89
Statistic values	0.9520	0.664	0.130	0.267	1.110	1.385
<i>P</i> values	0.330	>0.05	>0.05	>0.05	>0.05	>0.05

Note: † Descriptive statistics.

Table 2. Virological response compared between two groups [n (%)]

	Week 4 (RVR)	Week 12 (EVR)	Week 24	Week 36	Week 48 (ETVR)	Week 72 (SVR)
PEGASYS group (n=79)	59 (74.7)	61 (77.2)	65 (82.3)	71 (89.9)	74 (93.7)	63 (79.7)
IFN α group (n=38)	12 (31.6)	14 (36.8)	26 (68.4)	22 (57.9)	22 (57.9)	14 (36.8)
χ^2	19.981	18.175	2.851	16.092	22.299	20.992
<i>P</i> values	<0.001	<0.001	0.091	<0.001	<0.001	<0.001

Notes: † T test. Virological response was indicated by undetectable levels of HCV RNA (<1 000 copies per milliliter).

Table 3. Biochemical response compared between two groups [n (%)]

	Week 4 (RVR)	Week 12 (EVR)	Week 24	Week 36	Week 48 (ETVR)	Week 72 (SVR)
PEGASYS group (n=79)	32 (40.5)	41 (51.9)	42 (53.2)	64 (81.0)	64 (81.0)	64 (81.0)
IFN α group (n=38)	10 (26.3)	16 (42.1)	18 (47.4)	16 (42.1)	12 (31.6)	9 (23.7)
χ^2	2.245	0.985	0.345	17.963	27.545	35.939
<i>P</i> values	0.134	0.321	0.557	<0.001	<0.001	<0.001

Notes: † T test. Biochemical response was defined as the presence of normal ALT values (normalization of serum ALT concentrations to a value at or below the upper limit of normal). In this article, the reference value of normal serum ALT concentrations was < 37 U/L.

Table 4. Correlation between baseline HCV RNA level and virological response

Base-line RNA level†	PEGASYS group (n=79)	IFN α group (n=38)
<1 million IU/ml	84.0% (21/25)	60.0% (6/10)
≥1 million IU/ml	77.8% (42/54)	35.7% (8/28)
χ^2	0.410	Fisher
<i>P</i> values	0.522	0.127

Notes: †Correlation analysis. Base-line HCV RNA level (<1 million vs. ≥1 million IU/ml). Data ratio in the table was defined as complete responder/total number.

Table 5. Correlation between baseline ALT level and virological response

Base-line ALT quotient†	PEGASYS group (n=79)	IFN α group (n=38)
<1	75.0% (9/12)	33.3% (2/6)
1 and <3	80.0% (28/35)	31.3% (5/16)
≥3 and <10	81.3% (26/32)	43.8% (6/16)
χ^2	fisher	fisher
<i>P</i> values	0.865	1.000

Notes: †Correlation analysis. Base-line ALT level, calculated as the average of serum ALT values before treatment, divided by the upper limit of normal (<1, ≥1 and <3 vs ≥3 and <10). Ratio data in the table were defined as complete responder/total number. *P* values demonstrated comparisons to the third decimal place.

serum ALT values before treatment, divided by the upper limit of normal (<1, ≥1 and <3 vs ≥3 and <10).

Correlation between base-line RNA level and virological response

It was suggested that HCV RNA level before medication had no effect on virological response in both groups (*P* > 0.05, respectively) (Table 4).

Correlation between base-line ALT quotient and virological response

In the study of the effects of ALT quotient before medication suggests that it had no effect on virological response in both groups (*P* > 0.05) (Table 5).

Safety

Adverse effects

A adverse effects occurred during the treatment

such as influenza-like symptoms, myelosuppression, emotional disturbance and autoimmune disease, etc. The frequency and severity of adverse events were similar in both groups (*P* > 0.05) (Table 6).

DISCUSSION

Hepatitis C virus (HCV) infection is one of the major cause of chronic liver diseases, including cirrhosis, liver failure and hepatocellular carcinoma. Currently, no effective vaccine is available for HCV infection. Pegylated interferon in combination with ribavirin (RBV) is the standard of care (SOC) for patients with chronic hepatitis C.

