Original Article

The Role of Pegylated Interferon and Ribavirin in Chronic Hepatitis C Genotype 3: A Study of Real-World Practice in Southeast Asia

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Background: This is the report released after the 2012 implementation of a national program that gave all Thai citizens access to treatment for chronic hepatitis C genotypes 3.

Objective: The present study evaluated the effectiveness and safety of pegylated interferon-alfa [PEG-IFα] and Ribavirin [RBV], as well as predictive factors of sustained virological response [SVR].

Materials and Methods: The authors retrospectively enrolled 97 HCV genotype 3 treatment-naive infected patients who fit the study criteria and had received treatment at Srinagarind hospital from August 2012 to May 2015. Patients were given PEG-IFα either 2a or 2b plus RBV for 24 weeks and SVR analysis was conducted.

Results: Ninety-three patients had genotype-3a and four had genotype-3b. There was no difference in efficacy between PEG-IFα-2a and PEG-IFα-2b for achieving SVR (83.7% (36/43) vs. 87% (47/54), respectively, $p = 0.64$). Multivariate logistic regression analysis found that high platelet count (Adjusted odds ratio = 4.04, 95% CI 1.03 to 15.94) remained independent predictive factor related to higher SVR rates. Patients who had Rapid Virological Response [RVR] also achieved higher SVR rates (94.7% (54/57) vs. 72.5% (29/40), $p = 0.03$). Virological responses at various times were also strong predictive factors of SVR. Overall incidence of serious adverse events was 7%, (7/97). There were three cases of premature discontinuation (3.1%) and ten incidences of anemia (Hb <8g/dl) (10.31%). Anemia was managed mostly by PEG and RBV dose reduction.

Conclusion: Our analysis demonstrated the safety, tolerability and high SVR rates of PEG-IFα and RBV, especially patients who had RVR.

Keywords: Chronic hepatitis C, Genotype 3, Peg-interferon and ribavirin, Treatment, Thailand

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Many new direct-acting antiviral [DAA] drugs, specifically targeting viral replication, have recently been studied in clinical trials. The results of new DAAs are promising, which have recently been approved for the treatment of chronic hepatitis C virus [HCV] infection[1]. It is, however, still uncertain when these new agents will be introduced into the National Drug List. The reimbursement regimens have been under-reviewed with regard to cost-effectiveness and budget impact analysis. Therefore, the regimen that consists of 24 weeks of pegylated interferon-alfa [PEG-IFα) and Ribavirin [RBV] for chronic HCV patients infected by genotypes 3 is currently the only option for reimbursement[2].

With PEG-IFα and RBV combination therapy, the sustained virological response [SVR] rate is approximately 40 to 50% for HCV genotype 1 patients and approximately 70 to 80% for HCV non-genotype 1 patients in Western countries[3]. In contrast, the SVR rates are higher among Korean patients, reaching approximately 70% in genotype 1 patients and 80 to 90% in non-genotype 1 patients[4]. However, there is limited information regarding SVR in Thai patients infected with HCV genotypes 3. Studies have found female gender, young age, being infected with genotype 2 or 3, absence of cirrhosis, Asian ethnicity, and early

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inhibition of viral replication to be predictors of a better response to treatment. Recently, genome-wide association studies reported that the interleukin [IL] 28B single nucleotide polymorphism [SNP] is associated with the SVR to the PEG-IFα and RBV combination[5,6]. A study of Caucasian patients reported that rs8099917 SNP was helpful in the prediction of SVR in a group of patients with the non-favorable SNP rs12979860[7]. However, in Asia, the Korean studies showed that the majority of patients possess the genotypes that are favorable to interferon-based therapy, including the representative SNPs rs12979860 and rs8099917, which may limit the usefulness of the IL28B SNP in treatment response prediction[8-10].

The present study aimed to evaluate the effectiveness of PEG-IFα 2a and 2b combined with RBV in patients with chronic hepatitis C [CHC] genotype 3, and to evaluate predictive factors of SVR to PEG-IFα and RBV antiviral therapy in Thai population.