PEGASYS is a compound with sustained absorption, a slower rate of clearance and a longer half-life than unmodified interferon IFN α . It was

Table 6. Adverse effects [n (%)]

	Influenza-like syndrome	Myelosuppression	Emotional disturbance	Autoimmune diseases
PEGASYS group (n=79)	52 (65.8)	63 (79.7)	7 (8.9)	5 (6.3)
IFN α group (n=38)	24 (63.2)	30 (78.9)	4 (10.5)	2 (5.3)
χ^2	0.080	0.010	fisher	fisher
P values	0.777	0.920	0.746	1.000

Note: † Descriptive statistics.

reported that a significantly higher proportion of patients who received PEGASYS plus RBV had sustained virologic response (54-64 percent) compared to patients who received IFN α -2b plus RBV (44-47 percent) or PEGASYS alone (25-39 percent) or IFN α alone (12-19 percent).^{1,2} The proportions of chronic hepatitis C (CHC) patients treated with PEGASYS plus RBV in China who had sustained virologic responses were 72 percent, and the safety and tolerance were well.³ In our study, the PEGASYS group showed a more obvious therapeutic effect than abroad, 93.7% of the patients achieved ETVR at the end of treatment, and 79.7% reached SVR at week 72. Recently, genome-wide association study (GWAS) revealed that certain interleukin-28B (IL-28B) gene polymorphisms are strongly associated with responses to pegylated interferon and RBV therapy in patients chronically infected with HCV genotype 1, as well as with spontaneous clearance of HCV.⁴ Moreover, IL-28B gene polymorphisms were the strongest predictors of response to pegylated interferon and RBV in patients chronically infected with HCV genotypes 1 and 4.⁵ Some studies found that the protective rs12979860 C allele frequency was 91.0%-97.5% in east Asia population, which may be the possible reason why domestic patients had a higher SVR than abroad. Therefore, therapy of CHC recently entered a new era with the deployment of direct-acting antivirals (DAAs), and IL-28B genotyping will be also useful for personalized CHC treatment in the forthcoming era of DAAs.⁶

Our study also suggested that a regimen of PEGASYS plus RBV was associated with a higher rate of virologic response than IFN α group at weeks 4, 12, 36, 48 and 72. Sustained normalization of serum ALT concentrations at weeks 36, 48 and 72 were also more common in PEGASYS group than in IFN α group. Thus, PEG-IFN α -2a plus RBV had a significantly better efficacy than interferon alfa-2a

plus RBV.

The therapeutic effect of interferon is influenced by multiple factors.⁷⁻¹⁰ Host factors are common, including age, weight, base-line ALT or AST level, alcohol-intake history, route of transmission, time of transmission, adiposis hepatica or HIV-infected concomitant or not and compliance. Virological factors are also frequent, such as genotypes, viral load and liver fibrosis, etc. Therapeutic factors contain dosage and dosage form of IFN, therapeutic alliance or not, for instance.

Baseline factors are considered as predictable indexes of virological response. Some researchers applied multiple Logistic regression model to find that predictable factors concerning with SVR, such as γ -glutamyltransferase (GGT) concentration, viral genotypes and liver histologic characteristics, but not age, gender or weight index. While in our study, HCV RNA baseline levels had no effect on virological response in either PEGASYS group or IFN α group (also found in some domestic reports).¹¹ Meanwhile, the baseline ALT level had no effect on virological response in both groups.

It has been reported that the regimen of interferon plus RBV had little effects on HCV patients with normal ALT level, so it was not advised to use interferon on such patients but advised with follow-up in EASL (European Association for the Study of Liver) in 1999.¹² Studies on liver pathology found that even in patients with normal ALT quotient, 48%-87% of them already have chronic inflammation.^{13,14} HCV-infected patients with serum ALT concentration below or above the upper limit of normal (but below tenfold of the upper limit) were enrolled into our study, and ALT level before medication was found to have no effect on virological response in the PEGASYS group and IFN α group. In PEGASYS group, the SVRs of patients with normal, slightly-increased and markedly-increased ALT level were 75.0%, 80.0%

and 81.3%, respectively; which were 33.3%, 31.3% and 43.8% in IFN α group. In other words, in order to inhibit pathogenetic conditions from progressing, antiviral therapy especially pegylated interferon plus RBV should be administered for HCV infected patients with serum HCV RNA detectable but normal ALT level.