Materials and Methods

Study design and population

This was single-center retrospective cohort study conducted in patients with CHC receiving therapy using either pegylated interferon alfa-2a or pegylated interferon alfa-2b, which are considered to be the gold standard treatments according to the 2012 and 2015 Thai guidelines[11] and Thai reimbursement guidelines[2]. Patients that were included in this study were over 18 years old, infected with HCV genotype 3, had received at least one dose of either PEG-IFα-2a or -2b plus RBV during the period of August 2012 to May 2015 as naive therapy, had detectable serum HCV-RNA ≥5,000 IU/mL and significant fibrosis (defined as METAVIR ≥2 or Ishak ≥3 or a Fibroscan® liver stiffness examination resulted above 7.5 kPa before starting therapy). The authors excluded the patients into the analysis according to reimbursement criteria. These were patients who had significant comorbidities, e.g., uncontrolled psychiatric conditions (including severe depression), active cancer, organ transplantation, active substance abuse within the past 6 months, patients who had co-infection with Hepatitis B or HIV, decompensated cirrhosis (Child-Pugh class B or C), or alanine aminotransferase [ALT] >1.5 times of the upper normal limits without other causes of hepatitis.

Treatment protocol

The total treatment period was 24 weeks. The standard dose for PEG-IFα-2a or -2b and RBV followed the recommend dose detailed in local package inserts and in Thai clinical practice guidelines. HCV RNA was quantified (Roche TaqMan 2.0 HCV test; Roche, Mannheim, Germany) prior to treatment and at weeks 4, 12, 24, and 48. Three of these HCV RNA checks (at baseline and 24 and 48 weeks) were reimbursed by the national program, the rest were paid for by investigator. Whether a patient received the PEG IFα-2a or -2b and dose modification according to adverse events were at the discretion of the clinical physician.

Discontinuation of treatment

Patients who did not achieve an HCV RNA drop of >2 log10 from the baseline by week 12 (defined as null response to treatment) were considered unlikely to achieve SVR, and treatment was discontinued.

Definition of virological/treatment responses:

Rapid Virological Response [RVR] was defined as a negative HCV RNA at week four of therapy.

Complete Early Virological Response [cEVR] was defined as negative HCV RNA at week 12 of therapy.

Partial Early Virological Response [pEVR] was defined as a >2 log reduction in HCV RNA, compared to baseline level, at week 12 of therapy.

End of Treatment response [ETR] was defined as negative HCV RNA at the end of 24 weeks of treatment.

Sustained Virological Response [SVR] was defined as negative HCV RNA 24 weeks after therapy. The infection in this case was considered cured.

Ethical consideration

The proposal was approved by the ethical committee at Srinagarind Hospital, Khon Kaen University.

Outcome measurement

The patients' clinical data were collected from electronic and paper medical records. The SVR was defined as a documented serum HCV RNA level that was undetectable 24 weeks after the cessation of treatment. When available, we collected the following data:

Patient characteristics: baseline age, gender, body mass index [BMI], alcohol consumption habits.

Viral characteristics: Genotyping, HCV-RNA baselines and weeks 4, 12, 24, and 48.

Liver status assessment: baseline aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], albumin, platelets,

histology evaluation-METAVIR score, transient elastography (Fibroscan®), ultrasound

Monitoring of adverse events according to the treatment: complete blood count [CBC], liver function test [LFT] and thyroid stimulating hormone [TSH].

Statistical analysis

All of the patients who took at least one dose of the study medication were included in the efficacy analysis according to the intention-to-treat principle. The patients who withdrew from the study for any reason were categorized as non-responders in the efficacy assessment. The baseline demographic and disease characteristics data were summarized using descriptive statistics to assess comparability between SVR and non-SVR groups. The primary efficacy endpoint, the achievement of SVR, and virological response rates at various time points during treatment (Treatment week 0, 4, 12, 24, and 48) were summarized using descriptive statistics (n, %). Multiple logistic regression models were used to assess the relationship between SVR and patient demographic, metabolic and histological characteristics. Odds ratio [OR], 95% CI of the ORs, and Chi-square *p*-values from the logistic models were presented.

Results

Baseline characteristics

A total of 97 patients infected with HCV genotype 3, who fit in criteria received at least one dose of either PEG-IFα-2a or 2b plus RBV between August 2012 and May 2015, were included in the study. 89.7% were aged above 40 years and 69.1% were male. The proportion of patients with cirrhosis was 47.4% and those who had failed treatment had significantly higher rates of cirrhosis (78.6%) compared to patients who achieved SVR at week 24 (42.1%). The most common genotype in this study was HCV genotype 3a at 96% of patients. The remaining 4% of patients had genotype 3b. In addition, there were no differences in HCV-RNA between patients who failed treatment and those who achieved SVR at week 24 (Table 1).

Primary outcome

After 24 weeks of treatment, there was no difference in the number of patients who achieved SVR between those who received PEG-IFα-2a and those who received PEG-IFα-2b (83.7% and 87%, respectively; $p = 0.64$). Furthermore the difference in the rate of treatment failure between PEG-IFα-2a (16.3%) and PEG-IFα-2b (13%) was also non-significant ($p = 0.64$) (Figure 1).

Secondary outcomes

The treatment response of patients who achieved RVR (93.9%) in comparison to those who did not (68.8%) was significantly associated with higher SVR. This result was also consistent with cETR vs. non-cETR (91% vs. 25%) and ETR vs. non-ETR (89.3% vs. 0%) (Table 2).

The virologic rate at weeks 4, 12 and 24 was a predictive factor in determining SVR. At week 4, patients with undetectable HCV RNA had higher SVR in comparison to patients with detectable HCV RNA (93.9% vs. 68.8%). At week 12, SVR was even higher in comparison to patients with detectable HCV RNA (91% vs. 25%). At week 24, this difference was even more pronounced (89.3% vs. 0%) (Figure 2). This was further confirmed by multivariate regression analysis, which showed that undetectable HCV RNA at weeks 4 (Adjusted OR = 7.07, 95% CI 1.28 to 27.43, $p = 0.002$), 12 (Adjusted OR = 6.83, 95% CI 1.76 to 26.44, $p = 0.002$) and 24 (Adjusted OR = 6.70, 95% CI 1.73 to 25.67, $p = 0.002$) were significantly predictive of achievement of SVR.

According to further analysis using multivariate regression (Table 3), high platelet count over 150,000 per microliter (Adjusted OR = 4.04, 95% CI 1.03 to 15.94, $p = 0.077$) was independent predictor associated with high SVR.

Safety

During the 24-week treatment period, the overall incidence of adverse events was 7% (7/97 patients), and 3 patients prematurely discontinued treatment (3.1%, 3/97). The incidence of anemia observed during treatment was 10.31% (10/97), which was mostly managed by reducing PEG-IFα and RBV dosage.

Discussion

This retrospective study conducted in a Thai population with chronic hepatitis C demonstrated the efficacy and safety of treatment with a combination PEG-IFα and RBV in a real world practice. There was no difference in SVR achievement and failure between patients treated with PEG-IFα-2a and those treated with PEG-IFα-2b.

The majority of patients receiving treatment in this study were infected with HCV genotype 3a and the remainder were infected with 3b. This genotype

Table 1. Demographic and characteristics of the patients between SVR and treatment failure groups (non-SVR groups)

Variables	All n = 97 (%)	Treatment failure, n = 14 (%)	24 weeks SVR, n = 83 (%)	*p*-value
Age in years				
Mean ± SD	49±7.2	52±8.7	48±6.8	0.04**
Age group				
Above 40 years old	87 (89.7)	13 (92.9)	73 (89.2)	1.00*
Gender				
Male	67 (69.1)	10 (71.4)	57 (68.7)	0.55
BMI in kg/m^2				
Mean ± SD	24.4±3.8	25.3±4.3	24.2±3.7	0.32**
Alcohol consumption				
Yes, n (%)	61 (62.9)	9 (64.3)	52 (62.6)	0.99
CBC				
Hb; mean ± SD	13.5±1.5	13.5±1.9	13.6±1.5	0.86**
WBC; mean ± SD	6,521±1,677	6,867±2,133	6,463±1,596	0.41**
PMN; mean ± SD	3,163±1,255	3,672±1,837	3,078±1,122	0.10**
Plt; mean ± SD	150±58	119±51	156±58	0.03**
LFT				
AST; mean ± SD	98±52.9	102±33.9	96±55.5	0.69**
ALT; mean ± SD	119±62.1	112±37.6	120±565.5	0.66**
ALP; mean ± SD	92 ± 36.8	109±54.7	90±32.5	0.09**
AFP				
mean ± SD	14.99±27.1	17.9±31.5	14.5±26.7	0.74**
Cirrhosis***				
Yes, n (%)	46 (47.4)	11 (78.6)	35 (42.1)	0.02*
Fibrosis grade				
F 0-2, n (%)	30 (30.9)	1 (7.1)	29 (34.9)	0.06*
F 3-4, n (%)	67 (69.1)	13(92.9)	54(65.1)	
Fibroscan				
pKa±SD	20.3±13.5	24.9+15.8	19.4+12.9	0.20**
HCV Genotype				
3a, n (%)	93 (95.8)	12 (97.6)	81(97.6)	0.10*
3b, n (%)	4 (4.2)	2 (2.4)	2 (2.4)	
HCV RNA				
<800,000 IU/ml	13 (13.4)	1 (7.1)	12 (14.5)	0.69*
≥800,000 IU/ml	84 (86.6)	13 (92.9)	71 (85.5)	