The profile of adverse drug reactions (ADRs) to interferon plus ribavirin has been well described.¹⁵ The principal adverse effect of RBV is hemolytic anemia. Adverse effects associated with interferon includes fatigue, gastrointestinal disturbances, influenza-like symptoms, hematological abnormalities, neuropsychiatric effects (particularly depression), thyroid dysfunction, and dermatologic effects, such as alopecia and pruritus. The efficacy and safety profiles of PEGASYS plus RBV versus standard INF plus RBV were compared, which suggested a qualitatively similar profile of ADRs. All symptoms were temporal after therapy termination.

In general, the combination of PEG-IFN α -2a and RBV is well tolerated, and laboratory abnormalities and adverse events associated with its administration were typical for those associated with unmodified IFN α . Therefore, a combination of PEG-IFN α -2a and RBV is a safe and effective treatment for Chinese patients with HCV infection.

REFERENCES

1. Liu CH, Huang CF, Liu CJ, Dai CY, Liang CC, Huang JF, et al. Pegylated interferon- α 2a with or without low-dose ribavirin for treatment-naïve patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. *Ann Intern Med* 2013;159(11):729-738.
2. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347(13):975-982.
3. Xu DZ, Xie Y, Lu ZM, Luo KX, Jia JD, Wang YM, et al. Randomized, open-label and active controlled study of PEG-IFN α -2a in the treatment of chronic hepatitis C in China (in Chinese). *J Infect Dis* 2004;22(4):221-224.
4. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401.
5. Lin CY, Chen JY, Lin TN, Jeng WJ, Huang CH, Huang CW, et al. IL28B SNP rs12979860 is a critical predictor for on-treatment and sustained virological response in patients with hepatitis C virus genotype-1 infection. *PLoS One* 2011;6(3):e18322.
6. Matsuura K, Watanabe T, Tanaka Y. Role of IL28B for chronic hepatitis C treatment toward personalized medicine. *J Gastroenterol Hepatol* 2014;29:241-249.
7. Zhu Y, Chen S. Antiviral treatment of hepatitis C virus infection and factors affecting efficacy. *World J Gastroenterol* 2013;19(47):8963-8973.
8. Dhillon R, Rossi S, Herrine SK. Pegylated interferon 2a and 2b in combination with ribavirin for the treatment of chronic hepatitis C in HIV infected patients. *Therapeutics and Clinical Risk Management* 2008;4(4):789-796.
9. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meet West. *J Gastroenterol Hepatol* 2009;24:336-345.
10. Kogure T, Ueno Y, Fukushima K, Nagasaki F, Kondo Y, Inoue J, et al. Pegylated interferon plus ribavirin for genotype 1b chronic hepatitis C in Japan. *World J Gastroenterol* 2008;14:7225-7230.
11. Jin RJ, Wang XD, Chen YP. Study on efficacy and safety of Peginterferon alfa - 2a for chronic hepatitis C. *Practical Clinical Medicine* 2007;8(8):37-38.
12. Kolarski V. The European consensus on hepatitis C. *Vutr Boles* 1999;31(4):21-28.
13. Puoti C, Castellacci R, Montagnese F, Zaltron S, Stornaiuolo G, Bergami N, et al. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). *J Hepatol* 2002;37:117-123.
14. Okanou T, Makiyama A, Nakayama M, Sumida Y, Mitsuyoshi H, Nakajima T, et al. A follow-up study to determine the value of liver biopsy and need for antiviral therapy of hepatitis C virus carriers with persistently normal serum aminotransferase. *J Hepatol* 2005;43:599-605.
15. Farah R, Farah R, Makhoul N. Interferon-induced pulmonary sarcoidosis. *Int J Clin Pharmacol Ther* 2005;43:441-443.