The *p*-value from Chi-square

* The *p*-value form Fisher's Exact test, ** The *p*-value from Student t-test, *** Cirrhosis was diagnosed by F4 fibrosis score using Fibroscan® or liver biopsy (Metavir score)

distribution was consistent with a recent report on the genotypic distribution of hepatitis C virus in Thailand and Southeast Asia[12], in which genotype 3a was the genotype most frequently found in Thailand and Malaysia. In decreasing order, the most common HCV strains were genotype 3 (46.1%), genotype 1 (32.5%), genotype 6 (20.9%) and genotype 2 (0.5%). The rate of genotype 2 was zero in northeast Thailand. Genotype 3a (36.4%) was the most predominant genotype, followed by genotype 3b (9.7%).

The efficacies of both type of pegylated interferon-alfa were similar to those reported in a Korean study and meta-analysis[4,13]. In the present study of real-world practice, the side effects were low, further confirming the safety of this treatment combination of ribavirin and pegylated interferon. Platelet count was predictive factor of patients achieving higher SVR, which is consistent with other studies. Mangia et al[14] noted that a low platelet count (considered to be an indirect marker of advanced liver fibrosis) appeared to predict relapse in cases with genotypes 2 and 3. In an IDEAL study, a model constructed to consider the

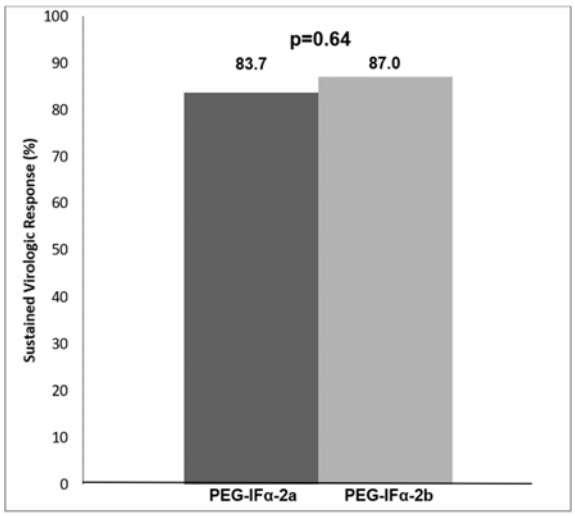

Figure 1. Sustained virological response rate (SVR, %) compare between peginterferon alfa (PEG-IFα) 2a and 2b.

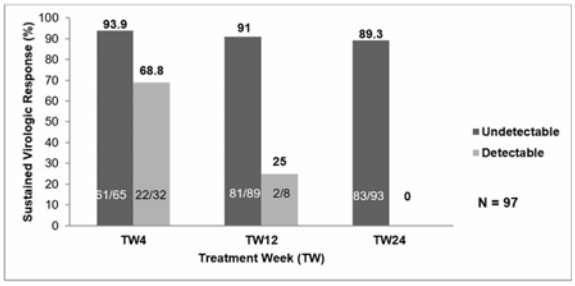

Figure 2. Intention to treat analysis of SVR vs. treatment failure according to treatment response at various time points during treatment.

independent effects of the IL28B SNP rs12979860 and RVR in the context of the other baseline predictors showed that RVR had the largest odds ratio for SVR (OR, 9.1; 96% CI, 5.8 to 14.0 vs. non-RVR non-CC genotype reference). Rapid virological response is, thus, the strongest predictor of SVR with PEG-IFα combination therapy [15].

The present study had several limitations. First, selection bias was present due to the retrospective study design. Second, the IL28B SNP was not included in the analysis due to no achieving the result of blood test.

Conclusion

High SVR was maintained with PEG-IFα and RBV, especially in selected patients with excellent on-treatment response. PEG-IFα and RBV should remain important for those patients with chronic HCV genotype 3 without cirrhosis who do not need or who

Table 2. Summary of treatment outcome

	SVR	Treatment failure	*p*-value
RVR	61 (93.9)	4 (6.1)	0.002*
Non-RVR	22 (68.8)	10 (31.2)	
cETR	81 (91.0)	8 (9.0)	<0.001*
Non-cETR	2 (25.0)	6 (75.0)	
ETR	83 (89.3)	10 (10.7)	<0.001*
Non-ETR	0 (0.0)	4 (100.0)	

* Fisher's exact test
RVR = Rapid virological response, cEVR = Complete early virological response, ETR = End of treatment response

Table 3. Multivariate logistic regression analysis of SVR baseline predictors and on-treatment response

Effects	Adjusted odds ratio	95% CI	*p*-value
Baseline characteristics			
Younger age	0.91	0.83 to 1.00	0.077
Male gender	0.91	0.22 to 3.82	0.901
Peginterferon 2b	1.21	0.34 to 4.30	0.760
BMI >25	1.12	0.35 to 3.67	0.840
Platelet >150	4.04	1.03 to 15.94	0.005
ALT >100	1.04	0.28 to 3.88	0.949
High viral load	0.51	0.05 to 4.78	0.555
Fibrosis F3-F4	0.61	0.17 to 2.19	0.451
On-treatment			
Undetectable at TW4	7.07	1.82 to 27.43	0.002
Undetectable at TW12	6.83	1.76 to 26.44	0.002
Undetectable at TW24	6.70	1.73 to 25.67	0.002

cannot afford new DAAs and are not receiving treatment.

What is already known on this topic?

In Thailand, pegylated interferon and ribavirin has been accepted for hepatitis C virus with or without HIV co-infection since April 2015.

What this study adds?

High SVR was maintained with PEG-IFα and RBV, especially in selected patients with excellent on-treatment response.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Thai Association for the Study of the Liver. Thailand practice guideline for management of chrnoic hepatitis C 2016 [Internet]. 2016 [cited 2016 Jun 9]. Available from: http://www.silomclinic.in.th/file/Hep_C_Guideline_2016.pdf.
2. Announcement of the Medical Committee under the Social Security Act B.E. 2533 [Internet] The Royal Thai Government Gazette, Book 131, Special Edition 217. October 30, 2014 [cited 2016 Jun 9]. Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2557/E/217/12.PDF.
3. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-65.
4. Jung YK, Kim JH. Is peginterferon and ribavirin therapy effective in Korean patients with chronic hepatitis C? Clin Mol Hepatol 2013;19:26-8.
5. 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.
6. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41:1100-4.
7. Fischer J, Bohm S, Scholz M, Muller T, Witt H, George J, et al. Combined effects of different interleukin-28B gene variants on the outcome of dual combination therapy in chronic hepatitis C virus type 1 infection. Hepatology 2012;55:1700-10.
8. Lyoo K, Song MJ, Hur W, Choi JE, Hong SW, Kim CW, et al. Polymorphism near the IL28B gene in Korean hepatitis C virus-infected patients treated with peg-interferon plus ribavirin. J Clin Virol 2011;52:363-6.
9. Sinn DH, Kim YJ, Lee ST, Gwak GY, Choi MS, Lee JH, et al. Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in Asian patients. J Gastroenterol Hepatol 2011;26:1374-9.
10. Heo NY, Lim YS, Lee W, Oh M, An J, Lee D, et al. No association between the IL28B SNP and response to peginterferon plus ribavirin combination treatment in Korean chronic hepatitis C patients. Clin Mol Hepatol 2014;20:177-84.
11. Thai Association for the Study of the Liver. Thailand practice guideline for management of chronic hepatitis B and C 2015 [Internet] June 2015 [cited 2016 Jun 9]. Available from: http://www.thasl.org/files/25.Thailand%20guideline%20for%20management%20of%20CHB%20%20and%20CHC%202015.pdf.
12. Wasitthankasem R, Vongpunsawad S, Siripon N, Suya C, Chulothok P, Chaiear K, et al. Genotypic distribution of hepatitis C virus in Thailand and Southeast Asia. PLoS One 2015;10:e0126764.
13. Andriulli A, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Meta-analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. Aliment Pharmacol Ther 2008;28:397-404.
14. Mangia A, Minerva N, Bacca D, Cozzolongo R, Agostinacchio E, Sogari F, et al. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. Hepatology 2009;49:358-63.
15. Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, 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 2010;139:120-9.e18.